

The Structure of Ballotenol, a New Diterpenoid from *Ballota nigra*

By **Giuseppe Savona** and **Franco Piozzi**,* Istituto di Chimica Organica, Università di Palermo, Via Archirafi, Palermo, Italy

James R. Hanson† and **Michael Siverns**, School of Molecular Sciences, University of Sussex, Brighton, Sussex BN1 9QJ

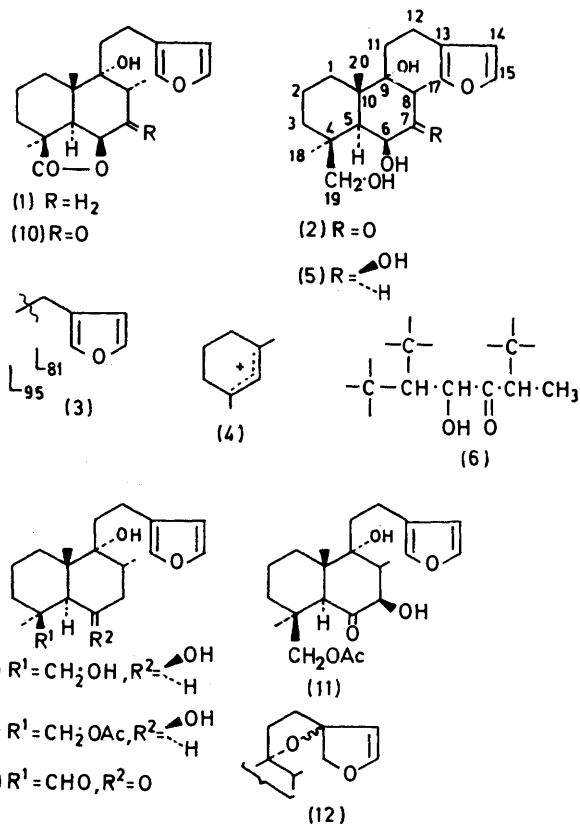
Ballotenol has been shown to be 15,16-epoxy-6 β ,9 α -19-trihydroxy- λ abda-13(16),14-diene-7-one (2).

A NUMBER of bicyclic diterpenoids related to marrubiin (1) have been isolated from *Ballota* (Labiatae) species.¹ We now present evidence in support of structure (2) for ballotenol. The compound showed i.r. absorption characteristic of a hydroxy-group, a cyclohexanone, and a furan ring. The ¹H n.m.r. spectrum contained signals attributable to a secondary and two tertiary methyl groups. Double irradiation experiments revealed the coupling between the secondary methyl (17-H₃) signal and a single-proton quartet (8-H), between a pair of single-proton AX doublets [δ 3.43 and 4.40 (19-H₂)], and between a single-proton doublet [δ 4.49(6-H)] and a methine-proton doublet [δ 2.21(5-H)]. The spectrum also contained signals typical of a β -substituted furan ring. The mass spectrum contained ions characteristic of a β -alkyl substituted furan (3) and an ion at *m/e* 109 which is associated with the fragment (4) in many diterpenoids. The ¹³C n.m.r. spectrum showed that the carbon atoms were disposed as three methyl groups, six methylene carbon atoms, and five fully substituted carbon atoms including a carbonyl group. The presence of a triplet at 67.0, a doublet at 74.9, and a singlet at 82.9 p.p.m. were evidence for the presence of a primary, a secondary, and a tertiary hydroxy-group.

Reduction of ballotenol with lithium aluminium hydride afforded a tetraol (5). The new CH·OH n.m.r. signal (δ 4.28) was identified by carrying out the reduction with lithium aluminium deuteride. Careful examination of the spectrum then revealed the relationship between the new CH·OH (7-H) and both the secondary hydroxy-group of ballotenol and the secondary methyl group. Double irradiation experiments confirmed the coupling between the 19-H₂ doublets, and irradiation at the frequency of the 7-H resonance led to collapse of the 8-H eight-line system to a quartet (*J* 7 Hz) and to sharpening of the 6-H signal to a doublet (*J* 2 Hz). Irradiation at the frequency of the 8-H signal led to collapse of the 17-H₃ methyl doublet to a singlet as well as to sharpening of the 7-H signal. Irradiation at the frequency of the 6-H signal led to sharpening of the 7-H

signal and to collapse of the 5-H doublet to a singlet. Hence ballotenol contained the system (6).

This evidence suggested the relationship to marrubenol (7).² In the ¹H n.m.r. spectrum of marrubenol the



19-H₂ proton resonance also appears as an AX doublet [δ 3.43 and 4.46 (*J* 12 Hz) in C₅D₅N]. This large difference in chemical shift between the two methylene hydrogen atoms is probably caused by a strong hydrogen bond with the C-6 hydroxy-group leading to restricted rotation of C-19. The ¹³C n.m.r. signals of marrubenol

* G. Savona, F. Piozzi, J. R. Hanson, and M. Siverns, *J.C.S. Perkin I*, 1976, 1607.

² W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward, and T. F. Holley, *J. Chem. Soc.*, 1953, 2540.

(7), its 19-monoacetate (8), and the oxo-aldehyde (9)³ were assigned by comparison with the spectra of other bicyclic diterpenoids.^{1,4} These particular derivatives were selected because they enabled the signals associated with the ring B carbon atoms to be defined. The location of the α -ketol system of ballotenol was then clear. In particular the triplet resonance associated with C-7

When a further sample of ballotenol was isolated from older plants, it contained a second component which lacked the furan ¹H n.m.r. signals; the spectrum contained instead one-proton signals at δ 4.08 and 4.55 (J 11 Hz) and 5.52 and 6.62 (J 3 Hz). The remaining resonances were similar to those of ballotenol, but the C-17 methyl signal appeared as a doublet, δ 1.10 (J 7 Hz).

¹³C N.m.r. signals (p.p.m. from Me₄Si; solvent C₆D₆N)

Compound	Carbon atom																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
(7)	35.7	19.0	38.7	43.9	49.9	65.7	40.5	31.1	77.6	39.2	34.1	21.9	126.7	111.5	143.3	138.7	16.6	28.4	68.1	20.2
(8)	35.7	18.8	36.3	43.8	50.4	66.1	40.5	31.4	77.6	38.6	33.6	21.9	126.5	111.5	143.3	138.7	16.7	27.7	68.4	20.7*
(9)	35.0	19.0	35.5	49.1	59.7	207.9	47.6	38.5	77.9	47.7	31.3	22.0	126.1	111.4	143.3	139.0	16.3	25.6	211.6	18.0
(2)	35.5	18.9	39.3	44.2	51.4	74.9	213.0	46.0	82.9	40.1	34.5	22.0	126.0	111.4	143.3	138.8	8.7	27.8	67.0	20.1
(5)	35.6	19.2	40.7	45.0	44.7	70.9	77.9 †	34.2	79.2	39.2	33.9	22.1	127.1	111.7	143.1	138.9	14.3	28.8	68.0	19.5

* Acetate 20.9, 172.4 † Removed on deuteration.

was replaced by a carbonyl singlet, and both C-6 and C-8 showed significant downfield shifts. On the other hand C-17 showed an upfield shift.

The hydroxy-group at C-6 was assigned a β - (axial) configuration since the coupling constant ($J_{5,6}$) was small (3 Hz) and the C-19 protons show the same chemical shift difference as in marrubenol. In an attempt to establish a relationship with ballotinone (10) the latter was reduced with lithium aluminium hydride. However the product was isomeric with the tetraol (5) obtained from ballotenol. An examination of the coupling constants (Figure) obtained from spin-decoupling experiments revealed a difference in $J_{7,8}$. In the reduction

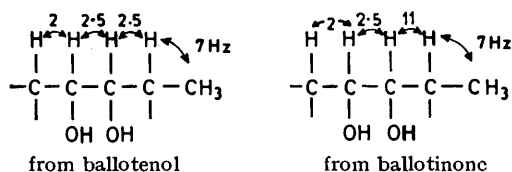


FIGURE Coupling constants in the reduction products

product of ballotenol, the magnitude of this suggested that there was an axial-equatorial relationship between these hydrogen atoms whereas in the reduction product of ballotinone there was a diaxial relationship. Hence in ballotenol (2) the C-8 methyl group was assigned a β -configuration.

Acetylation of ballotenol gave a 19-monoacetate with a ¹H n.m.r. spectrum consistent with the disposition of the ring B ketol system as in ballotenol. This compound was converted spontaneously into an isomer in the spectrum of which the 5-H signal (δ 3.20) was a singlet and a doublet appeared at δ 3.90 (J 9 Hz), assigned to a 7-H. Hence the isomer contains a 6-oxo-7-hydroxy-function and is the product of a ketol isomerization (11) in which the driving force is probably the relief of the diaxial C(6)-C(20) interaction. The magnitude of $J_{7,8}$ implies a diaxial relationship between these protons, *i.e.* an equatorial 7-hydroxy-group and an equatorial 8-methyl group, which suggests that there may have been epimerization at C-8 or that ring B has now adopted a boat conformation.

³ R. A. Appleton, J. W. B. Fulke, M. S. Henderson, and R. McCrindle, *J. Chem. Soc. (C)*, 1967, 1943.

The sample slowly decomposed to afford ballotenol; hence this second component was the 'pre-furan' equivalent (12) of ballotenol.

EXPERIMENTAL

General experimental details have been described previously.¹

Ballotenol, isolated from *Ballota nigra*,¹ had m.p. 142° (decomp. 150°), $[\alpha]_D^{20}$ 0° (*c* 0.38 in pyridine) (Found: C, 68.1; H, 8.2. C₂₀H₃₀O₅ requires C, 68.6; H, 8.6%), ν_{\max} 3 500, 3 250sh, 3 100br, 1 710, and 875 cm⁻¹, δ (C₆D₆N) 1.05 (3 H, s), 1.29 (3 H, d, J 7 Hz), 1.62 (3 H, s), 2.21 (1 H, d, J 3 Hz) 2.70 (2 H, m), 3.43 (1 H, d, J 12 Hz), 3.81 (1 H, q, J 7 Hz), 4.40 (1 H, d, J 12 Hz), 4.49 (1 H, d, J 3 Hz), 6.38br (1 H, s), 7.40 (1 H, s), and 7.50 (1 H, s), *m/e* 350, 332, 291, 275, 209, 123, 109, 95, and 81 (base peak). The **monoacetate**, prepared with acetic anhydride-pyridine, had m.p. 150° (decomp.), ν_{\max} 3 500, 1 730br, and 875 cm⁻¹, δ (CDCl₃) 1.07 (3 H, s), 1.12 (3 H, d, J 7 Hz), 1.44 (3 H, s), 1.92 (1 H, d, J 3 Hz), 2.05 (3 H, s), 3.55 (1 H, q, J 7 Hz), 4.32 (1 H, d, J 3 Hz), 4.55 (2 H, s), and 6.27, 7.25, and 7.35 (each 1 H, s), *m/e* 392(M⁺), 374, 333, 317, 291, 275, 211, 209, 191, 151, 123, 109, 95, and 81. On passing through a column of silica gel in ethyl acetate-light petroleum this rearranged to the **isoacetate**, an oil, δ (CDCl₃) 0.90 (3 H, s), 1.08 (3 H, s), 1.28 (3 H, d, J 7 Hz), 2.05 (3 H, s), 2.50 (2 H, m), 3.20 (1 H, s), 3.90 (1 H, d, J 9 Hz), 4.48 (1 H, d, J 15 Hz), 4.88 (1 H, d, J 15 Hz), and 6.27, 7.25, and 7.35 (each 1 H, s), *m/e* 392(M⁺), 374, 333, 332, 317, 291, 275, 257, 209, 191, 180, 149, 123, 109, 95, and 81.

Reductions with Lithium Aluminium Hydride.—(a) Ballotenol (150 mg) in tetrahydrofuran (10 ml) was treated with lithium aluminium hydride (100 mg) at room temperature for 1 h. The solution was treated with an excess of 2% sodium hydroxide solution, and the product recovered in ethyl acetate and purified by dry column chromatography on silica in 70% ethyl acetate-light petroleum to give an oil, ν_{\max} 3 200br and 875 cm⁻¹, δ (C₆D₆N) 1.25 (3 H, s), 1.40 (3 H, d, J 7 Hz), 1.55 (3 H, s), 2.30 (1 H, d, J 2 Hz), 2.58 (1 H, octet, J 7 and 2.5 Hz), 3.50 (1 H, d, J 12 Hz), 4.28 (1 H, t, J 2.5 Hz), 4.55 (1 H, d, J 12 Hz), 4.60 (1 H, d, J 2 Hz), and 6.48, 7.35, and 7.60 (each 1 H, s), *m/e* 352(M⁺), 334, 316, 235, 181, 153, 123, 109, 95, and 81 (base peak).

⁴ S. O. Almqvist, C. R. Enzell, and F. W. Wehrli, *Acta Chem. Scand.*, 1975, **B29**, 695; B. L. Buckwalter, I. R. Burfitt, A. A. Nagel, E. Wenkert, and F. Naf, *Helv. Chim. Acta*, 1975, **58**, 1567.

(b) Under similar conditions, ballotinone also gave an oil, ν_{\max} 3 250br and 875 cm^{-1} , δ ($\text{C}_5\text{D}_5\text{N}$) 1.16 (3 H, s), 1.50 (3 H, s), 1.54 (3 H, d, J 7 Hz), 2.50 (this octet partly obscured by adjacent signal), 3.56 (1 H, d, J 12 Hz), 4.10 (1 H, q, J 2.5 and 11 Hz), 4.55 (1 H, d, J 12 Hz), 4.60 (1 H, d, J 2 Hz), and 6.48, 7.35, and 7.60 (each 1 H, s), m/e 352, 334, 286, 221, 181, 153, 149, 123, 109, 95, and 81 (base peak).

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