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β-ELEMEN-9β-OL FROM *ACHILLEA AGERATUM*

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Key Word Index—*Achillea ageratum*; Compositae; sesquiterpene alcohol; β-elemen-9β-ol.

Abstract—The oil obtained from a hexane extraction of the flowers and leaves of *Achillea ageratum* L. yielded a new sesquiterpene alcohol, β-elemen-9β-ol. Its structure and stereochemistry have been established by chemical and physico-chemical methods.

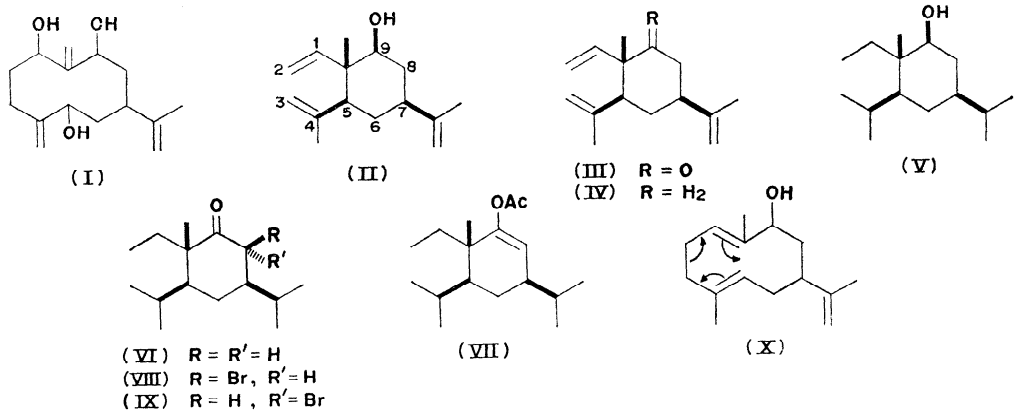
RECENTLY we reported[1] the isolation and structure determination of a new germacrane sesquiterpene, ageratriol (I), from *Achillea ageratum* L. (Compositae). In order to examine the biogenetic route to I, we have examined the oil obtained by steam distillation of the residue of a hexane extraction of the flowers and leaves of *A. ageratum*. It contains about 20 components, of which the most abundant is 1,8-cineole (~60%). From the high boiling fraction, after repeated chromatography on silica gel and final purification on GLC, a new compound β-elemen-9β-ol (II), $C_{15}H_{24}O$, (b.p. 113–115°/0·3 mm) was obtained (~25% of the original oil).

The β-elemene skeleton in II was demonstrated by treating[2] with $NaBH_4$ in MeOH the tosylhydrazone of ketone III (b.p. 87–90°/0·25 mm), obtained from β-elemen-9-ol by Jones oxidation. A mixture of two hydrocarbons was obtained from the reaction; the most abundant (70%), which was isolated by preparative GLC, shows physical and spectroscopic data in agreement with that reported[3] in the literature for β-elemene (IV). Furthermore, this compound (b.p. 115–116°/10 mm) has the same R_t on GLC as that of an authentic sample.

The position of the hydroxyl, indicated as being in C-9 by the double doublet at 3·46 δ (*J* 3·7 and 11 Hz) of the hydrogen α to the hydroxyl in the NMR spectrum of II, is substantiated as follows: II is reduced (PtO_2, *n*-hexane) to the saturated alcohol V (m.p. 105·5°) which, by Jones oxidation, yields the ketone VI (b.p. 100–102°/1 mm); the ORD and CD curves of this compound show negative Cotton effect, in agreement with the suggested stereostructure. When VI is treated with Ac_2O–$HClO_4$ in CCl_4[4] the enolacetate VII is obtained, which exhibits in its NMR spectrum a broad signlet at 5·32 δ due to an olefinic proton, thus excluding C-6 position for the hydroxyl group. The enolacetate was treated with Br_2 in CCl_4 and, subsequently, with MeOH,[5] to yield a 3:2 mixture of the two bromoketones VIII (b.p. 120°/1 mm) and IX (m.p. 74°), which were then separated by preparative

[1] L. GARANTI, A. MARCHESINI, U. M. PAGNONI and R. TRAVE, *Tetrahedron Letters* 1397 (1972).
[2] L. CAGLIOTI, *Tetrahedron* **22**, 487 (1966).
[3] V. SYKORA, V. HEROUT and F. SORM, *Coll. Czech. Commun. Chem.* **21**, 267 (1956); T. IRIE, K. YAMAMOTO. and T. MASAMUNE, *Bull. Chem. Soc. Japan* **37**, 1053 (1964).
[4] D. H. R. BARTON, R. M. EVANS, J. C. HAMLET, P. G. JONES and T. WALKER, *J. Chem. Soc.* 747 (1954).
[5] P. Z. BEDOUKIAN, *Org. Syn.* Coll. Vol. 3, 127 (1955).

GLC. The type of multiplicity of the signals at 4·45 δ (1H, *dd* (*J* 3·7 and 1·5* Hz), H–C–Br) in the NMR spectrum of VIII and at 4·76 δ (1H, *d*(*J* 11 Hz), H–C–Br) in that of IX clearly indicates the presence of a hydrogen atom α to the carbon bearing the bromine atom, thus confirming C-9 position for the ketonic group.



The values of the coupling constants of the double doublet signal of the C-9 proton in the NMR spectrum of β-elemen-9β-ol suggests that the hydroxyl group is equatorially oriented. This fact, and the results previously described, establish the stereostructure of β-elemen-9β-ol implicit in II.

Since the derivatives of β-elemene normally result from Cope-re-arrangement of germacrane precursors,[6] one may assume that β-elemen-9β-ol is a transformation product of an X-structure-like compound. An attempt is now being made to isolate the precursor using fresh material.

EXPERIMENTAL

Plant material. The plants of *Achillea ageratum* were harvested in northern Sardinia in July.

Isolation of β-elemen-9β-ol (II). The flowers (10 kg) were extracted with *n*-hexane (60 l.) by percolation at room temp. The solvent was evaporated *in vacuo* to afford a dark yellow oil (110 g) which, by steam distillation, yielded a volatile mixture (40 g). The low boiling fraction, consisting chiefly of 1,8-cineole, was eliminated by careful distillation. The residue (14 g) was chromatographed on silica gel (300 g) and eluted with light petrol.–ether, to give β-elemen-9β-ol (9 g), which was further purified (98%) by distillation, b.p. 113–115°/0·3 mm, and obtained in a pure state by preparative GLC (SE 30 on Chromosorb W, 160°). MS: (M^+) 220 *m/e*. NMR[7] ($CDCl_3$): 0·96 (3H, *s*, CH_3–C), 1·73 (6H, *s*, CH_3–C=C), 3·46 (1H, *dd*(*J* 3·7 and 11 Hz), H–C–O), 4·6–5·33 (6H, *m*, CH_2=C) and 5·76 δ (1H, *dd*(*J* 11·2 and 17 Hz), H–C=C). IR (film): 3420, 3080, 1640, 1065, 975, 890 cm^{-1}. $[\alpha]_D^{20}$ −19·9° (*c*, 2 CH_3OH). (Found: C, 81·71; H, 11·17. $C_{15}H_{24}O$ requires: C, 81·82; H, 10·9%.)

β-Elemen-9-one (III). The β-elemen-9β-ol (0·9 g) was dissolved in pure acetone (20 cm^3). Jones' reagent was added dropwise at 0° until a persistent orange colour was formed. After 10 min the mixture was diluted with H_2O (40 cm^3) and extracted with ether (3 × 15 cm^3). Removal of ether *in vacuo* afforded the ketone III (a single peak in GLC), which was purified by distillation (0·82 g), b.p. 87–90°/0·25 mm. MS: (M^+) 218. NMR ($CDCl_3$): 1·19 (3H, *s*, CH_3–C), 1·78 (6H, *s*, CH_3–C=C), 4·7–5·32 (6H, *m*, CH_2=C), 6·04 δ (1H, *dd*(*J* 10·5 and 17·7 Hz), H–C=C). IR (film): 1700 cm^{-1}. $[\alpha]_D^{20}$ −50° (*c*, 2 MeOH).

* Long-range coupling, 'M' arrangement, with C-6 equatorial proton.

[6] R. V. H. JONES and M. D. SUTHERLAND, *Austral. J. Chem.* **21**, 2255 (1968); R. V. H. JONES and M. D. SUTHERLAND, *Chem. Commun.* 1229 (1968); K. NISHIMURA, N. SHIMODA and Y. HIROSE, *Tetrahedron Letters* 3097 (1969).

[7] NMR spectra were recorded on a Varian HA-60 spectrometer, using $(CH_3)_4Si$ as internal standard.

β-Elemene from III. 0·75 g of β-elemen-9-one was stirred with tosylhydrazine. HCl (1·2 g) in MeOH (15 cm^3) and then refluxed on a H_2O bath for 1 hr. The mixture was cooled, concentrated *in vacuo* and, after addition of H_2O (10 cm^3), extracted with ether (3 × 10 cm^3). The residue from ether extract, chromatographed on silica gel, eluting with light petrol.–ether (4:5), yielded the tosylhydrazone (0·98 g), homogeneous in TLC. On crystallization, fine needles (0·6 g) were obtained, m.p. 127°. $[\alpha]_D^{20}$ −5·1° (*c*, 2 MeOH). (Found: C, 68·51; H, 7·59; N, 7·05. $C_{22}H_{30}N_2O_2S$ requires: C, 68·39; H, 7·77; N, 7·25%.)

To a stirred solution of tosylhydrazone (0·55 g) in MeOH (20 cm^3) $NaBH_4$ (1·3 g) was added at 20° over a period of 20 min. The solution was further stirred for 1 hr and then extracted with *n*-pentane (3 × 10 cm^3). Removal of *n*-pentane furnished a product (0·29 g) for which GLC analysis showed two peaks (7:3). On preparative GLC (Carbowax 5% on chromosorb W) the major product was isolated and then purified by distillation, b.p. 115–116°/10 mm. GLC analysis gave a single peak, MS: (M^+) 204 *m/e*. NMR ($CDCl_3$): 1·0 (3H, *s*, $C\underline{H}_3$–C), 1·75 (6H, *s*, CH_3–C=C), 4·6–5·1 (6H, m, $C\underline{H}_2$=C) and 5·82 δ (1H, *dd*(*J* 10·2 and 17·4 Hz), $\underline{H}$–C=C).

β-elemen-9-ol (V). A solution of II (1·2 g) in *n*-hexane was hydrogenated over PtO_2 (0·2 g) until the absorption corresponded to 3 mol of H_2. After filtering off the catalyst, the filtrate afforded β-eleman-9-ol (1·2 g) which was purified by crystallization (*n*-hexane), m.p. 105·5°. MS: (M^+): 226 *m/e*. NMR ($CDCl_3$): 3·53 δ (1H, *dd*(*J* 4·3 and 10·8 Hz), $\underline{H}$–C–O). IR (Nujol): 3300 cm^{-1}. $[\alpha]_D^{20}$ −8·6° (*c*, 4·6 $CHCl_3$).

β-Eleman-9-one (VI). A solution of β-eleman-9-ol (1·1 g) in acetone (25 cm^3) was oxidized under the same conditions as that of I and worked up to afford an oil (0·95 g) which was purified by distillation *in vacuo*, b.p. 100–102°/1 mm. MS: (M^+) 224 *m/e*. IR (film): 1708 cm^{-1}. $[\alpha]_D^{20}$ −28·3° (*c*, 6 $CHCl_3$). ORD[8] (*c*, 0·20 CH_3OH), 20°, $[\phi]_{317}$ −2051°; $(\phi)_{275}$ +2073°. CD[8] (*c*, 0·20 MeOH), 20°, $[\theta]_{340}$ 0; $[\theta]_{296}$ −3300; $[\theta]_{240}$ 0; Γ36 nm.

Enolacetylation of VI. β-Eleman-9-one (0·8 g) in CCl_4 (15 cm^3) was treated at room temp. with 50% aqueous $HClO_4$ (2 drops) in Ac_2O (1 cm^3). After 1 hr at room temp. the solution was washed with ice-cold 5% NaOH and H_2O, then dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by distillation (0·65 g), b.p. 103–105°/0·1 mm. NMR ($CDCl_3$): 2·12 (3H, *s*, $C\underline{H}_3$–O–C=O) and 5·32 δ (1H, br. *s*, H–C=C). IR: (film) 1755, 1210 cm^{-1}.

Bromoketones VIII *and* IX. (a) *From the enolacetate* VII. The compound VII (0·5 g) was dissolved in CCl_4 (5 cm^3) and a solution (10%) of Br_2 in CCl_4 was added at room temp. dropwise until a persistent colour was formed. After 10 min, MeOH (0·5 cm^3) was added; the mixture was shaken thoroughly and left at room temp. for 6 hr after which it was diluted with H_2O (5 cm^3). The organic layer was separated and the aqueous solution extracted further with CCl_4 (2 × 10 cm^3). The residue from combined CCl_4 extracts was separated into the components VIII and IX (3:2) by preparative GLC (Carbowax 5%). (VIII). b.p. 120°/1 mm. NMR ($CDCl_3$): 1·36 (3H, *s*, $C\underline{H}_3$–C), 4·45 (1H, *dd* (*J* 3·7 and 1·5 Hz), $\underline{H}$–C–Br). IR (film): 1698 cm^{-1} (IX). m.p. 74°. NMR ($CDCl_3$): 1·07 (3H, *s*, $C\underline{H}_3$–C) and 4·76 δ (1H, *dJ*(11 Hz), $\underline{H}$–C–Br). IR (Nujol). 1710 cm^{-1}. (b) *By direct bromination of the ketone* VI. The ketone VI (0·5 g) in HOAc (10 cm^3) was treated with excess bromine at room temp. The mixture was left for 1 hr and then worked up in the usual manner to furnish a mixture (0·6 g) (3:7) of the two bromoketones VIII and IX.

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[8] K. Morikawa and Y. Hirose, *Tetrahedron Letters* 2899 (1968); 869 (1969) reported for a VI-like compound, obtained from (−)-δ-elemenol, CD and ORD values considerably lower than those found here.