

AGEROL, THE PRECURSOR OF  $\beta$ -ELEMEN-9 $\beta$ -OL.

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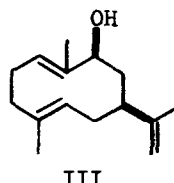
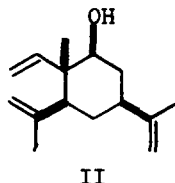
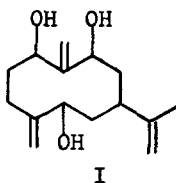
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In previous papers we described the isolation of a new germacrane derivative, ageratriol I<sup>(1)</sup>, and of a new sesquiterpenic alcohol,  $\beta$ -elemen-9 $\beta$ -ol II<sup>(2)</sup>, from Achillea ageratum L. (Compositae).

Since it had already been established that many elemene-type derivatives are transformation products of cyclodecadiene precursors<sup>(3)</sup>, and in view of the fact that tlc assay (silica gel, light pet.-acetone 9:1) of the unconcentrated crude hexane extract of fresh flowers of A. ageratum revealed the presence of a new compound alongside traces of  $\beta$ -elemen-9 $\beta$ -ol, an attempt was made to isolate the II-precursor.

The residue obtained by evaporation of the hexane at r.t. was chromatographed repeatedly on silica gel, and, after distillation in vacuum (95°/0,02mm) and recrystallization at -30° from pentane, agerol III, C<sub>15</sub>H<sub>24</sub>O<sup>(4)</sup>, m.p. 63-64°,  $[\alpha]_D^{20} + 11,8^\circ$  (c, 2 CH<sub>3</sub>OH),  $\nu_{\max}$  (nujol) 3300 cm<sup>-1</sup>, was obtained.

In the nmr spectrum<sup>(5)</sup> (CDCl<sub>3</sub>) of III there are peaks at 1,47 (br.s.), 1,56 (br.s.) and 1,77 (s) for three methyls on double bond, at 4,1 (m) for a hydrogen  $\alpha$  to a hydroxyl group and probably allylic, at 4,7 (d) for an olefinic methylene and, finally, a very broad signal at 4,3-5,4  $\delta$  for two olefinic protons.

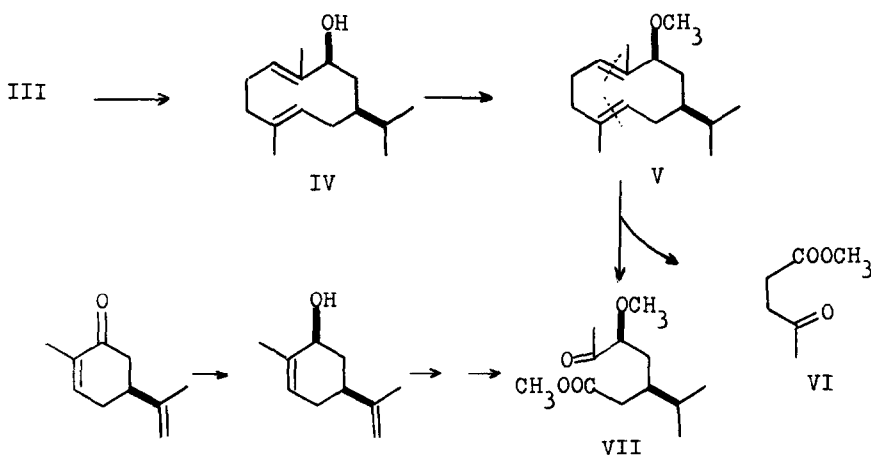


The structure and configuration given for agerol by formula III are consistent with the following findings. When III is heated<sup>(6)</sup> for 30' at 180° in a nitrogen atmosphere it is quantitatively transformed into II, b.p. 112-114°/0,3

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mm,  $[\alpha]_D^{20} - 19,7^\circ$  (c, 2 CH<sub>3</sub>OH). Partial hydrogenation of III, with tris-(triphenylphosphine)-chlororhodium as catalyst, yields a dihydroderivative, C<sub>15</sub>H<sub>26</sub>O, m.p. 61-62°,  $[\alpha]_D^{20} + 2,7^\circ$  (c, 2 CH<sub>3</sub>OH),  $\nu_{\max}$  (nujol) 3250 cm<sup>-1</sup>. The nmr spectrum (CDCl<sub>3</sub>), with peaks at 0,9 (6H, d, CH<sub>3</sub>-C), 1,46, 1,53 (3H each, br. s., CH<sub>3</sub>-C=), 3,95 (1H, m, H-C-O) and 4,2-5,4  $\delta$  (2H, br. m., H-C=), shows that the isopropenylic double bond has been reduced to form IV. The dihydroagerol IV was converted into methylether V, C<sub>16</sub>H<sub>28</sub>O, b.p. 93-95°/0,1 mm,  $[\alpha]_D^{20} - 14^\circ$  (c, 2 CH<sub>3</sub>OH), by treatment with NaH-CH<sub>3</sub>I in tetrahydrofurane. Ozonolysis of V at -60° in CH<sub>2</sub>Cl<sub>2</sub>, followed by Pd/C catalyzed reduction, yielded a mixture of two main compounds. Oxidation with 2% aqueous KMnO<sub>4</sub> and subsequent CH<sub>2</sub>N<sub>2</sub> treatment of the reaction mixture yielded the methylester of the levulinic acid (VI) and a ketomethyl-ester VII, C<sub>12</sub>H<sub>22</sub>O<sub>4</sub>,  $[\alpha]_D^{20} - 36^\circ$  (c, 2 CH<sub>3</sub>OH),  $\nu_{\max}$  (film) 1730, 1715 cm<sup>-1</sup>, nmr (CDCl<sub>3</sub>): 0,87 (6H, d, CH<sub>3</sub>-C), 2,16 (3H, s, CH<sub>3</sub>-C=O), 3,32 (3H, s, CH<sub>3</sub>-O-C), 3,4-3,7 (1H, m, H-C-O) and 3,65  $\delta$  (3H, s, CH<sub>3</sub>-O-C), isolated by preparative gaschromatography.

The structure of 3-isopropyl-5-methoxy-6-keto-heptoic acid methylester and the absolute configuration of the two asymmetric centres were established by comparison with the four stereoisomers of VII obtained<sup>(7)</sup> from the (+)- and

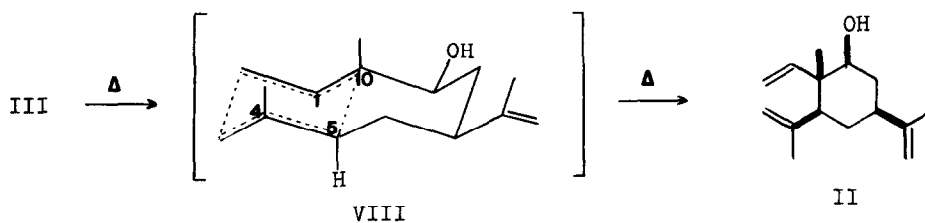


from the (-)-carvone. Both the asymmetric centres present in agerol proved therefore to have an S configuration.

These chemical correlations confirm the absolute configuration already assigned by us to  $\beta$ -elemen-9 $\beta$ -ol<sup>(2)</sup>.

The conformation of the ten-membered ring in agerol may be deduced<sup>(8)</sup> on the basis of the stereochemical aspects of the Cope rearrangement. According to the

Woodward-Hoffmann theory, which predicts a four-centre cyclohexane chair-like transition state for this thermal sigmatropic change<sup>(9)</sup>, the double bonds in 1-10 and in 4-5 in agerol must have a trans configuration and a crossed orientation. Knowledge of the absolute configuration of II indicates<sup>(10)</sup> that the methyl groups in C-10 and C-4 must be orientated as shown in VIII and not in the opposite direction.



A biogenetic study of III is in the process of being carried out in order to determine its role as intermediary between germacrene A<sup>(11)</sup> and ageratriol I.

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#### References and notes.

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- (4) Satisfactory elemental analyses were obtained for all new compounds reported herein.
- (5) nmr spectra were recorded at 60 MHz on a Jeol instrument, using  $(\text{CH}_3)_4\text{Si}$  as internal standard.
- (6) Agerol is indistinguishable on glc (5% carbowax 20M 170°, injector heater off) from  $\beta$ -elemen-9 $\beta$ -ol II.

- (7) The preparation of the four stereoisomers of VII is the subject of a forthcoming publication.
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