

AGERATRIOL, A NEW SESQUITERPENE FROM ACHILLEA AGERATUM L.

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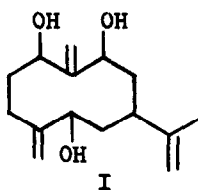
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Achillea ageratum L. is a species of the compositae family which grows wild in Mediterranean countries.

Chloroform extraction of the leaves and flowers of this plant, previously extracted with n-hexane, yields on concentration a crystalline compound, ageratriol (I) (about 0,3% from fresh tissue).



Ageratriol (I) [$C_{15}H_{24}O_3$ ($^{\circ}$); m.p. 195 $^{\circ}$; $[\alpha]_D^{20} +30,5^{\circ}(c, 2)^{(\circ\circ)}$] behaves like a pure product (t.l.c. and g.l.c. as silylether); its i.r. spectrum (nujol) exhibits $-OH$ (3320 cm^{-1}) and $=CH_2$ ($1650, 885\text{ cm}^{-1}$) absorptions. The n.m.r. spectrum ($^{\circ\circ\circ}$) (C_5D_5N) shows signals at 1,69 (3H, s, $CH_3-C=$), 4,1-4,7 (3H, br. m, $CH-OH$), 4,75 (2H, m, $CH_2=C-$), 5,2 (2H, br. s, $CH_2=C-$), 5,55, 5,86 (1H each, br. s, $H=C-$) and 6,1 δ (3H, m, $C-OH$, disappeared on exchange with CF_3COOH). There are no vicinal hydroxyl groups, as indicated by periodic acid titration.

Acetylation of I yields a triacetate (II) [b.p. 181-183 $^{\circ}/1,5\text{mm}$; $[\alpha]_D^{20} + 56^{\circ}$ (c, 2,1) which exhibits in its n.m.r. spectrum (C_5D_5N) a downfield shift (about 0,6 ppm) of the signals at 4,1-4,7 δ .

Catalytic hydrogenation (PtO_2-AcOH) of I affords a stereoisomeric mixture of hexahydrocompounds (m.p. 59-65 $^{\circ}$); its n.m.r. spectrum (C_5D_5N) shows four methyl groups (0,9-1,5 δ) and no olefinic protons; furthermore, the broad signal due to the three hydrogens α to the hydroxyl groups is displaced upfield

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to 3,5-4,2 δ .

In view of the above results, ageratriol should be considered a monocyclic compound having three allylic hydroxyls and three methylenic groups, one of which is present in an isopropenyl group, (in agreement with C-methyl and C-methylene determinations).

Triacetylageratriol (II) can be hydrogenated (PtO_2 , n-hexane, 1,6 moles H_2) to yield a mixture of III [b.p. 194-196°/0,6mm; $[\alpha]_D^{20} +44,6^\circ$ (c, 3)] and IV [b.p. 170-172°/0,3mm; $[\alpha]_D^{20} +7,2^\circ$ (c, 2)], together with some starting material and hexahydroderivative. When this mixture is mildly treated with dilute alkali a product is obtained which, after AgNO_3 -silica gel chromatography, yields the pure dihydroageratriol V [m.p. 200-201°; $[\alpha]_D^{20} -9,3^\circ$ (c, 2)] and the monoacetylated tetrahydroageratriol VI [m.p. 165°; $[\alpha]_D^{20} -60^\circ$ (c, 2)].

The n.m.r. spectrum ($\text{C}_5\text{D}_5\text{N}$) of V reveals the presence of two secondary methyl groups (isopropyl) while the signal due to the vinyl-methyl disappears; furthermore, no shifts of hydrogen α to hydroxyl are observed.

The n.m.r. spectrum ($\text{C}_5\text{D}_5\text{N}$) of the tetrahydroageratriol VII [m.p. 150-151°; $[\alpha]_D^{20} -31,5^\circ$ (c, 2)], obtained from VI by warm alkali, reveals a new methyl group (3H, d, 1,25 δ) and an upfield shift (about 0,8 ppm) of one of the protons α to the hydroxyl groups. Therefore, this hydroxyl must be allylic to the second hydrogenated methylene.

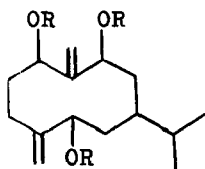
Since all three protons α to the hydroxyl groups were shifted upfield in the n.m.r. spectrum of hexahydroageratriol, we can infer that both the remaining hydroxyls must be allylic to the third methylene group.

These results were further supported by titrations carried out on compounds VIII and IX: dihydrotriacetylageratriol (III) was treated with ozone to give the triacetyldiketone X (40% yields) [m.p. 86-87°; $[\alpha]_D^{20} -39,5^\circ$ (c, 2); n.m.r. spectrum (CDCl_3): 0,85, 0,96 (3H each, d, $\text{CH}_3-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{CH}$), 2,07, 2,11, 2,15 (3H each, s, $\text{CH}_3-\text{CO}-\text{O}$), 4,76, 5,15 (1H each, q, $\text{H}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OAc}$) and 5,45 δ (1H, t, $\text{H}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OAc}$)], which, when reduced with LiAlH_4 , afforded a pentahydroxycompound (VIII) as oily mixture of stereoisomers which consumed 3 equivalents of periodic acid, supporting the presence of the groups $-\overset{\text{O}}{\underset{\text{OH}}{\text{C}}}-\overset{\text{O}}{\underset{\text{CH}_2}{\text{C}}}-\overset{\text{O}}{\underset{\text{OH}}{\text{C}}}-$ and $-\overset{\text{O}}{\underset{\text{OH}}{\text{C}}}-\overset{\text{O}}{\underset{\text{CH}_2}{\text{C}}}-$ in ageratriol; tetra-

hydrotriacetylageratriol (IV), treated as above, afforded a tetrahydroxycompound (IX), which consumed 2 equivalents of periodic acid.

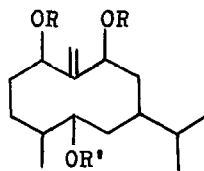
Definite substantiation of the above results and the assignation of a cyclo-decanic structure to ageratriol is afforded by studies on the products obtained by degradative oxidation.

When the pentahydroxycompound VIII was oxidated with $\text{KMnO}_4\text{-NaIO}_4^{(1)}$ succinic and β -isopropylglutaric acids were obtained. Furthermore, when dihydrotriacetylageratriol (III) is treated with *m*-chloroperbenzoic acid in boiling CH_2Cl_2 epoxidation occurs at the less hindered methylene and the resulting epoxycompound



III R = Ac

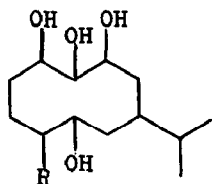
V R = H



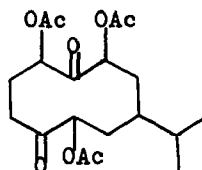
IV R = R' = Ac

VI R = H R' = Ac

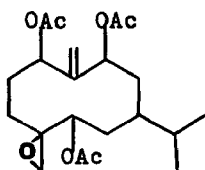
VII R = R' = H



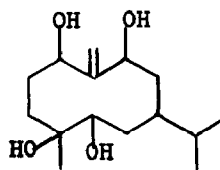
VIII R = OH

IX R = CH₃

X



XI

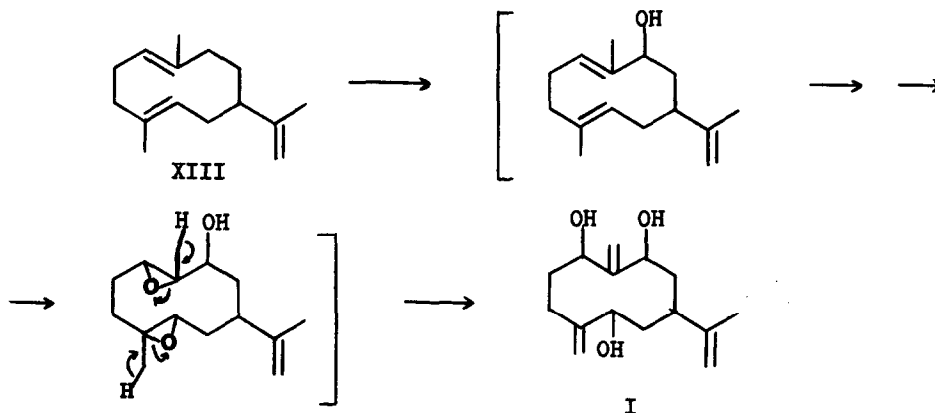


XII

XI [b.p. 200-202°/0.5mm; $[\alpha]_D^{20} +13,6^\circ(c, 1,5)$; n.m.r. (CDCl_3): 0,83, 0,95 (3H each, d, $\text{CH}_3\text{-CH}$), 2,04 (6H, s, $\text{CH}_3\text{-CO-O}$), 2,1 (3H, s, $\text{CH}_3\text{-CO-O}$), 2,8, 3,27 (1H each, d, $J=3,7$ Hz, H-C-O), 4,45 (1H, t, CH-OAc), 4,97, 5,47 (1H each, q, CH-OAc) and 5,55, 5,67 δ (1H each, s, H-C-O)], when reduced with LiAlH_4 , yields the tetrahydroxyderivative XII, which when oxidated by $\text{KMnO}_4\text{-NaIO}_4^{(1)}$ affords levulinic acid, thus indicating the presence of a methyl group on the C-4 position of ageratriol.

Further extensive study on the absolute configuration of the asymmetric carbons is now in progress.

The ageratriol structure has very interesting biogenetic features, concerning the probable derivation from the recently isolated germacrene A⁽²⁾ (XIII) and the oxidation pattern involving carbons rarely oxidated in this sesquiterpene group.



The allylic hydroxylation may obviously be the latest step of this suggested scheme.

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References and notes.

- (^o) Satisfactory elemental analyses were obtained for all new compound reported herein.
- (^{oo}) Specific rotations were determined in CH₃OH solution on a Perkin Elmer model 141 polarimeter.
- (^{ooo}) n.m.r. spectra were determined on a Varian Associates HA-60 spectrometer, using (CH₃)₄Si as internal standard.
- (1) R.U. Lemieux and E. Von Rudloff, Can. J. Chem., **33**, 1701, 1710, 1714 (1955).
- (2) A.J. Weinheimer, W.W. Youngblood, P.H. Washecheck, T.K.B. Karns and L.S. Ciereszko, Tetrahedron Letters, 497 (1970)