

A NEW TYPE OF SESQUITERPENE LACTONE ISOLATED FROM ARTEMISIA ANNUA L.

ARTEANNUIN B

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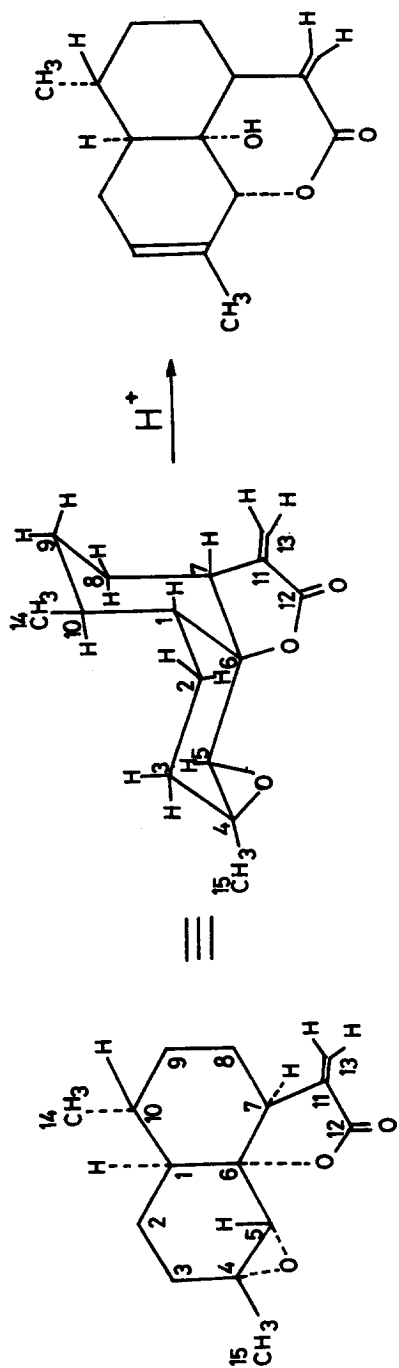
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(Received in UK 11 June 1973; accepted for publication 28 June 1973)

We report the structure of a new sesquiterpene lactone isolated from Artemisia annua L. (collected in October 1970, Belgrade area, Yugoslavia). The structure of this lactone (I) (colorless crystals, m.w. 248, m.p. 152°, $[\alpha]_D^{20} -6^\circ$), which we named Arteannuin B, belongs to the new type of sesquiterpene lactone with the cadinane skeleton. This structure is suggested based upon the following arguments:

Arteannuin B (I) has molecular formula $C_{15}H_{20}O_3$ (h.r.m.s. and combustion analysis). Bands in i.r. at 1780 at 1780 (γ -lactone $\nu_{C=O}$) and 1665 cm^{-1} ($\nu_{C=CH_2}$), λ_{max} at 215 m μ (ϵ 5820) in u.v. and two doublets in n.m.r. ($J = 3\text{Hz}$) at δ 5.41 and 6.61 (β, β' -vinyl protons) confirm γ -lactone ring. In n.m.r. spectrum (220 Mc, $CDCl_3$, Me_4Si), there are no other signals below δ 2.73, indicating that lactonic oxygen is bonded to a tertiary C-atom (double bond at C-6 is excluded by both hydrogenation and brutto formula). C-6 can be a tertiary atom either if it belongs to the three rings or if the substituents like OH, CH_3 or CH_3CO are attached to it. However, there is no OH band in i.r., and the other two substituents are excluded for the following reasons: n.m.r. spectrum shows only two methyl groups indicated by a doublet at δ 0.98 ($J = 6\text{Hz}$; $10-CH_3$) and a singlet at δ 1.33 (CH_3CO), and a very sharp singlet (1H) at δ 2.66 is assigned to the epoxide proton (epoxide ring is also confirmed by 1260, 938 and 863 cm^{-1} bands in the i.r.). When γ -lactonic ring is involved in chemical transformations (hydrogenation, isomerization of C=C, formation of pyrazolone derivative, $NaBH_4$ reduction to diol) and epoxide is kept unchanged the above two singlets retain their positions. However, when acid hydrolysis is carried out these two signals disappear, and the new 3H singlet appears at δ 1.85 (CH_3 attached to double bond). These facts lead to the conclusion that the tertiary methyl group is on epoxide ring and not linked to C-6 atom. Consequently, it can be concluded that C-6 belongs to the three rings as it is shown in formula (I).

Such a position of the lactone ring together with the "isoprene rule"² imply the cadinane skeleton (i.e. two fused six-membered rings). Each of the



(I)

ARTEANNIN B

(II)

protons at C-1 ($\delta 2.05$, $J_{1,10} = 12\text{Hz}$, $J_{1,2} = 3\text{Hz}$, $J_{1,2'} = 3\text{Hz}$) and at C-7 ($\delta 2.73$, $J_{7,8} = 12\text{Hz}$, $J_{7,8'} = 3\text{Hz}$, and $J_{7,13} = 3\text{Hz}$) has a coupling constant which corresponds to the axial-axial coupling in the cyclohexane ring. Therefore, it can be concluded that both protons, at C-1 and at C-7, have axial orientations in a six-membered ring. The shape of the 10-CH_3 signal in 60 Mc spectrum is also indicative. It is not resolved and looks like an A_3B system. Second order coupling is possible only if C-10 proton is axial (axial proton has a signal at the higher field than the equatorial one) and, in addition, due to the anisotropy of the rest of the molecule, this proton is paramagnetically shifted to the still higher field. As a consequence, difference in chemical shifts of the 10-CH_3 protons compared to a coupling constant is small and an A_3B spectrum results. Thus, the existence of one six-membered ring (fused with another six-membered ring) is proved. At the same time, stereochemistry at C-1, C-7 and C-10 carbon atoms is also determined.

ORD and OD curves (ORD, CH_3OH , 0.11%) [α]₅₈₉ - 185°, min [α]₂₇₆ - 2801°, [α]₂₅₅ 0° and max [α]₂₁₄ + 9018°; OD min at 256 nm - 4545°) indicate trans fused δ -lactone ring³. Epoxide ring has been located on C-4 and C-5 because only this structure can satisfy the next two requirements: (1) epoxide proton gives a very sharp singlet because there are no other protons in its neighbourhood, and (2) in acid media Arteannuin B gives a δ -lactone (II). Only 4,5-epoxide with methyl group on C-4 fulfils both requirements. The structure of (II) is deduced based on the evidence given below. M.w. 248.142 corresponds to the brutto formula $\text{C}_{15}\text{H}_{20}\text{O}_3$, m.p. 190°. In i.r. (KBr) spectrum there is a band for OH group at 3400 cm^{-1} (this OH group is tertiary since lactone II can not be acetylated); then a C=O band (in KBr at 1690 and in CHCl_3 at 1720 cm^{-1} - hydrogen bond), and C=C band at 1620 cm^{-1} . Two triplets ($J_{\text{gem}} = J_{\text{all.}} = 1.3\text{ Hz}$) at $\delta 5.68$ and 6.56 in n.m.r. spectrum of (II) (60 Mc, CDCl_3) together with i.r. data prove δ -lactone ring with $\beta, \beta' = \text{CH}_2$. Two broad singlets at $\delta 5.58$, base width cca 17 Hz, and at $\delta 5.01$, base width cca 12 Hz are attributed to C-3 and C-5 protons, respectively. In fact, these two "singlets" are actually multiplets, but due to the small gem. allylic and homoallylic coupling constants are overlapped and give broad singlets. 4-CH_3 group gives a multiplet (all. and homoall. coupling) at $\delta 1.85$ (methyl group on a double bond). Between $\delta 2.0$ and 2.8 there are multiplets for four protons (three allylic and one on C-1). 10-CH_3 group gives again an unresolved signal at $\delta 0.98$. By hydrogenation of the δ -lactone (II), all signals in the low field are removed as well as the multiplets between $\delta 2.0$ and 2.8 (except one for C-10 proton). C-5 Proton gave a doublet at $\delta 4.53$ ($J = 6.5\text{ Hz}$) and that indicates an axial-axial coupling, i.e. 4-CH_3 has an equatorial orientation. All three methyl groups gave doublets: 10-CH_3 at $\delta 0.93$ ($J = 5.5\text{ Hz}$), 4-CH_3 at $\delta 1.21$ ($J = 7.5\text{ Hz}$) and 11-CH_3 at $\delta 1.35$ ($J = 8\text{ Hz}$). Proton on C-11 gave a very broad multiplet at δ cca 3.1 (coupling with a methyl group and one proton at C-7). All above spectral data confirm the structure (II).

δ -Lactone (II) can be obtained only if the structure of the Arteannuin B (I)

is correct⁴, since only 4 β -methyl-4 α ,5 α -epoxide can afford δ -lactone (II). Mass spectra of Arteannuin B (I) and δ -lactone (II) also confirm the suggested structures.

We are now investigating the chemistry of the new lactone (I) and the results obtained will be published shortly.

REFERENCES

1. To whom all correspondence should be addressed.
2. N. H. Anderson, *Phytochemistry*, **9**, 145 (1970).
3. T. G. Wadell, W. Stöcklin and T.A. Geissman, *Tetrahedron Letters*, 1313 (1969).
4. X-ray analysis run independently at two different places has confirmed the structure of Arteannuin B and these results will appear soon elsewhere.