

## SHORT COMMUNICATION

# SESQUITERPENE LACTONES OF *ARTEMISIA CARRUTHII*\*

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(Received 5 August 1971)

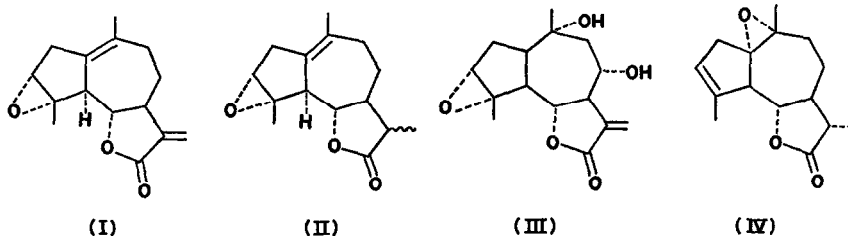
**Abstract**—*Artemisia carruthii* Wood (*A. vulgaris wrightii*) contains a guaianolide, ludartin, which is I accompanied by the corresponding 11,13-dihydro compound, II.

## RESULTS AND DISCUSSION

IN FURTHER examination of plants belonging to the *vulgaris* complex of *Artemisia* (Section Abrotanum), a specimen of *A. carruthii* Wood<sup>1</sup> has been studied, with the isolation of a new sesquiterpene lactone at first named ludartin. The substance, the elemental analysis of which corresponded with the molecular formula  $C_{15}H_{18}O_3$ , had m.p. 100–102°, and appeared homogeneous on a TLC chromatogram. Its mass spectrum revealed, however, that the substance isolated by chromatography and purified by recrystallization, was actually a mixture of two compounds differing by two mass units; namely, of two compounds  $C_{15}H_{18}O_3$  (M-246) and  $C_{15}H_{20}O_3$  (M-248), the peak heights of which had the relative intensities 52 and 62 respectively. In accord with this, two (M-15) peaks at 231 (rel. int. 19) and 233 (rel. int. 15), respectively, were observed. The intensity values relate to a base peak at  $m/e$  43 (100).

Of the three oxygen atoms in the ludartins, two are in the  $\gamma$ -lactone grouping. Since neither a carbonyl nor hydroxyl group was revealed by the IR spectrum, the third oxygen atom was assumed to be present in an epoxide or ether grouping. Examination of the 60 MHz and 100 MHz NMR spectra, and the application of decoupling experiments, led to conclusions that are summarized in the expressions I and II for the two lactones that constituted the mixture.

In the 100 MHz spectrum the C-13 protons appear as the pair of doublets ( $J = 3$  Hz) at  $\delta$  5.34 and 6.06, characteristic of the exomethylene grouping of I. Reduction of ludartin



\* Contribution No. 2872.

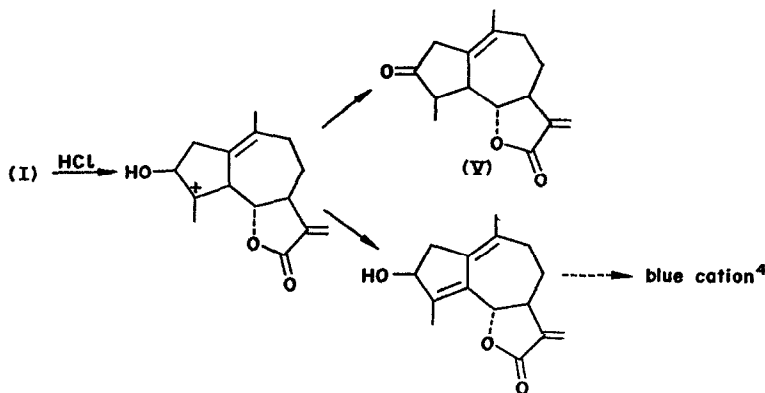
<sup>1</sup> Collected and identified by Dr. JAMES R. ESTES, University of Oklahoma, Norman, Oklahoma. Voucher Nos. 1049, 1050, 1074, 1082 (J.R.E.).

with  $\text{NaBH}_4$  caused the disappearance of these signals. The C-6 protons in I and II exhibit slightly different chemical shifts and appear as juxtaposed triplets ( $J = 10$  Hz) at  $\delta$  3.61 and 3.81. The 10 Hz coupling constant indicates the mutual *trans*-diaxial relationship of the C-5, C-6 and C-7 protons, and establishes the stereochemistry at these positions shown in I and II. The C-5 proton appears as a broadened doublet ( $J = 10$  Hz) at  $\delta$  3.05. Spin decoupling experiments confirmed the coupling of the C-5 and C-6 protons. Irradiation of the doublet of H-5 caused the H-6 triplets to collapse to broadened complex signals. Conversely, irradiation of H-6 (at about  $\delta$  3.7) caused alteration in the pattern of the H-5 signals. The C-7 proton could not be clearly discerned, but decoupling experiments showed that it was a part of an unresolved complex at about  $\delta$  2.0.

The proton at C-3, part of the epoxide grouping, appears as a broadened singlet at  $\delta$  3.35. This signal is similar in appearance and chemical shift to that of the C-3 protons of cumambrin-B epoxide<sup>2</sup> ( $\delta$  3.29), in agreement with the formulation I (and II).

The C-4 and C-10 methyl groups appear as juxtaposed singlets between  $\delta$  1.61 and  $\delta$  1.7, integrating for six protons. In the more clearly resolved 100 MHz spectrum, these signals can be seen to consist of four closely grouped singlets, as is to be expected if the chemical shifts of the methyl groups of I and II are not identical. Since there is no vinyl proton (other than those of the exocyclic methylene group, C-13), these observations indicate that the two methyl groups are found, respectively, on the epoxide grouping (C-4) and in the vinylic position at C-10. The chemical shift of the methyl group at C-4 of cumambrin-B epoxide<sup>2</sup> (III) is  $\delta$  1.60, in accord with that ( $\delta$  1.6–1.7) observed for the ludartins. Moreover, the C-10 methyl group of arborescin (IV) (a C-1/C-10 epoxide) is seen at  $\delta$  1.33.<sup>3</sup> The deshielding effect of the neighboring lactone oxygen atom (at C-6) upon a  $\beta$ -oriented C-4 methyl group can be expected from inspection of a Dreiding model constructed as in I, and supports both the placement of the epoxide grouping at C-3/C-4 and the  $\beta$ -configuration of the C-4 methyl group. It is also apparent that if the epoxide were at C-1/C-10, and the vinylic methyl group at C-4, the vinyl proton at C-3 would be seen in the NMR spectrum.

The C-11 methyl group in II is seen to consist of two doublets at  $\delta$  1.19 ( $J = 6$  Hz) and  $\delta$  1.20 ( $J = 7$  Hz). This indicates that II is actually a mixture of the  $\alpha$ - and  $\beta$ -C-11 methyl isomers. When the mixture (I + II) was reduced with  $\text{NaBH}_4$ , the lower-field doublet



<sup>2</sup> M. A. IRWIN and T. A. GEISSMAN, *Phytochem.* **8**, 305 (1969).

<sup>3</sup> R. B. BATES, Z. CEKAN, V. PROCHAZKA and V. HEROUT, *Tetrahedron Letters* 1127 (1963).

( $\delta$  1.19) increased in intensity to become more intense than the doublet at  $\delta$  1.10. The usual result of this reduction of the exocyclic methylene lactones is to produce the C-11  $\alpha$ -methyl compound, and it is therefore concluded that the lower-field signal is that of the  $\alpha$ -, the higher-field signal that of the  $\beta$ -isomer at C-11. In the spectrum of the original mixture, the signal at  $\delta$  1.10 is about twice that of the signal at  $\delta$  1.19. Thus, the material isolated is a mixture of about 50% I, 35% II- $\beta$ -methyl and 15% II- $\alpha$ -methyl. Attempts to separate these into the pure components were defeated by a lack of sufficient material and by their almost identical behavior on chromatography.

The ludartins give a blue color ( $\lambda_{\max}$  595 nm) when treated with HCl in ethanol, a result which is in complete accord with the structures shown.<sup>4</sup> The low intensity observed ( $\epsilon \sim 100$ ) for the color is undoubtedly due to the tendency for rearrangement of the epoxide to the 3-keto isomer (V) under acidic conditions; the form leading to the blue cation is evidently formed to a smaller extent:

### EXPERIMENTAL

*Artemisia carruthii* Wood (1.87 kg)<sup>1</sup> was dried and ground and extracted with  $\text{CHCl}_3$ . The tarry residue (225 g) obtained by removal of the solvent was extracted with  $\text{EtOH-H}_2\text{O}$  (1:2) and the clarified aqueous solution extracted with  $\text{CHCl}_3$ . From the final  $\text{CHCl}_3$  extract was obtained 56 g of a brown oil. This was chromatographed over 200 g of silica gel with: (a)  $\text{CHCl}_3$ -benzene, 1:1 (1200 ml); (b)  $\text{CHCl}_3$  (1000 ml); and (c) acetone. The first 500 ml of eluate gave a deep blue color with  $\text{EtOH-conc. HCl}$ , and showed a prominent high  $R_f$  spot on TLC. Later fractions gave only small amounts of two- $R_f$  mixtures.

Rechromatography of the first (500 ml) fraction gave fractions containing the ludartins. Removal of the solvents gave an oil that crystallized from ether-light petroleum as rosettes of colorless needles, m.p. 100–102° (0.69 g). The inseparable mixture of ludartins gave a single compact spot on TLC, the  $R_f$  of which was nearly the same as that of costunolide and parthenolide. Upon spraying the TLC plate with conc.  $\text{H}_2\text{SO}_4$ , the ludartins showed an immediate dark purple color, costunolide a brown-orange, parthenolide, orange. *Anal.*  $\text{C}_{15}\text{H}_{18}\text{O}_3$  requires C, 73.14; H, 7.37;  $\text{C}_{15}\text{H}_{20}\text{O}_3$  requires C, 72.55; H, 8.12. Found, C, 72.99; H, 7.39.

The mass spectrum (direct insertion, 70 eV) showed:  $m/e$  248 (relative intensity 52),  $\text{M}_1^+$ ; 246 (63),  $\text{M}_2^+$ ; 233 (15),  $\text{M}_1-15$ ; 231 (19)  $\text{M}_2-15$ ; 43 (100). The IR spectrum showed peaks at  $1770\text{ cm}^{-1}$  ( $\gamma$ -lactone) and  $1675\text{ cm}^{-1}$  (double bond). The NMR spectrum has been described in the text.

**Reduction with  $\text{NaBH}_4$ .** When the ludartin mixture was reduced with  $\text{NaBH}_4$  (2 hr, ice bath), the product was an oil which did not crystallize. Its NMR spectrum lacked the low-field doublets of the exocyclic methylene group, and showed double doublets for H-6 at  $\delta$  3.86 ( $J = 9.5, 11\text{ Hz}$ ) and 3.65 ( $J = 8.5, 11\text{ Hz}$ ); a broadened singlet for H-3 at  $\delta$  3.43; a broadened doublet at  $\delta$  3.0 for H-5; methyl signals at 1.68 (doublet,  $J = 1\text{ Hz}$ ) and 1.61 (singlet). The C-11 methyl groups appeared as doublets ( $J = 7\text{ Hz}$ ) at  $\delta$  1.21 and 1.10, the former now being more intense than the latter (while in the unreduced compound, the  $\delta$  1.10 doublet is about the intensity of the other).

**Acknowledgement**—This study is part of a program supported by research grant GM-14240, U.S. Public Health Service. Dr. G. Chmurny assisted in carrying out the double resonance measurements and analyses are by Miss Heather King.

<sup>4</sup> T. A. GEISSMAN and T. S. GRIFFIN, *Phytochem.* (in press, 1971).

**Key Word Index**—*Artemisia carruthii*; Compositae; sesquiterpenoid lactones; guaianolides; ludartin.