The Structure of Salonitenolide and the Preferential C-8 Relactonization of Germacranolides Containing C-6 and C-8 Lactonizable α-Oxygen Groups

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Summary The structure revision of the germacranolide salonitenolide and the preferential C-8 relactonization of germacranolides containing C-6 and C-8 lactonizable α-oxygen groups are described.

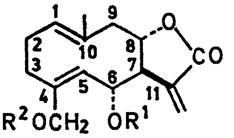
ONE of the more difficult problems encountered in the structure analysis of germacranolides which contain hydroxyl or esterified hydroxyl groups at both the C-6 and C-8 positions is to distinguish between the two alternative positions of lactonization. Investigations based upon germacranolides skeletons after hydrolysis of the natural products are especially ambiguous with respect to the original point of lactonization since relactonization may theoretically occur at either C-6 or C-8.

We recently established that artemisiifolin (Ia), the major sesquiterpene lactone from populations of *Ambrosia artemisiifolia* L. (Compositae), is a member of the C-8 lactone series.[1] Structure (Ia) was previously assigned to salonitenolide, a germacranolide from *Centaurea salonitana* Vis. (Compositae);[2] we now report results which indicate that salonitenolide can be formulated as (IIa), the C-6 isomer of artemisiifolin. Recently, n.m.r. evidence was published which suggested that the lactone function of cnicin (IId), a germacranolide also isolated from *Centaurea* species, is attached at C-6 rather than C-8.[3] Results described here confirm this aspect of the structure revision of cnicin. Finally, we report a general relactonization rule for germacranolides which contain both C-6 and C-8 lactonizable α-oxygen functions: upon strong alkaline treatment followed by acidification, this type of germacranolide always relactonizes to C-8.

The following transformations established structure (IIa) for salonitenolide and confirmed structure (IId) for cnicin: (i) Salonitenolide was converted into artemisiifolin by treatment with an excess of aqueous 10% NaOH for 1 hr. and subsequent acidification with dil. H_2SO_4. Since artemisiifolin (Ia) has been unambiguously established as a C-8 lactone, salonitenolide must be the C-6 isomer (IIa). Additional evidence to support structure (IIa) for salonitenolide was provided by the following n.m.r. analysis: Salonitenolide was converted into a di-trimethylsilyl ether (IIb) by a standard procedure; the ether exhibited a double triplet (J 9 and 5) at 4·00 p.p.m. (δ scale), for a proton on a carbon atom bearing a trimethylsilyloxy-group. In the n.m.r. spectrum of salonitenolide diacetate (IIc) the double triplet appeared in an overlapping region around 5 p.p.m.† These results require that salonitenolide have a hydroxyl group at C-8. (ii) Cnicin was hydrolysed to the C-6 lactone salonitenolide under mild conditions and to the C-8 lactone artemisiifolin under more vigorous conditions: when a solution of cnicin in dioxan was treated with an aqueous solution containing a stoicheiometric amount of K_2CO_3 (the pH of the reaction medium was maintained below 9), extraction of the alkaline solution (*i.e.*, without acidification) yielded only salonitenolide. This is the first report of the preparation of a C-6 lactone by hydrolysis of a natural acylated germacranolide of this type. When cnicin was hydrolysed with an excess of aqueous NaOH, acidification afforded only artemisiifolin.[4] These results clearly establish that cnicin belongs to the C-6 lactone series.

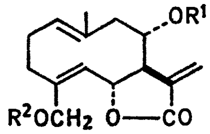
Two other examples of the preferential relactonization to C-8 of germacranolides containing both C-6 and C-8 α-oxygen function were observed with chamissonin (III) and chihuahuin (IV). Chamissonin, a germacranolide from *Ambrosia* species whose structure was recently revised,[5] is a C-8 lactone; it is reformed after strong alkaline treatment and subsequent acidification. Chihuahuin, a newly-isolated germacranolide from *Ambrosia confertiflora* D.C.,[6] was shown to be a C-6 lactone on the basis of n.m.r. studies; it yielded the C-8 lactone chamissonin after strong alkaline treatment and then acidification.

The results reported here establish unambiguously for the first time the preferential relactonization to C-8 of germacranolides having both C-6 and C-8 α-oxygen functions; this rule is therefore applicable to other germacranolides such as onopordopicrin (IIe),[7] scabiolide (Ib),[8] and arctiopicrin (IIf).[8]



(Ia) $R^1 = R^2 = H$

(Ib) $R^1 = CO\cdot\overset{Me}{\underset{OH}{C}}\cdot CH_2OH$, $R^2 = Ac$



(IIa) $R^1 = R^2 = H$

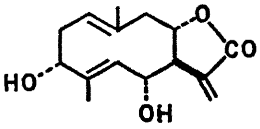
(IIb) $R^1 = R^2 = SiMe_3$

(IIc) $R^1 = R^2 = Ac$

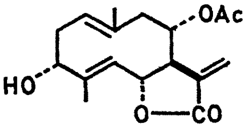
(IId) $R^1 = CO\cdot\underset{\underset{CH_2}{\|}}{C}\cdot\underset{OH}{CH}\cdot CH_2OH$, $R^2 = H$

(IIe) $R^1 = CO\cdot\underset{\underset{CH_2}{\|}}{C}\cdot CH_2OH$, $R^2 = H$

(IIf) $R^1 = CO\cdot\underset{Me}{CH}\cdot CH_2OH$, $R^2 = H$



(III)



(IV)

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† The spectra were recorded in $CDCl_3$ with Me_4Si as internal standard.

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