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DEHYDROSAUSSUREA LACTONE FROM COSTUNOLIDE AND REVERSIBILITY IN THE GERMACRANOLIDE-COPE REACTION

Tikam C. Jain, Calvin M. Banks and John Edmund McCloskey

Department of Chemistry, University of Victoria
Victoria, British Columbia, Canada

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Costunolide[1,2](I) has been isolated in 15% yield in contrast to a trace amount of dihydrocostunolide[3] (II) from the essential oil of costus roots, *Saussurea lappa* Clarke. Interestingly enough, saussurea lactone (III) has been reported[4] from the same source in an unspecified yield; however, its origin *via* the thermolysis of (II) during the distillation of the essential oil has been suggested.[5] In light of this remark it is intriguing that so far there has been no parallel report of (IV) from the essential oil containing (I) in an appreciable amount.* A recent communication[6] prompts us to report the conversion of costunolide (I) to dehydrosaussurea lactone** (IV) required in connection with a project dealing with the lactonic constituents of costus root oil.*** In addition, we also wish to report on the reversibility of thermal conversion of a *trans*-1,2-divinylcyclohexane unit to a *trans,trans*-1,5-cyclodecadiene system observed during these studies.

Costunolide (I) in methanol with excess of dimethylamine at -20° for 96 hours yielded costunolide amine[8] (V) [m.p. 109-110°, $[\alpha]_D^{28}$ + 122.3° (c, 0.65); ν_{max}^{KBr}: 2840, 2820 and 2785 cm^{-1} (C-H stretching in-NMe_2); 1755 cm^{-1} (γ-lactone); mass spectrum m/e ($\%\Sigma_{27}$): 277 (1.50, molecular ion), 58 (46.60, base peak); N.M.R. spectrum ($CDCl_3$) τ: 5.03-5.44

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* Despite the thermal instability of (I), we have been able to demonstrate its partial survival by isolating (I) along with (IV) from our thermolytic experiments (*vide infra*).

** Because of its close structural relationship with the previously reported saussurea lactone (III), we have christened the compound (IV) as dehydrosaussurea lactone. In order to avoid any confusion from the literature, we propose that the term "saussurea" should be strictly reserved for the lactone (III) first reported[4] in 1951. Consequently, this term recently used to describe costus lactones[7] should be corrected.

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(multiplet, 3H, vinylic and C-6 protons), 7.74 (s, 6H, -NMe$_2$) 8.30, 8.58 (singlets with finer splittings, 3H each, methyl on sp^2 carbon)].[*] Heating of costunolide amine (V) in an atmosphere of nitrogen at 205-210° for 5 minutes[**] afforded dehydrosaussurea lactone amine[***] (VI). [m.p. 120-122°, $[\alpha]^{32}_{D}$ + 82.9° (c, 1.21)] whose structure was further attested by its N.M.R. spectrum which displayed diagnostic olefinic proton resonances: a one-proton quartet of lines centered at 4.16 τ representing X part of an ABX system in -CH=CH$_2$ unit,[9] a four-proton multiplet centered at 5.10 τ attributed to olefinic methylene protons. Treatment of the methiodide of (VI) with 5% aq. NaHCO$_3$ solution for 1 hour at room temperature[10] furnished dehydrosaussurea lactone (IV) in almost quantitative yield.[****]

The final proof of the structure of dehydrosaussurea lactone (IV) [m.p. 84-85°, $[\alpha]^{25}_{D}$ + 65.7° (c, 1.12); ν^{KBr}_{max}: 1765, 1635 and 890 cm^{-1} (α,β-unsaturated α-methylene γ-lactone); U.V. spectrum: λ^{EtOH}_{max} 211.5 mμ (ε8630); mass spectrum m/e (%Σ_{27}): 232 (0.10, M$^+$); N.M.R. spectrum (CDCl$_3$) τ:3.89 4.56 (doublets, J=3.0 Hz, 1H each, >C=CH$_2$ next to >C=O), 4.13 (q, 1H, olefinic methine), 5.08 (m, 4H, olefinic methylene), 5.87 (q, 1H, C-6 hydrogen), 8.20 (d, J=1.0 Hz, 3H, vinyl methyl), 8.93 (s, 3H, tertiary methyl)] was provided by its catalytic hydrogenation (PtO$_2$-HOAc) to hexahydrodehydrosaussurea lactone (VII) [m.p. 122-124°, $[\alpha]^{25}_{D}$ + 39.4° (c, 1.02)] identical with an authentic specimen[5] (mixed m.p. and I.R. spectrum). This chemical correlation unambiguously establishes the stereo-structure of dehydrosaussurea lactone implicit in (IV).

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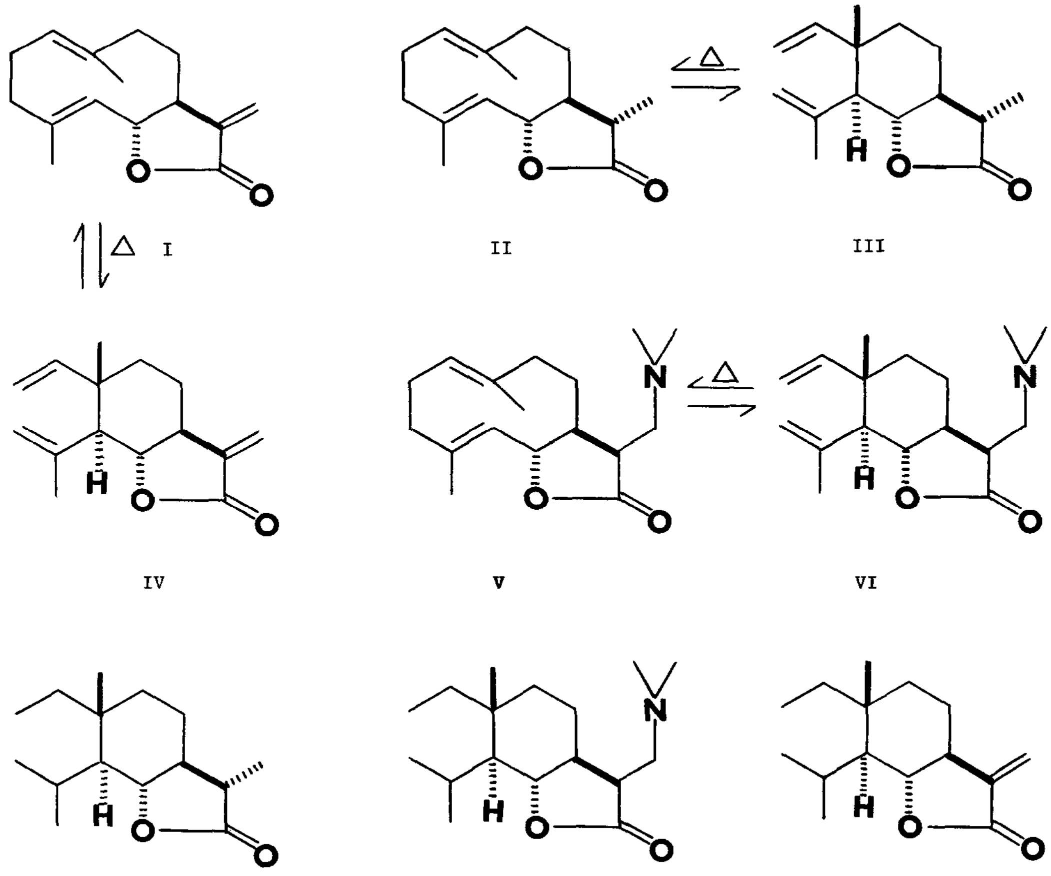
[*] Unless otherwise stated, specific rotations were determined in CHCl$_3$ solution on a Perkin-Elmer model 141 polarimeter. N.M.R. spectra were obtained with a Varian Associates HA-60 spectrometer using tetramethylsilane as internal standard.

[**] It is worthy of note that prolonged thermolysis leads to the elimination of tertiary nitrogen yielding costunolide (I) in 0.7% yield. In fact, one could follow the course of reaction by the disappearance of -NMe$_2$ signal in the N.M.R. spectrum of the crude thermolytic product. A detailed account of this observation will be given in the full paper.

[***] This name is referred to in reference 6 without preparing the parent lactone (IV). Furthermore, neither the physical constants nor the yields for this and related compounds are reported therein.

[****] The facile elimination of quaternary nitrogen in the methiodide of (VI) in basic medium is greatly assisted by the lability of hydrogen α to the lactonic carbonyl. This method is undoubtedly superior to the conventional Hofmann-elimination recently applied by Kelkar *et al.* for the preparation of some conjugated α-methylene γ-lactones.[6] The use of higher temperature in the latter method restricts its practical application towards the synthesis of heat sensitive lactones such as (IV). We have confirmed this premise by preparing (IX) [m.p. 80.0-81.5°, $[\alpha]^{25}_{D}$ + 58.6° (c, 0.95)] from (VIII) [m.p. 62-64°, $[\alpha]^{25}_{D}$ + 65.8° (c, 1.15)] following both procedures.



I II III

IV V VI

VII VIII IX

During the course of this investigation it was observed that heating of an analytical specimen of saussurea lactone (III) at 230 ± 10° for 3 minutes in an atmosphere of nitrogen led to a reproducible mixture* containing saussurea lactone (III) and dihydrocostunolide (II) in the ratio of 2:1. Finally, these products were isolated and their structures were persuasively assigned by examinations of the I.R. and N.M.R. spectra; further

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* The mixture was analyzed by the N.M.R. spectroscopy as well as by the actual isolation of the constituents. This ratio is based on the average of several runs conducted under identical conditions. Although this reaction has been previously carried out on (II) and presumably on (V), no record of its reversibility has ever appeared in the literature[5,6].

corroborated by comparison with authentic specimens[2,5] (mixed m.p., I.R, N.M.R. and mass spectra). Again, heating of pure (VI) and (I) furnished identical results. To the best of our knowledge, this communication constitutes a second report[**] wherein the reversibility of the Cope reaction in a germacranolide has been rigorously established. In the final analysis, these observations offer a note of caution one has to exercise during the isolation of natural products containing germacrane or elemane skeletons.

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[**] For the first report in this context, see reference 11.