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THE THERMOLYSIS OF DIHYDROCOSTUNOLIDE

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Although the Cope rearrangement has been recently observed in several naturally occurring ten-membered carbocyclic compounds (e.g. I → II)$^{(1)}$ or their derivatives with *trans, trans*-cyclodeca-1,5-diene systems$^{(2)}$, none has recorded formation of bicyclic products. Herein, we wish to report for the first time such results obtained during the thermolysis of dihydrocostunolide (I). Heating of dihydrocostunolide (I) in an atmosphere of nitrogen at 230±10° for 6 hours afforded a mixture from which three bicyclic crystalline lactones (III, IV and V) were isolated in variable yields*. The α-isomer (III) [m.p. 139-140°, $[\alpha]^{20}_{D}$ + 85.3°(c,0.73)] and the β-isomer (IV) [m.p. 139-141°, $[\alpha]^{25}_{D}$ + 164°(c,0.70)]† were identified by their rigorous comparison with authentic materials (mixed m.p., I.R., N.M.R. and mass spectra)$^{(3)}$.

The third γ-isomer (V) [m.p. 88-89°, $[\alpha]^{25}_{D}$ + 32.2°(c,1.11); ν^{KBr}_{max} 1777 cm^{-1} (γ-lactone); mass spectrum m/e(%Σ_{18}): 234 (3.06, M$^+$), 219 (13.01, M-CH$_3$, base peak)] analyzed for $C_{15}H_{22}O_2$, further confirmed by high resolution mass measurements (Found: 234.1622. Calcd.: 234.1620). Evidence for structure (V) was garnered from its n.m.r. spectrum ($CDCl_3$) which displayed a broad one-proton signal centered at 5.43τ due to the hydrogen at C-6. This downfield shift‡ is compatible with the location of double bond between C-4 and C-5, a fact further corroborated by the complete absence of any vinyl

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* The overall yields of the three crystalline isomers actually isolated from several experiments fluctuated from 12-21% (III), 7-13% (IV) and 1-10% (V). Furthermore, the ratio of these isomers also varied considerably.

† 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 Me_4Si as internal standard.

‡ The corresponding C-6 proton in (III) and (IV) appeared as a triplet centered at 6.11τ and 6.01τ respectively.

signal in the olefinic proton region. Furthermore, the tetrasubstituted double bond in (V) caused a pronounced downfield shift of the angular methyl resonance appearing as a singlet at 8.88τ in contrast with the corresponding signal at 9.10τ and 9.05τ in (III) and (IV) respectively[*]. Finally, a singlet (with a fine shoulder) at 8.15τ due to C-4 Me and a doublet at 8.78τ (J=6.5Hz) due to C-11 Me are consistent with the structure (V), further proven by its synthesis from α-santonin (VI), a compound of established absolute configuration(4).

Catalytic hydrogenation of α-santonin (VI) by Barton's method(5) followed by chromatographic purification furnished dihydrosantonin (VII) [m.p. 100-101°, $[\alpha]^{24}_{D}$ + 84.2° (c,0.64); overall yield: 60%]. Treatment of (VII) with ethanedithiol in glacial acetic acid - BF_3-etherate afforded the thioketal (VIII) [m.p. 167.5-169.0°, $[\alpha]^{20}_{D}$ + 43.6°(c,1.03); ν^{KBr}_{max} 1780 cm^{-1} (lactonic carbonyl); N.M.R. spectrum ($CDCl_3$)τ:8.81 (s, 3H, C-10 Me), 8.75 (d, 3H, C-11 Me partly overlapped with C-10 Me signal), 7.89 (d, 3H, J=1.5Hz, C-4 Me), 6.67 (m, 4H, $-S-CH_2-CH_2-S-$), 5.42 (broad multiplet, 1H, C-6H); mass spectrum $m/_e(\%\Sigma_{18})$: 324 (3.27, M^+), 264 (3.67, base peak)] which upon desulfurization with Raney nickel in ethanol gave 6,11βH-eudesm-4-en-6,13-olide (V) [m.p. 88-89°, $[\alpha]^{24}_{D}$ + 32.7°(c,0.91)] found identical with the γ-isomer (V) obtained from dihydrocostunolide (I) by mixed melting point determination, g.l.c. behaviour as well as by the comparison of their I.R., N.M.R. and mass spectra.[†]

This correlation confirms the structural assignment and establishes the absolute stereochemistry designated in (V). It is noteworthy that acid-catalyzed cyclization of dihydrocostunolide (I) proceeding through a stepwise process(6) involving tertiary carbocationic intermediate (IX) could conceivably lead to three isomers (III, IV and V). However, during our intensive studies[‡] of acid-catalyzed cyclization of (I), we have not been able to detect the γ-isomer (V). Consequently, the thermocyclization of (I) yielding the long sought γ-santenolide (V) is of special significance.

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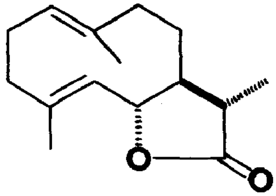
[*] In fact, one could monitor the course of thermolysis by examining these signals in the n.m.r. spectrum of the crude thermolytic product.

[†] Comparative spectra will be presented in the Ph.D. thesis of Mr. J. E. McCloskey.

[‡] Unpublished results secured by Mr. J. E. McCloskey.



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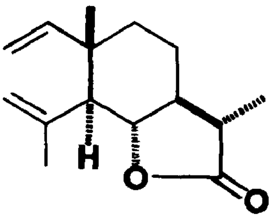

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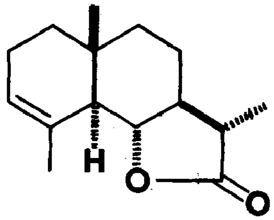

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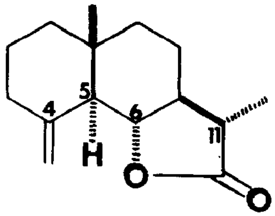

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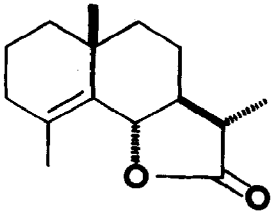
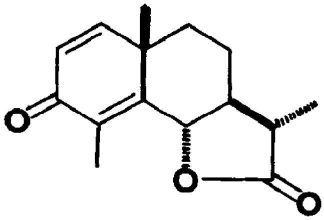


V



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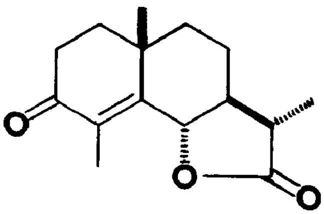

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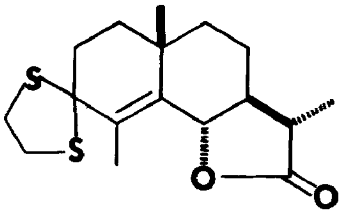

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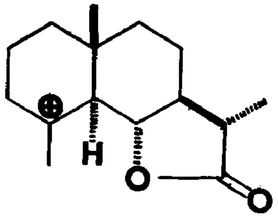

IX

Further work is in progress to investigate the mechanistic aspects of this thermocyclization.

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