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REVISION OF THE STRUCTURE OF CNICIN

Z. Samek, M. Holub, V. Herout and F. Šorm

Institute of Organic Chemistry and Biochemistry,
Czechoslovak Academy of Sciences, Prague, Czechoslovakia

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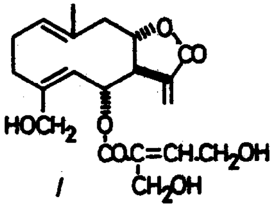
During a systematic comparative study of the PMR spectra of native germacranolides in connection with the solution of other problems inherent in this group of substances we also carried out a detailed analysis of the PMR spectrum of cnicin [for the gift of the samples we thank Prof. T. J. Mabry and Dr. M. Yoshioka of the University of Texas at Austin, U.S.A., and Prof. B. Drożdż of the Academia Medyczna in Poznań, Poland; the melting points and the IR spectra of these samples corresponded to the data from the literature (1,2)]. However, the PMR spectrum of this substance was in disagreement with the proposed formula I (3) which was deduced from experiments and conclusions published in previous papers (1,2,4).

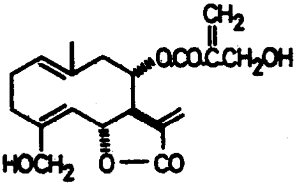
The 100 MHz PMR-spectrum of cnicin (Varian HA-100), measured in d_6-DMSO solution with the addition of $CDCl_3$ [internal standard hexamethyl disiloxane (HMDS), chemical shifts are given as δ(TMS)-values using $\delta_{(HMDS)} = 0.06$ ppm] is shown in Fig. 1a and a part of this spectrum after addition of deuteroacetic acid is shown in Fig. 1b. From the exchange and double resonance experiments ("frequency-swept") the following assignment of the spectrum (first-order analysis) results: In the "low-field part" of the spectrum the characteristic signals of four protons of the $CH_2{=}C(R){-}CO{-}$ type are present. Two of them, H_a (6.22 ppm) and H_b (5.98 ppm) have $^2J_{a,b} = 1.4$ Hz and different allylic couplings with the proton H_c forming after the exchange (Fig. 1b) a quartet at 4.36 ppm ($^4J_{a,c} \neq 0 \ll 1$, $^4J_{b,c} = 1.2$ Hz) due to two vicinal couplings with two protons H_d and $H_{d'}$ ($|J_{c,d} + J_{c,d'}| \cong 10.5$ Hz, splittings 4 and 6.5 Hz) the signals of which are localised in the 3.03 - 3.63 ppm region where they form, after exchange, a typical AB-part of an ABX-system with $^2J_{d,d'} = 11$ Hz and $|J_{c,d} + J_{c,d'}| \cong 10.5$ Hz (H_d: 3.51 ppm; $H_{d'}$: ~3.27 ppm). Before the exchange (Fig. 1a) the protons H_c, H_d and $H_{d'}$ exhibit couplings with OH-protons [signals $\underline{H}O-\overset{|}{\underset{|}{C}}H_c$ localised in the 4.76-5.17 ppm region and $\underline{H}O-\underset{|}{C}(H_dH_{d'})$ forms a broad triplet at 4.63 ppm].

The other two protons of the $CH_2=C(R)-CO-$ type, forming two broadened doublets at 6.09 and 5.73 ppm, belong to protons $H_{(13)}$ and $H_{(13')}$ from the γ-lactone ring ($^2J_{13,13'} \neq 0 \ll 1$) in agreement with the presence of the usual allylic couplings with the proton $H_{(7)}$ the multiplet of which is localised at 3.27 ppm (overlapped by the multiplet of proton $H_{d'}$; $^4J_{13,7} = 3.30$ and $^4J_{13',7} = 3.0$ Hz). The localisation of the signals of the proton $H_{(7)}$ makes it possible to assign other characteristic protons common in lactones of germacranolide type as follows: $\underline{H}_{(8)}$ ~5.05 ppm (the multiplet coincides with the multiplet of $H_{(1)}$); $\underline{H}_{(6)}$: 5.23 ppm ($J_{6,7} \cong 8.0$ and $J_{6,5} \cong 10.0$ Hz); $\underline{H}_{(5)}$: 4.85 ppm (a broad doublet, $J_{5,6} \cong 10.0$ Hz, $^4J_{5,15}$ and $^4J_{5,15'} \neq 0 \ll 1$); $\underline{H}_{(15)}$ and $\underline{H}_{(15')}$ form the AB part of the ABX system in the 3.73 - 4.23 ppm region (different couplings with OH proton; splittings 4.0 and 5.0 Hz; OH proton in the region 4.76 - 5.17 ppm) and after exchange the AB-quartet with centers at 4.09 and 3.86 ppm ($^2J_{15,15'} = 14$ Hz, $^4J_{15,5}$ and $^4J_{15',5} \neq 0 \ll 1$); $\underline{H}_{(1)}$: ~5.05 ppm (the multiplet coincides with the multiplet of $H_{(8)}$; $^4J_{1,14} \neq 0$); $\underline{H}_{(14)}$: 1.46 ppm ($^4J_{14,1} \neq 0$).

From the assignment of the PMR-spectrum the subsequent structural features follow: 1/ The continuity of the couplings of protons H_a, H_b, H_c, H_d and $H_{d'}$ clearly indicates the presence of a fragment $CH_2=C(-CO-)-CH(OH)-CH_2OH$ in the molecule of cnicin, and hence also the presence of 3,4-dihydroxy-1-butene-2-carboxylic acid as the ester component. 2/ The magnitude of vicinal couplings (first-order values) and the distribution of chemical shifts of protons of the ten-membered ring and of its usual substituents corresponds very well with the topology of the bonds, which, for example, exists in the molecule of onopordopicrin (II) the PMR-spectrum (5) of which is also very similar to the spectrum of cnicin, with the exception of signals of protons of the steric side chain. Therefore it can be assumed that the orientation of the γ-lactone ring of cnicin is the same as in onopordopicrin. On the basis of the PMR-spectrum of cnicin the formula III may be now proposed. This differs from the original1y deduced formula I in the orientation of the γ-lactone ring and in the nature of the esterifying acid. These conclusions as well as certain results described in previous papers (1,4) are now checked by chemical means. The detailed discussion of the cnicin problem will be the subject of a subsequent paper.



I



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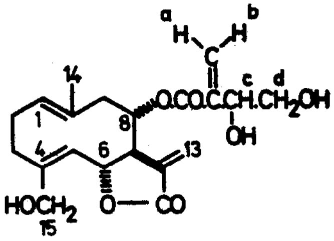

III

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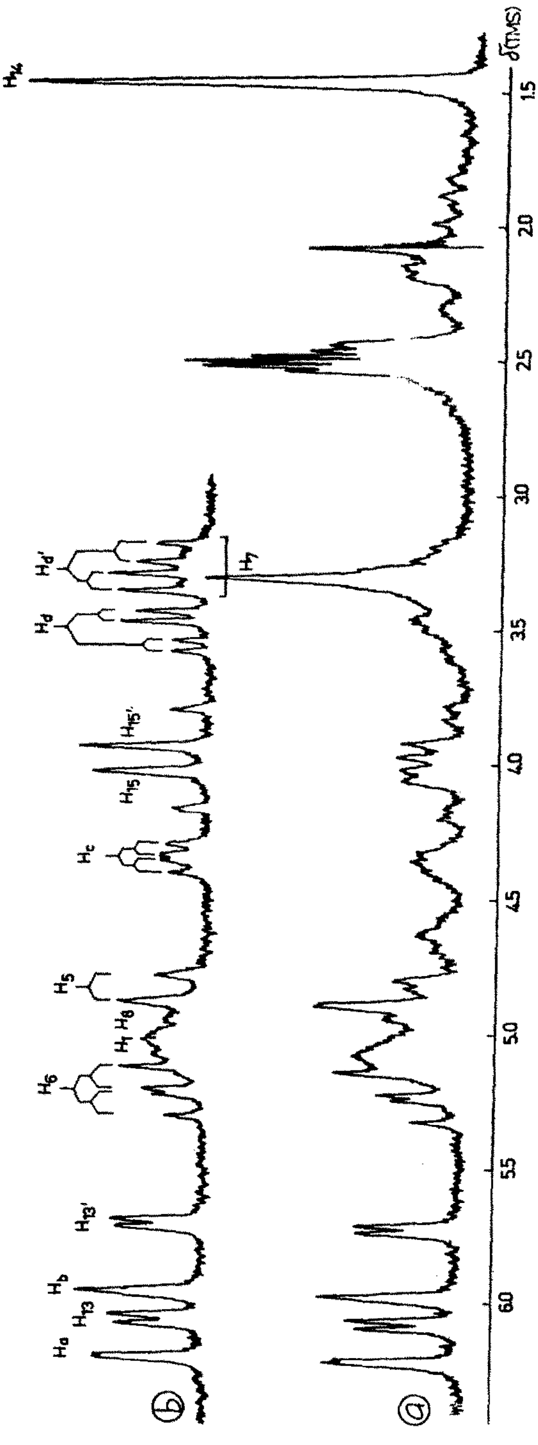

Fig. 1: 100-MHz-Spectrum of Cnicin