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CONTRIBUTION ON THE STRUCTURE OF CNICIN, THE BITTER PRINCIPLE FROM CNICUS BENEDICTUS L.

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IN a preliminary note,[1] we assigned to cnicin, the bitter principle from Cnicus benedictus L., the molecular formula $C_{20}H_{26}O_7$ and a partial structure I, according to which, cnicine was a dihydroxyguaidienolide esterified with a dihydroxypentenoic acid, not characterized in detail. In view of our recent results, however, cnicin is a monocyclic trihydroxyester-lactone of molecular formula $C_{20}H_{28}O_7$* and structure II or III; it belongs thus to the group of sesquiterpenic lactones with a ten-membered ring in the molecule. Cnicin is esterified by α,β-bis-(hydroxymethyl)acrylic acid.

The volatile C_5-acid, reported in our preceding paper,[1] obtained from cnicin after hydrogenolysis and subsequent saponification, afforded the p-bromophenacyl ester of m.p. 53°, underpressed on admixture of the corres-

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* **Elemental analyses of this substance which, because of its unstability, can be hardly prepared in a pure state, did not enable us to decide unambiguously between formulae $C_{20}H_{26}O_7$ and $C_{20}H_{28}O_7$. The first alternative, i.e. the formula with the lower hydrogen content might be explained only by the fact that instead of a dihydroxy-acid a hydroxy-aldehydo-acid, present in a cyclo-hemiacetal form, is bond to cnicin.**

[1] M. Suchý, V. Herout and F. Sorm, Chem. & Ind. 517 (1959).

ponding derivative of authentic methylethylacetic acid. On hydrogenation, cnicin afforded a product of the molecular formula $C_{20}H_{32-34}O_7$ and m.p. 146° which on subsequent hydrolysis yielded another product of reduction of the acid present in cnicin, which was characterized as a hydroxy-lactone IV of molecular formula $C_5H_8O_3$. Now, we have obtained its crystalline 3,5-dinitrobenzoate of m.p. 122° (Found: C, 46.82; H, 3.24; N, 9.11% : Calc. for $C_{12}H_{10}O_8N_2$: C, 46.46; H, 3.25; N, 9.03%). The above melting point agrees with that of the corresponding derivative of the known α-hydroxymethyl-γ-butyrolactone (IV).[2] The location of the ethylenic linkage of the original acid III, present in cnicin in the form of an ester, followed from its allylic position to both hydroxyl groups and further from its α,β-position to the esterified carboxyl group.

The proof of the carbon skeleton of cnicin has been established by a series of further experiments. On hydrogenation with PtO_2 in methanol, cnicin afforded a mixture which was saponified and the resulting neutral product separated by chromatography on alumina. The last eluates afforded two crystalline compounds of m.p. 118°, $[\alpha]_D^{20}$ + 4.4° (chloroform, c = 1.94) (V) and m.p. 112°, $[\alpha]_D^{20}$ - 28.7° (ethanol, c = 2.08) (VI). (Found for V: C, 66.66; H, 9.66% ; for VI: C, 66.51; H, 9.61% : Calc. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69%). The infra-red spectra of compounds V and VI differ in details only and exhibit the same absorption bands due to a carbonyl group in γ-lactone (1764 cm^{-1}) and to a hydroxyl group (3380-3470 cm^{-1} and 3625-3630 cm^{-1}) (measured in chloroform solution). Both compounds are

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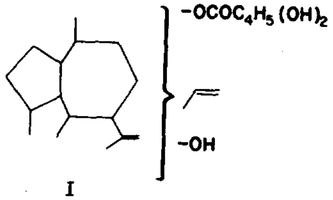
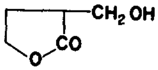
[2] W. J. McGraw, U.S. 2,624.723 Jan. 6, 1953.

thence monocyclic dihydroxy-lactones.

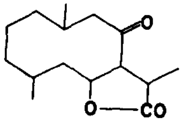
On treatment with chromic acid in acetic acid, compounds V and VI afforded two different lactone-keto acids; m.p. 220°, $[\alpha]_D^{20}$ - 19.4° (ethanol, c = 1.74) (VII) and m.p. 188° $[\alpha]_D^{20}$ ± 0° (ethanol, c = 0.7) (VIII). (Found for VII: C, 63.94; H, 8.00% ; for VIII: C, 63.49; H, 7.90% : Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85%). Infra-red spectra of the acids VII and VIII exhibited absorption bands due to a carbonyl group in a γ-lactone (1781 or 1788 cm^{-1} resp.) and to a carboxyl group (1731 of 1736 cm^{-1} resp.).



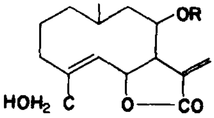
I



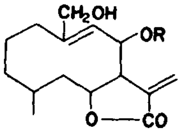
IV



IX



II



III

II, III: R = $-OCOC(CH_2OH){=}CHCH_2OH$

The formation of a carboxyl group in the course of oxidation of dihydroxy lactones V and VI constitutes the proof that one of the hydroxyl groups of the sesquiterpenic lactone moiety of cnicin is primary in character. This explains the lower values for the C-methyl group (0.86) obtained by the Kuhn and Roth method. From the presence of an absorption band at 1700 cm^{-1}, due to a keto group, in the infra-red spectrum of VII and VIII it follows that the second hydroxyl group present in diol-lactones V and VI is secondary in character and is located on a medium-sized ring.

The non-crystalline chromatographic fraction which preceded fractions containing compounds V was oxidized with chromic acid in acetic acid. The reaction mixture obtained afforded, besides some lactone-keto acid VII, a neutral material of m.p. 135°. The latter, according to the mixed melting point and infra-red spectrum, was found to be identical with the keto-lactone, prepared from arctiopicrin. The constitution of the keto-lactone, expressed by formula IX, was elucidated[3,4] in this Laboratory.

All these findings constitute the proof that cnicin is a new lactone belonging to the sesquiterpenic germacrane type with a ten-membered ring in its molecule. The keto-lactone IX was obviously formed on oxidation of hitherto non-isolated hydroxy-lactone X which resulted after hydrogenolysis of the primary hydroxyl group present in original cnicin. This also proves one of the double bonds of cnicin to be in allylic position to the primary hydroxyl group.

The mixture obtained on hydrogenation of cnicin afforded on subsequent oxidation acidic material only, the infra-red spectrum of which did not exhibit

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[3] M. Suchý, V. Herout and F. Šorm, Croatica Chem. Acta **29**, 247 (1957).

[4] M. Suchý, V. Herout and F. Šorm, Chem. Listy **52**, 2110 (1958); Coll. Czech. Chem. Comm. **24**, 1542 (1959).

frequencies characteristic for a keto group. The above acidic material was saponified and the obtained product oxidized by means of chromic acid to yield lactone-keto acid VI. From the above finding it follows that the secondary hydroxyl group on C_8 in cnicin is esterified by the moiety of acid III.

Cnicin, on oxidative degradation by nitric acid catalysed with vanadium pentoxide afforded acidic material from which, by means of modified preparative paper chromatography[5,6] four dicarboxylic acids were isolated in a pure state: succinic acid (m.p. 183°), methylsuccinic acid (m.p. 112°), α-methylglutaric acid (m.p. 79°) and α-methyladipic acid. The latter was characterized as its S-benzylthiuronium salt, m.p. 169°, undepressed on admixture of an authentic sample, and further by means of the infra-red spectrum of its dimethyl ester. In view of paper chromatography, the mixture of acids contained a dicarboxylic C_8 acid which has not yet been identified.

All these findings indicate that cnicin possesses one of the two alternative formulae II and III. Work on the structure and determination of the absolute configuration of cnicin is in progress. The results will be published in full detail in Collection of Czechoslovak Chemical Communications.

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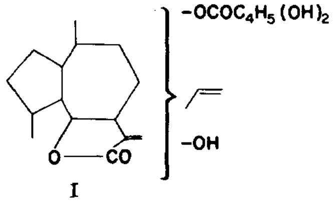
[5] V. Šanda, Ž. Procházka and H. LeMoal, Chem. Listy **52**, 1546 (1958); Coll. Czech. Chem. Comm. **24**, 420 (1959).

[6] V. Sýkora, V. Herout and F. Šorm, Chem. Listy **52**, 1314 (1958); Coll. Czech. Chem. Comm. **23**, 2181 (1958).

ERRATUM

M. Suchý, V. Benešová, V. Herout and F. Šorm: Contribution on the structure of cnicin, the bitter principle from *Cnicus Benedictus L.*, *Tetrahedron Letters* No. 10, pp. 5-9 (1959).

Due to an oversight, the lactone group in formula I on p. 7 of the above article was omitted. The correct formula I is reproduced below.



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