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THE CONSTITUTION OF ARCTIOPICRIN*

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On the basis of previous investigations[1-3], the structure (1) was proposed for arctiopicrin. Because this formulation had biogenetically surprising features - for instance, the location of the isolated ethylenic linkage - and because certain chemical aspects were unsatisfactory the substance has been subjected to a reinvestigation.

Amongst chemically disquieting features implicit in the structure were the following. First, the acid-catalysed and reductive cyclisation to compounds of the eudalene series required a rather complex migration involving deconjugation of an initially-formed allylic cation. Secondly, the evidence for the position or nature of the hydroxyl group was consistent with an alternative formulation. In addition, studies in the germacrolide series also raised doubts[4] concerning the correctness of 1. We now present

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evidence leading to the formulation (2) for arctiopicrin.

The n.m.r. spectrum of arctiopicrin (60 Mc/s in $CDCl_3$; Varian DP-60) clearly required a different proton distribution from that in 1. The spectrum after exchange with D_2O is represented in Fig. 1, the region 150-260 c.p.s. (from TMS) before deuteration is reproduced in the inset. In addition to showing the position of the hydroxyl protons in the normal spectrum, deuterium exchange served to sharpen two other multiplets each due to two protons. These may be assigned, therefore, to two different $-CH_2-OH$ groupings only one of which, that of the β-hydroxybutyryl side chain, is further coupled to other nuclei. Confirmatory evidence for this assignment is given by the proton spectrum of hexahydroarctiopicrin* diacetate, which shows two multiplets each due to two protons, centred at 272 and 297 c.p.s. respectively. This shift to low field upon acetylation is characteristic of the change $-CH_2OH \rightarrow -CH_2OAc$. (The low field shift for the C_4 hydroxymethyl protons will be the lesser since the effect of the C_4-C_5 double bond is also removed by the hydrogenation.) From Fig. 1, it can be seen that the lower field $-CH_2O-$ multiplet (G) is a typical AB pattern with J_{AB} = 12.5 c.p.s. and may be assigned to the C_4 substituent. The remaining $-CH_2O-$ multiplet must arise from the $-CH_2O-$ protons of the β-hydroxybutyryl group. To obtain further proof for the latter assignment, spin decoupling experiments were carried out using a NMR Specialties Inc., Model PD-60 Unit. The sharp doublet (L) at δ 1.18 p.p.m. is expected to arise from the methyl protons of the β-hydroxybutyryl grouping due to spin coupling with the methine proton which will also couple with the $-CH_2O-$ protons. Spin decoupling confirmed that this is indeed the case, since double irradiation at 88 c.p.s. towards low field from the doublet results in its collapse to a single band, while irradiation at 67 c.p.s. towards high field from the

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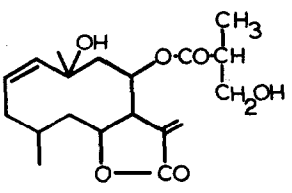
* Previously termed tetrahydroarctiopicrin.



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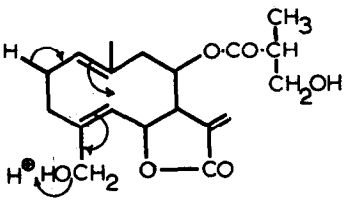

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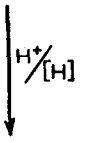

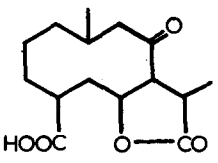

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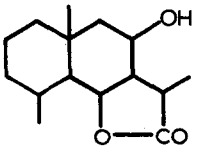


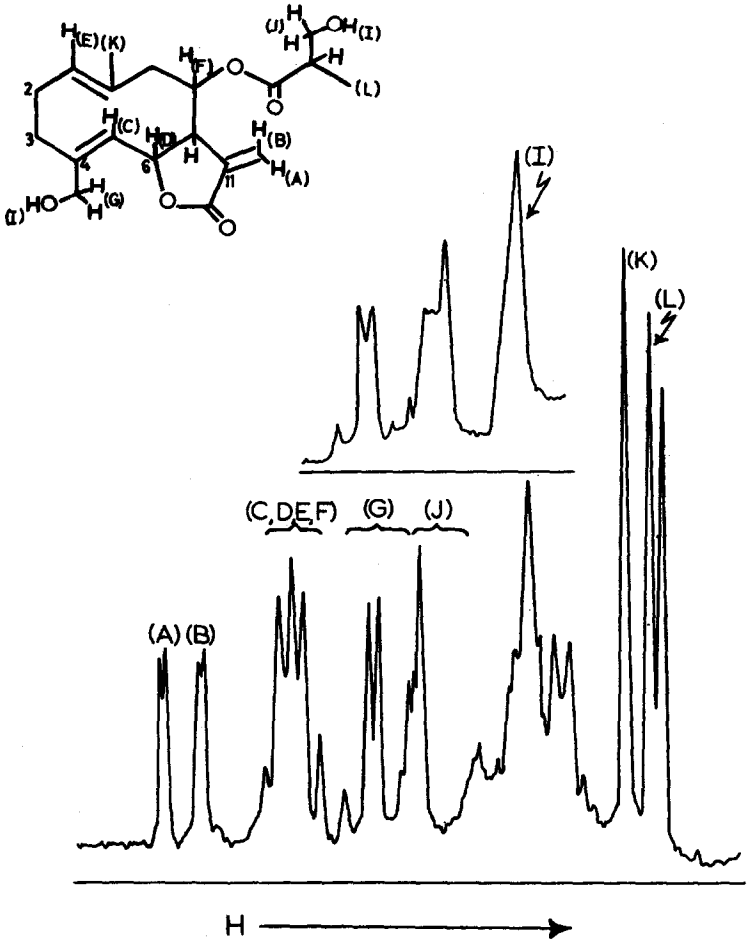
3

$-CH_2O-$ pattern tends to narrow and sharpen this multiplet. Thus, both groups of protons are coupled to the same proton. These experiments confirm the nature of the β-hydroxybutyryl grouping.

These conclusions, derived from the n.m.r. spectra of arctiopicrin and its derivatives, have been confirmed chemically. The oxidation of hexahydroarctiolide, m.p. 145°, denoted as tetrahydroarctiolide in our preceding paper[1], has been repeated under different conditions (excess chromic acid in acetone solution) to give a lactonic-keto acid, $C_{15}H_{22}O_5$ (4) as the main acidic product. This compound, m.p. 174°, absorbed at 1170, 1710, 1765 and 2400 - 3400 cm^{-1} in the infrared (methyl ester: ν_{max} 1170, 1438, 1711, 1731,

FIG 1

N.m.r. Spectrum of Arctiopicrin



1778 cm^{-1}). We obtained again the previously reported[1] neutral hydroxy keto-lactone, the primary hydroxyl group of which remained untouched under the conditions of the oxidation. This fact previously[1-4] led us to conclude, erroneously, that the hydroxyl group was tertiary in character.

Aside from providing unequivocal evidence that the arctiolide nucleus contains a primary hydroxyl group attached to quaternary carbon (thus excluding structure 1) the following features are apparent from the n.m.r. spectrum: (a) the singlet signal (K) at 1.48 p.p.m. must arise from a methyl group on a quaternary carbon bearing oxygen, or be attached to a double bond. Under the present requirements the latter must obtain; (b) the pair of doublets (A and B) (5.89 and 6.29 p.p.m.) at low field with small coupling constants $J \simeq 2$ c.p.s. established the presence of an exo-methylene grouping. These chemical shifts are typical of protons β to carbonyl; (c) a group of peaks (C-F) appear at relatively low field in the region 280-315 c.p.s. and are due to four protons. No specific assignments are possible, but the presence of such protons requires a third ethylenic linkage in arctiopicrin, and the absence of any saturated methylene protons. Chemical evidence for the presence of an additional ethylenic linkage has now been obtained by titration with monoperphthalic acid.

With this evidence a number of formulations for arctiopicrin are possible. However, bearing in mind the cyclisation-reduction to 3, only 2 remains. Its authenticity is conclusively established by the ozonolysis of arctiopicrin to give, after decomposition with hydrogen peroxide, succinic acid with no trace of lævulic acid.

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