

## Nuclear Magnetic Resonance Investigations of Xanthoperol

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It has by nuclear magnetic resonance investigations been found that xanthoperol has the structure of 9,10-diketoferruginol, but with the configuration at C-11 probably inverted.

The structure I, without configurational implications, has been previously proposed for xanthoperol<sup>1</sup>. The evidence for this structure were indirect and it was therefore necessary to study it further, especially as the biogenetic relationship between the proposed structure and the structures of the other diterpene compounds in *Juniperus communis* L.<sup>2,3</sup> was obscure.

The nuclear magnetic resonance spectrum of xanthoperol in CDCl<sub>3</sub> at 60 Mc has been taken and is presented in Fig. 1. The reference is pure benzene in an external space. The peak at -51 cps arises from residual CHCl<sub>3</sub> in the solvent while the small peak immediately adjacent to the CHCl<sub>3</sub> peak is almost certainly due to residual benzene which has been used in the crystallisation of the compound. The assignments of the two benzene ring protons, H-8 at -95 cps and H-5 at -30 cps, are based on comparison of this spectrum with the spectra of a number of alkaloids<sup>4</sup> in which it has been found that a keto group conjugated with the ring shifts the resonance of the adjacent benzene ring proton down to the vicinity of -100 cps relative to the zero of reference. The resonance from the phenolic hydrogen, -11 cps, has been identified by its temperature dependence. The signal-to-noise ratio obtainable in this solution makes it rather difficult to see the seven lines from the C-H proton in the isopropyl group, but there is little doubt that they lie at about +200 cps, since a reproducible series of peaks with about the right spacing has been observed in this vicinity in several spectra. The spacing of the two peaks

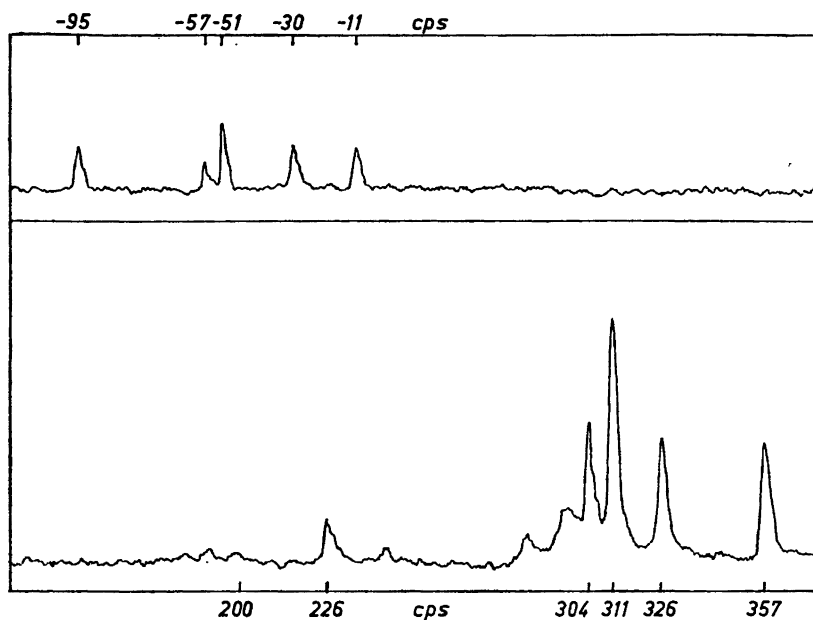


Fig. 1. Nmr-spectrum of xanthoperol in  $\text{CDCl}_3$ , external reference benzene. 60 Mc.

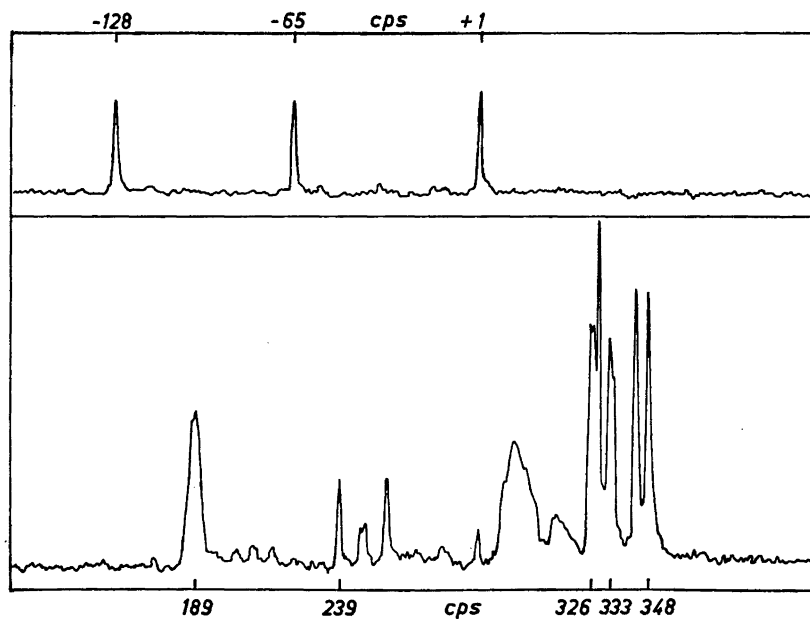
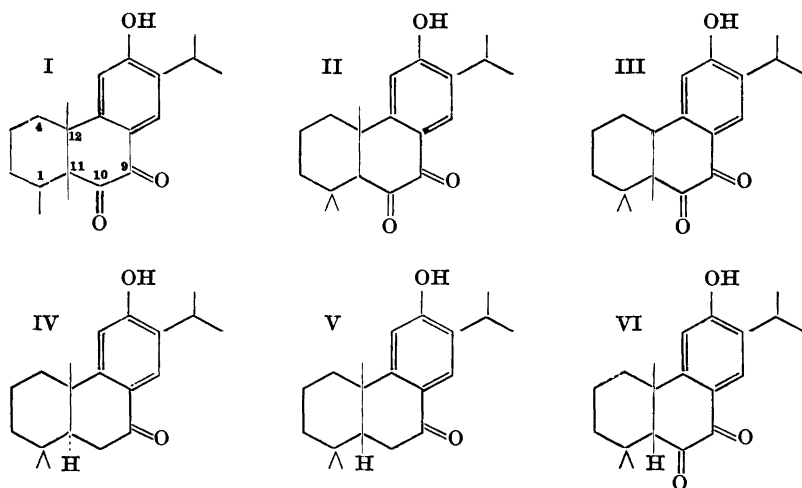


Fig. 2. Nmr-spectrum of 9-ketoferruginol in deuterated tetrahydrofuran, external reference benzene. 60 Mc.

at 304 cps and 311 cps, 7 cps apart, is on the other hand completely characteristic of the spin coupling for the *isopropyl* group methyl doublet. The fact that the line at 311 cps is twice as large as the one at 304 cps can only be explained on the basis of an accidental overlap by one other methyl group in the molecule. In addition, there are two methyl group lines at 326 and 357 cps, both of which are equally as sharp as the line at 311 cps. This fact shows that none of the methyl groups in the A-ring is attached to a carbon atom which also possesses a hydrogen, in which case the methyl group resonance would be split into a doublet. Therefore, structure I is not acceptable. These leaves two structures, II and III, with a geminal dimethyl group. The line at 357 cps is assigned to the angular methyl since angular methyl groups in steroids generally fall at higher positions than side chain methyls<sup>5</sup>. The lines at 311 and 326 cps therefore correspond to the *gem.*-dimethyl group.

The assignments given above have been confirmed from the spectrum of 9-ketoferruginol in fully deuterated tetrahydrofuran (Fig. 2). The spectrum shows clearly three sharp methyl group peaks and two slightly broader peaks



belonging to the doublet from the *isopropyl* methyl groups, all lying between 326 and 348 cps from external benzene. These numbers must all be diminished by about 25 cps to correct for the difference in the diamagnetic bulk susceptibilities of deuterated tetrahydrofuran and chloroform. One can then compare the numbers with those obtained for xanthoperol and it is found that the two peaks previously assigned to the *isopropyl* methyls in xanthoperol correspond within a few cycles to those which are assigned to the same groups in 9-ketoferruginol. The two benzene ring protons give resonances at  $-65$  and  $+1$  cps and when we correct for the bulk susceptibility effect, we find that these two peaks correspond fairly well, both in position and spacing, to the two peaks in xanthoperol which were assigned to the benzene ring protons. The phenolic proton must give a resonance at  $-128$  cps which indicates an enormous shift to low field compared with the position found in xanthoperol.

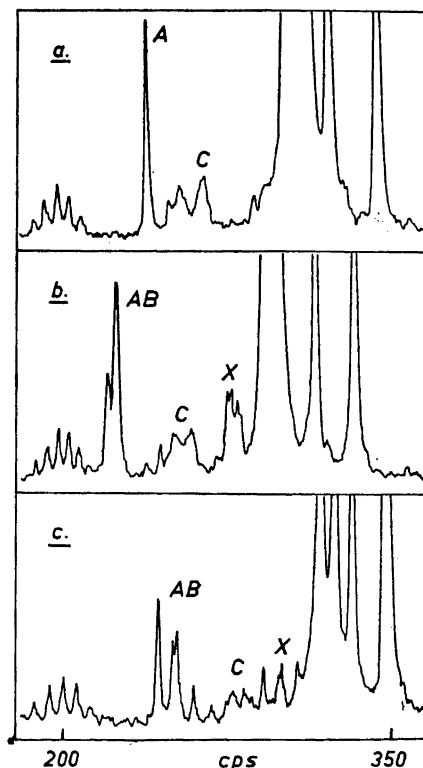


Fig. 3. The high-field end of the nmr-spectra of *a.* xanthoperol, *b.* its monoketonic reduction product, and *c.* 9-ketoferruginol. All spectra are taken in pyridine at 60 Mc with external benzene as reference.

This is probably due to formation of a strong hydrogen bond between this proton and the solvent since a shift towards lower field would be expected in that case.

The decision between structures II and III for xanthoperol must be based on a study of the peak at 226 cps (Fig. 1) which is assigned to the angular hydrogen. The position of this peak could be accounted for in a satisfactory way by either of these structures. However, only structure II places this hydrogen far enough from other hydrogen nuclei so that no spin coupling would be expected, and therefore only structure II accounts for the sharpness of this line. It is very unlikely that if the angular hydrogen were located at C-12 it would not couple its spin fairly strongly to one or the other of the two protons on C-4. For a closer study of this coupling the high-field end of the spectra of xanthoperol, its monoketonic reduction product<sup>1</sup> and 9-ketoferruginol have been taken in pyridine solution (Fig. 3). Unfortunately, the three spectra were not run at exactly the same scale factor and no internal reference compound was added with the result that the spectra cannot be perfectly lined up and compared directly.

The central five lines of the seven-line multiplet due to the C—H proton in the *isopropyl* side chain are now clearly seen at 200 cps. Xanthoperol

has a single sharp line labelled A which is assigned to the proton on C-11, the methyl group on C-12 accounting for its lack of spin coupling. The resonance from this proton moves toward higher fields when the adjacent keto group is reduced and becomes the pattern of four lines marked X in the mono-keto product. The four lines almost certainly arise from spin coupling to the two protons on C-10 to give an ABX pattern<sup>6</sup> similar to the one for 9-ketoferruginol. The AB pattern in the mono-keto reduction product is not so well defined as in 9-ketoferruginol, however, because the couplings are smaller, as can be seen in the X pattern. The shape of the AB pattern in the monoketo reduction product is predicted with  $J_{AB} = 16$  cps,  $J_{AX} = 5$  cps,  $J_{BX} = 2.5$  cps, and  $\delta_{AB} = 14$  cps at 60 Mc. The AB pattern in 9-ketoferruginol is satisfactorily described by  $J_{AB} = 16$  cps,  $J_{AX} = 7.2$  cps,  $J_{BX} = 8.5$  cps, and  $\delta_{AB} = 7$  cps at 60 Mc. The nmr spectra are, therefore, most compatible with structure II for xanthoperol, since III would not be expected to yield an ABX pattern in its mono-keto reduction product. The structure for the mono-ketonic reduction product accordingly has to be changed and since it differs, for reasons discussed more closely elsewhere<sup>7</sup>, from 9-ketoferruginol (IV) only in its configuration at C-11 it must be assigned the configuration in structure V. The change from *trans* to *cis* ring fusion has therefore changed one of the spin couplings quite a lot, but left the other relatively unchanged. The configuration of xanthoperol cannot be conclusively determined from its nmr spectra but a closer examination of the region C (Fig. 3) which is tentatively assigned to the C-4 protons, and the spacing of the methyl groups seems to indicate a much closer relationship between xanthoperol and the *cis*-form characteristic of the mono-keto reduction product rather than the *trans*-form characterized by 9-ketoferruginol. This result points to the *cis*-form for xanthoperol as given by the configuration in VI.

#### EXPERIMENTAL

The nmr spectra were taken at Varian Associates, Palo Alto, California, with a 60 Mc High Resolution NMR Spectrometer in a field of 14 100 gauss.

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