Isolation of Centaurepensin, a Guaianolide Sesquiterpene Lactone Ester Containing Two Chlorine Atoms; Determination of Structure and Absolute Configuration by X-Ray Crystallography

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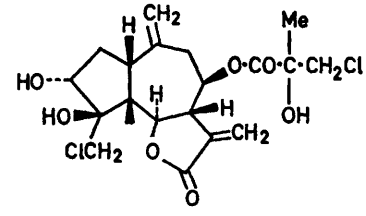
Summary Centaurepensin, an unusual guaianolide sesquiterpene lactone ester containing two chlorine atoms was isolated from *Centaurea repens* and its structure and absolute configuration were determined by *X*-ray diffraction methods.

CENTAUREPENSIN was isolated from a methanol extract of the whole plant‡ *Centaurea repens L.* ("Russian Knapweed"). After removal of the methanol the residue was partitioned between aqueous ethanol and chloroform§ and the material in the chloroform layer was chromatographed on silica gel. Elution with benzene–ethyl acetate mixtures yielded crystalline centaurepensin, m.p. 214—215°, $[\alpha]_D^{24}$ +107·2° (*c* 1·064, tetrahydrofuran). Elemental analysis and mass spectrometry indicated the molecular formula $C_{19}H_{24}Cl_2O_7$.

In view of the obvious complexity of the material and the small amount available it was decided to derive the structure by *X*-ray diffraction methods.

Suitable crystals were obtained from ethanol. They were monoclinic, space-group $P2_1$ with $a = 10{\cdot}478$, $b = 9{\cdot}254$, $c = 11{\cdot}507$ Å, $\beta = 113{\cdot}15°$, $D_m = 1{\cdot}41$ g cm^{-3}, $D_c = 1{\cdot}41$ g cm^{-3}, $Z = 2$. The intensities of 1624 reflexions were measured with Cu-K_α radiation on an automatic Picker diffractometer. 1548 of the measurements were significantly above background values.

A sharpened Patterson map was computed but the positions of the two chlorine atoms could not be located. The structure was then solved by direct phasing methods using the multiple solution approach.[1] Three reflexions were chosen to define the origin and three other reflexions were assigned as symbols. All atoms in the molecular



(I)

formula were located from three successive Karle maps and a chemically reasonable structure (I) was obtained. The

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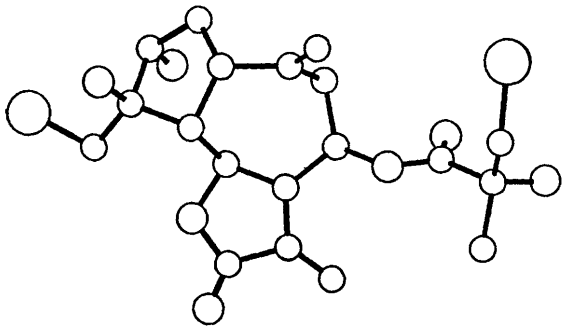
‡ Collected in Canada and kindly supplied by Messrs. Fisons, Agrochemical Division

§ A control extraction not employing halogenated solvents was also performed to ensure that centaurepensin is not an artefact.

initial interpretation of the maps presented some problems because of the lack of connectivity between a peak at a chlorine position and any recognisable structural fragments.



FIGURE

The structure was refined by full-matrix least-squares calculations with anisotropic temperature factors assigned to each atom. All hydrogen atoms were located from a difference map and included as fixed atoms in further refinement calculations, which converged at $R = 5{\cdot}0\%$. The conformation of the molecule is illustrated in the Figure.

The absolute configuration was determined by a comparison of the generalised R factors for the two enantiomorphs and application of Hamilton's statistical R factor ratio test.[2] In making these calculations the chlorine positions were refined to convergence for each of the two enantiomorphs. The ratio of the generalised R factors was 1·085 and the assignment can be made at the 99·9% significance level. This was confirmed by comparing 17 randomly selected, experimentally determined Bijvoet pairs of reflexions with calculated values for the two enantiomorphs.

Centaurepensin is of interest in that it is the first sesquiterpene derivative containing two halogen atoms to be reported, though three somewhat similar compounds containing one chlorine atom[3] have recently been described. Also, the esterifying function, (*S*)-β-chloro-α-hydroxyisobutyric acid does not appear to have been found previously in nature.

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