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CONFORMATION OF IRIDOMYRMECIN AND ISOIRIDOMYRMECIN

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Continued interest in the chemistry of iridomyrmecin and its epimer, isoiridomyrmecin[1,2] has led to determination of their detailed structures by X-ray crystallographic methods.

Isoiridomyrmecin

A preliminary analysis[3], based on the hOl and hkO data at room temperature and using optical transform methods[4], appeared to be in accord with a chair conformation of the six-membered ring. Such a conclusion would have confirmed suggestions[2] put forward on chemical grounds but was found difficult to reconcile with evidence regarding the planarity of the lactone group obtained in X-ray analyses of himbacine hydrobromide[5] and of the bromodilactone from jacobine[6]. The existence of apparently contradictory evidence regarding the lactone group, combined with the extremely high temperature factor (B = 7.5), made it desirable to extend the investigation to lower temperatures.

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[1] R. B. Bates, E. J. Eisenbraun and S. M. McElvain, J. Amer. Chem. Soc. 80, 3420 (1958).

[2] G. W. K. Cavill, Revs. Pure Appl. Chem. 10, 169 (1960).

[3] J. F. McConnell and B. P. Schoenborn, IUPAC Symposium on the Chemistry of Natural Products Abstracts p.44 (1960).

[4] H. Lipson and C. H. Taylor, Fourier Transforms and X-ray Diffraction, Bell (1958).

[5] J. Fridrichsons and A. McL. Mathieson,
a) IUPAC Symposium on the Chemistry of Natural Products Abstracts p.44 (1960).
b) Acta Cryst. 15, 119 (1962).

[6] A. McL. Mathieson and J. C. Taylor, Tetrahedron Letters No. 17, 590 (1961).

At -130°C, the dimensions of the monoclinic cell are $\underline{a}$ = 10.09, $\underline{b}$ = 6.41, $\underline{c}$ = 7.50Å, β = 96.4°; the space group is $P2_1$ with two molecules in the unit cell. The $\underline{x}$ and $\underline{z}$ parameters were determined mainly from the $\underline{h}0\underline{l}$ data and the $\underline{y}$ parameters from the generalised projections based on the $\underline{h}1\underline{l}$ and $\underline{h}2\underline{l}$ data. The structure was refined by difference syntheses, the final stages being by least squares, the reliability index being 0.14 for the three layers[7]. The molecular skeleton, which differs somewhat from the earlier model[3] is shown in Fig. 1a while a more conventional configurational representation is given in Fig. 2a.

Iridomyrmecin

The structure determination was carried out using $\underline{h}0\underline{l}$, $\underline{h}1\underline{l}$, $\underline{h}2\underline{l}$ and $\underline{h}3\underline{l}$ data collected at -150°C. The crystals are monoclinic with unit cell dimensions $\underline{a}$ = 11.96, $\underline{b}$ = 5.25, $\underline{c}$ = 7.48Å, β = 97.1°; the space group is $P2_1$ with two molecules in the unit cell. The molecular skeleton was determined mainly in the $\underline{b}$-axis projection by analysis of the zero-layer Patterson projection P(u,w) and Harker sections, $P(u,\frac{1}{2},w)$ and P(u,0,w). The final refinement of the $\underline{x}$, $\underline{y}$, $\underline{z}$ parameters was carried out by least squares methods, the final reliability index for the four layers being 0.14[8]. The molecular skeleton is shown in Fig. 1b and a more conventional configurational representation in Fig. 2b.

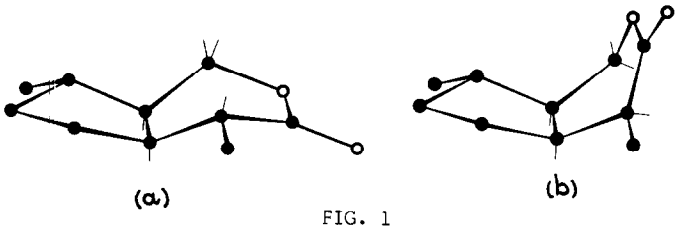
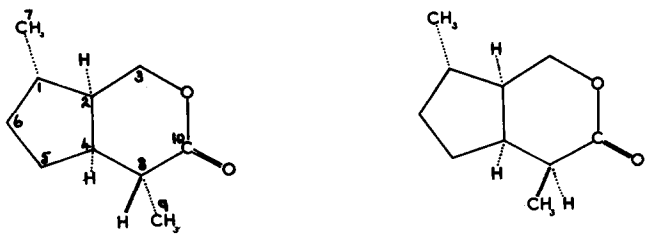


FIG. 1

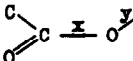
[7] J. F. McConnell and B. P. Schoenborn, Acta Cryst. in press.

[8] J. F. McConnell, A. McL. Mathieson and B. P. Schoenborn, in preparation.



(a) FIG. 2 (b)

The configurations at 1, 2 and 4 were earlier settled by their relationship to the nepetalinic acids[1] but that at 8 remained indeterminate. From the relationship of guaiol to the nepetalinic acids[9] and to bulnesol[10], Dolejš, Mironov and Šorm[10] inferred the configuration of the remaining undefined asymmetric centre in the nepetalinic acids on the basis of the cis-addition of hydrogen to the double bond in bulnesol. Hence they deduced the assignment of configuration for C_8 in iridomyrmecin and isoiridomyrmecin. The present analyses has confirmed their conclusions, isoiridomyrmecin being represented by Fig. 2a and iridomyrmecin by Fig. 2b.

Previously, the lactone group appears to have been considered to be of sufficient flexibility to permit accommodation in a six-membered ring with a chair conformation e.g. ref. 2. However it has become clear from the results of X-ray analysis[5,6] that the lactone group  is planar. For a six-membered ring this constraint imposes a boat conformation. The X-ray analyses show that the boat conformation is present in both compounds (Fig. 1). Associated with the planarity of the lactone group is the double-bond character of bond x which has been found in the X-ray analyses[5,6] to be approximately 0.1Å shorter than bond y. For the two iridomyrmecins, the mean values of the bonds x and y are 1.36 and 1.46Å respectively.

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[9] E. J. Eisenbraun, T. George, B. Riniker and C. Djerassi, J. Amer. Chem. Soc. 82, 3648 (1960).

[10] L. Dolejš, A. Mironov and F. Šorm, Tetrahedron Letters No. 11, 18 (1960).

With the configurations as defined in Fig. 2 and the planarity condition for the lactone group, there are alternative possible conformations which were considered during the X-ray analyses. These are shown in Fig. 1A and B. In each case, the factor which appears to determine the actual conformation is the preferential location of C_9 in the equatorial position, the orientation of the lactone group being of lesser significance. In isoiridomyrmecin, the cyclopentanoid ring is <u>exo</u> to the six-membered ring whereas, in iridomyrmecin, it is <u>endo</u>. In both compounds, C_6 lies out of the plane formed by 1, 2, 4 and 5 and away from the six-membered ring.

An adequate explanation of the difference in biological activity of iridomyrmecin and isoiridomyrmecin does not appear to depend on their epimeric relationship but may be more closely related to the overall shape of the molecules. Thus isoiridomyrmecin, which has considerable cat-nip activity, is a relatively flat molecule whereas iridomyrmecin is markedly buckled, cf. Figs. 1a and b. In this context, it is of interest to note that in nepetalactone (the main factor in cat-nip) the planarity of the lactone group allied with the adjacent double bond should make the complete six-membered ring planar, Fig. 3. An X-ray investigation of this compound is contemplated.

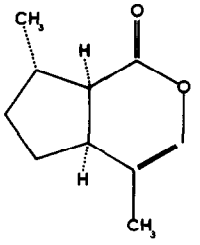

FIG. 3