The Crystal Structure of 3-Epicaryoptin and the Reversal of the Currently Accepted Absolute Configuration of Clerodin

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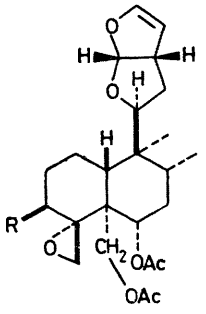
Summary Evidence, based on an *X*-ray assignment of the chirality of 3-epicaryoptin and a fresh *X*-ray study of clerodin bromolactone, is presented for the reversal of the long-held absolute configuration of clerodin, and new terminology is suggested to avoid confusion in future.

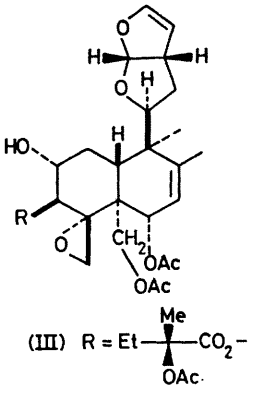
THE structure, stereochemistry, and absolute configuration of clerodin were assigned in 1961/2 from an *X*-ray study of its bromolactone.[1] Since then a large and growing number of compounds have been shown to contain the clerodane nucleus, and, as many of them are insect antifeedants or have antitumour, antimicrobial, or antifungal properties, interest in them has grown rapidly of late. An *X*-ray

study of 3-epicaryoptin, an antifeedant, carried out at Imperial College has yielded the absolute stereochemistry (I) shown in the Figure. It is opposite to that assigned to clerodin, despite the fact that caryoptin, 3-epicaryoptin, and clerodin have been shown physico-chemically to share a common absolute stereochemistry.[2,3] Further evidence for a common chirality was adduced[3] from c.d. exciton chirality studies of dibenzoates of these three compounds, but, as this chirality appeared to be antipodal to that published for clerodin, these compounds were reported as exceptions to the exciton chirality theory and attempts were made to explain away the contradiction.

In view of this conflict a fresh *X*-ray study of clerodin bromolactone has been carried out at Glasgow starting from new intensity data. This has verified the earlier *X*-ray work, but shown that an unfortunate error occurred in the preparation of the diagrams and stereoformulae. Clerodin must now be represented by (II). Both (I) and (II) match



(I) R = OAc
(II) R = H



(III) R = Et—C(Me)(OAc)—CO_2—

the *X*-ray assignment of clerodendrin A (III),[4] which must be considered secure as hydrolysis yields (*R*)-(—)2-acetoxy-2-methylbutyric acid whose known chirality matches (III).[5] This conclusion is confirmed by the as yet unpublished chiroptical data obtained by Dr. Harada for a number of derivatives of these three compounds and of caryoptin.[6]

As clerodin has given its name and chirality to this large subgroup of diterpenes, the reversal has extensive repercussions. A preliminary survey indicates that most of the known *trans*-fused clerodanes must now be assigned the old *ent*-clerodin configuration. Many of them had been assigned configurations on the basis of well established general chiroptical rules and need not be reversed. To them can be added all six of the *X*-ray assignments in this group, *viz.* 3-epicaryoptin (I), clerodin (II), clerodendrin A (III), cascarillin,[7] and two different heavy-atom derivatives of teucvin.[8,9] A few, however, such as ajugarin[10] and fruticolone[11] were anti-correlated by c.d. with clerodin itself, so they now have the old clerodin chirality. We hope to discuss these consequences in a later publication, but authors in this area are urged to review their chirality assignments carefully.

We consider that, if confusion is to be avoided in future, there is need for new terminology which must be unambiguously linked with the past but which by its use will indicate that note has been taken of this reversal. We suggest that the majority formerly known as *ent*-clerodanes

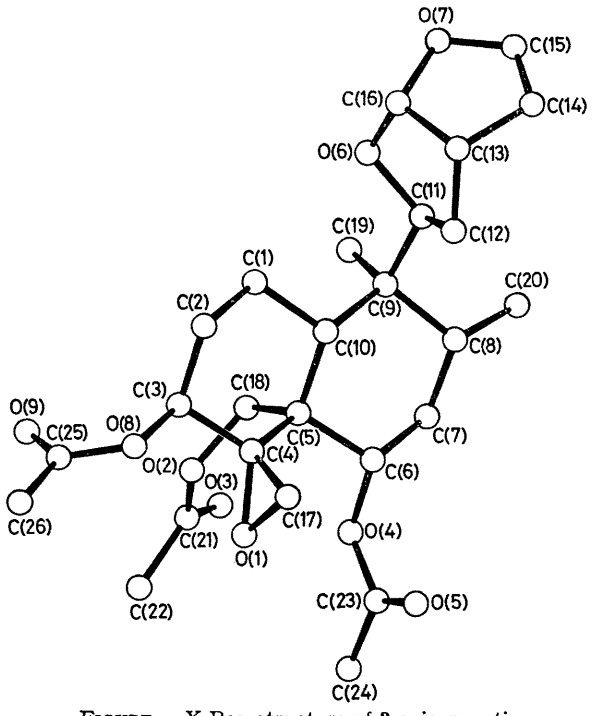


FIGURE. *X*-Ray structure of 3-epicaryoptin.

be renamed *neo*-clerodanes; the few like ajugarin and fruticolone then become *ent-neo*-clerodanes.

The specimen of 3-epicaryoptin used was extracted from a new source, *Clerodendrum inerme* (Linn) Gaertn. (Verbenaceae), which is a small straggling shrub widely grown in India as a hedge plant since sheep and cattle do not feed on its leaves.[12] Hexane extract of the leaves afforded a compound, $C_{26}H_{36}O_9$, m.p. 165 °C, $[\alpha]_D$ −63·6° (*c*, 1·8, $CHCl_3$) in 0·2% yield. Its i.r. spectrum (KBr) matched that of 3-epicaryoptin kindly supplied by Dr. Kato.[2] Details of its chemistry and of a number of new derivatives will be presented elsewhere. The crystals are monoclinic, $P2_1$, $a = 7{\cdot}876$, $b = 17{\cdot}278$, $c = 9{\cdot}697$ Å, $\beta = 100{\cdot}24°$, $Z = 2$. 2605 Reflexions were measured on a Siemens diffractometer with Cu-K_α radiation, of which 109 were reckoned unobserved, and the structure was solved by use of the MULTAN program. Allowance for the anomalous scattering from its nine oxygen atoms gave $R^-/R^+ = 0{\cdot}0541/0{\cdot}0538 = 1{\cdot}0056$ which gives a probability against the assignment of $< 6 \times 10^{-5}$.[13,14]†

The crystals of clerodin bromolactone were kindly supplied by Professor Sir Derek Barton, the source being the aptly named *Clerodendrum infortunatum*. 1706 Reflexions measured on a diffractometer with Mo-K_α radiation gave R^-/R^+ (excluding centric terms) = $0{\cdot}091/0{\cdot}066 = 1{\cdot}38$, a most emphatic assignment. This is only the second instance, in a current total of *ca.* 800 *X*-ray assignments of chirality, where a re-examination has shown that an error of some sort had been made in the original assignment. With modern facilities an error is very unlikely, but there were several places in each of the earlier studies where a slip could occur, so it is just possible that a few

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

more mistakes remain to be discovered. Should a similar conflict come to light in the future it is hoped that spectroscopists will feel encouraged by the circumstances in the present case to have more confidence in their own assignment and to ask for a re-examination of the *X*-ray work.

Added in proof: Since this manuscript was submitted two other papers have come to our notice. One[15] is yet another *X*-ray assignment (of haplociliatic acid) to the *neo*-clerodanes. The other[16] describes chemical and c.d. studies of four congeners, teucrins H_1—H_4. H_1 and H_4 are assigned the *neo*-clerodane chirality on the basis of α-β unsaturated lactone c.d. and that seems secure, but H_3 (like ajugarin and fruticolone) exhibits a (−) c.d. attributed to the 6-oxo group, opposite to that of clerodin and caryoptin,[3,17] so it appeared to match H_1 and H_4. But, if the 6-oxo c.d. evidence is to be accepted, H_3 joins the exceptions and now improbably becomes antipodal to H_1 and H_4. As 6-oxo c.d. led to wrong conclusions for clerodin and caryoptin, we regard assignments based on such evidence in this context as doubtful, and indeed question whether ajugarin, fruticolone, and teucrin H_2 are exceptions after all. Efforts are in hand to settle the point.

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