

Unambiguous Determination of the Stereochemistry of Methylcopper- and Lithium Tetrahydridoaluminate-induced Allene Formation in the Steroid Series. A Revision of Literature Data

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The structure of the allene obtained from mestranol methane sulphinate and methylcopper has been determined by X-ray analysis; the allene turns out to be the 21 α -Me compound, and not the erroneously reported 21 β -Me epimer.

Because of their two cumulated double bonds allenes may exhibit chirality. Chiral allenes have been obtained *via*, amongst other methods, organocopper-induced 1,3-substitution of optically active propargylic esters. An intriguing problem in this connection is the difference in stereochemistry reported for organocopper-induced 1,3-substitution of propar-

glyc esters in the steroid series on the one hand and of non-steroidal ones on the other. For non-steroids the substitution preferentially proceeds *anti*,¹ but, for steroids, a *syn* stereochemistry has been assumed,² supposing the Lowe-Brewster rules to be valid.

In view of a recent stereochemical study of the reaction of

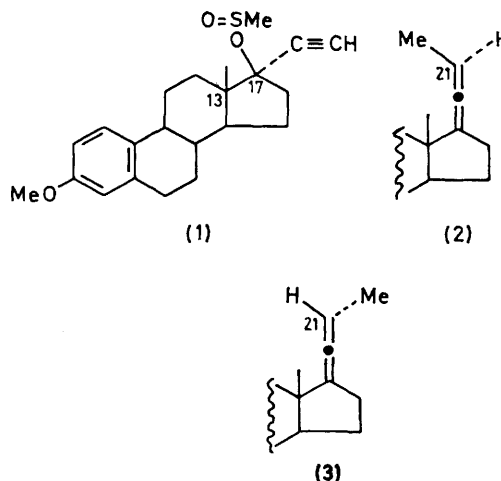
steroidal allenic sulphoxides with methyl-lithium,³ serious doubt was cast upon the structure assignment of steroidal allenes. We therefore decided to determine the structure of such allenes unambiguously by *X*-ray analysis. For this study an optically pure allene was prepared by reaction of mestranol methane sulphinate (1) with methylcopper according to the procedure given in ref. 4. The allene produced melts at 71.0–71.5 °C and shows a negative optical rotation ($[\alpha]_D^{25}$ in CH_2Cl_2 –16.0°). In the ^1H n.m.r. spectrum (CDCl_3 , Me_4Si) the signal for 13-Me is found at 0.86 p.p.m. Thus far it was assumed that this allene possessed a 21β -Me group (2).² Its correct structure has now been elucidated by *X*-ray analysis.

Crystal data: $\text{C}_{22}\text{H}_{28}\text{O}$, $M = 308.46$, orthorhombic, space group $P2_12_12_1$, $a = 27.854(9)$, $b = 9.945(2)$, $c = 13.159(3)$ Å, $U = 3644.0(15)$ Å³, $D_c = 1.12$ g cm⁻³ for $Z = 8$. Data were collected on a Syntex $P2_1$ diffractometer with graphite-monochromated Mo- K_α radiation for $2\theta_{\text{max}} = 47^\circ$. The structure was solved by direct methods on the basis of 1584 independent reflections having $I > 2.5\sigma(I)$ by use of YZARC 80⁵ and refined with SHELX 76⁶ to $R = 0.065$.†

This analysis showed unequivocally that the methylcopper-induced substitution of (1) does not give allene (2) but the *anti* substitution product (3) instead, *i.e.* the allene with α -orientation of the 21-Me group with respect to the steroid nucleus in both conformations ($Z = 8$, so there must be two independent molecules in the asymmetric unit with space group $P2_12_12_1$) that mainly differ in the orientation of the methoxy-group at C-3. This interesting finding implies that the stereochemistry assigned to some other reactions likewise needs revision. Thus, methylcopper-induced substitution of the 17-epimer of (1) gives allene (2), and not allene (3) as was recently reported.⁷ Also the stereospecific formation of allenes (2) and (3) by reduction of the corresponding 17-hydroxy-17-propynyl steroids is now established to be an *anti* instead of a *syn*⁸ 1,3-substitution reaction.

Finally we note that the Lowe–Brewster rules are not valid

† These crystal data were obtained by Prof. M. van Meerssche, Louvain-York Crystal Structure Solving Service, Université de Louvain, 1348 Louvain-la-Neuve, Belgium. Similar data, though less precise, were found by Dr. J. A. Kanters, Laboratorium voor Structuurchemie, Rijksuniversiteit, Padualaan 8, Utrecht, The Netherlands. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.



for allenes (2) and (3). These rules are also violated by some trisubstituted allenes in the non-steroid series,⁹ and are therefore of restricted value for configuration assignment of allenes.

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References

- G. Tadema, R. H. Everhardus, H. Westmijze, and P. Vermeer, *Tetrahedron Lett.*, 1978, 3935, and references cited therein.
- L. A. van Dijck, B. J. Lankwerden, J. G. C. M. Vermeer, and A. J. M. Weber, *Recl. Trav. Chim. Pays-Bas*, 1971, **90**, 801.
- G. Neef, U. Eder, and A. Seeger, *Tetrahedron Lett.*, 1980, **21**, 903.
- P. Vermeer, H. Westmijze, H. Kleijn, and L. A. van Dijck, *Recl. Trav. Chim. Pays-Bas*, 1978, **97**, 56.
- J. P. Declercq, G. Germain, and M. M. Woolfson, *Acta Cryst. A*, 1979, 622.
- G. M. Sheldrick, SHELX 76: Program for Crystal Structure Determination, University of Cambridge, England, 1976.
- H. Westmijze and P. Vermeer, *Tetrahedron Lett.*, 1979, 4101.
- L. A. van Dijck, B. J. Lankwerden, and J. G. C. M. Vermeer, *Recl. Trav. Chim. Pays-Bas*, 1979, **98**, 553, and references cited therein.
- M. Bertrand, G. Gil, and A. Kumar, *Nouv. J. Chim.*, 1980, **4**, 69.