Synthesis of Substituted α-Methylene Lactones: Determination of Product Structure by *X*-Ray Crystallography

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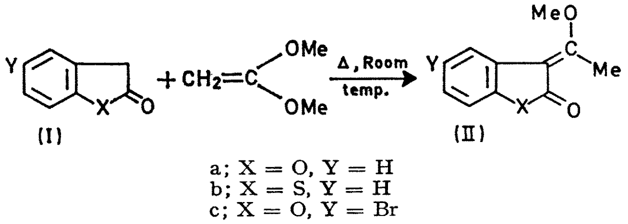
Summary Lactones (Ia—c) undergo a ready, completely stereoselective thermal reaction with 1,1-dimethoxyethylene giving substituted α-methylene lactones in good yield.

SYNTHESIS of α-methylene lactones has received considerable attention recently because of interest in the anticancer properties of these substances.[1] We now describe a synthesis of substituted α-methylene lactones under unusually mild conditions.



a; X = O, Y = H
b; X = S, Y = H
c; X = O, Y = Br

Irradiation of benzofuran-2(3*H*)-one at room temperature produces *o*-quinonemethide[2] which can be trapped by nucleophiles such as methanol[3] or 1,1-dimethoxyethylene.[2] In the latter reaction the yield of the *ortho*-lactone is greater than 90% and a minor by-product is isolated. The by-product is the result of a competing thermal reaction between the lactone and 1,1-dimethoxyethylene. This reaction is completely stereoselective and takes place in high yield at room temperature. An ether solution of (Ia) (2·07 g) and 1,1-dimethoxyethylene (5·0 g) left at room temperature for 7 d loses solvent and produces, after recrystallization, the product (IIa) (1·92 g, 71%). The reaction is successful for the sulphur analogue (Ib, 83%) and the bromolactone (Ic, 80%). The product structure was established by *X*-ray crystallographic analysis of (IIc).

Crystals of (IIc) are clear plates with well-defined edges. Preliminary Weissenberg photographs displayed $2/m$ Laue symmetry and the systematic extinctions $h0l$ ($l = 2n+1$) and $0k0$ ($k = 2n+1$) uniquely determine the monoclinic space group $P2_1/c$ (C^5_{2h}). Lattice constants, determined on a fully automated Hilger–Watts four-circle diffractometer, were $a = 7{\cdot}45$ (1), $b = 11{\cdot}91$ (1), $c = 12{\cdot}35$ (1) Å and $\beta = 106{\cdot}13$ (7)°. Measured density indicated $Z = 4$. All reflections in hkl and $hk\bar{l}$ octants with $2\theta \leqslant 110°$ were collected by stationary crystal–stationary counter techniques with Ni-filtered Cu-K_α X-rays. After Lorentz and polarization corrections 1121 reflections were judged observed. A three-dimensional Patterson synthesis revealed the Br position and the remaining 14 non-hydrogen atoms were easily located in the Br-phased electron density synthesis. Full-matrix least-squares refinement with anisotropic temperature factors for all atoms reduced the conventional discrepancy index to its present minimum of 0·107 for all of the observed reflections.

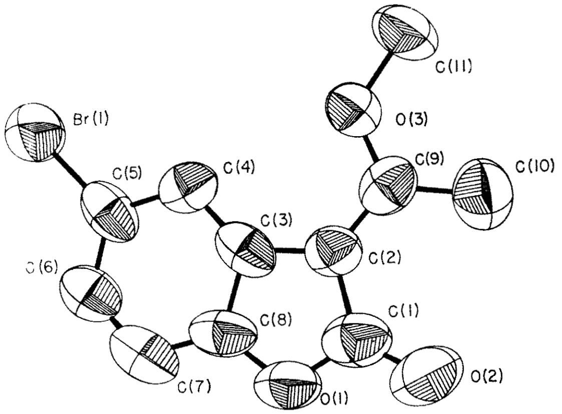
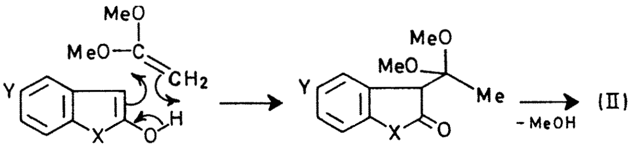


FIGURE. *Computer generated drawing of the final* X-*ray structure of* (IIc).

The Figure is a computer generated drawing of the final X-ray structure. All bond distances and angles (e.s.d.'s of 0·02 Å and 1·0°, respectively) agree well with generally accepted values. A final difference map showed no peaks larger than 1·0 e Å^{-3} and no anomalously short intermolecular contacts were found.



The mechanism of the transformation of (I) to (II) probably involves enolization of (I) followed by reaction with 1,1-dimethoxyethylene. In accord with this view, deuteriation of the α-position of the lactone gives a product which contains deuterium in the vinyl methyl group.

This research was supported by a grant from the National Institute for Arthritis and Metabolic Disease and the Ames Laboratory for Atomic Research.

(*Received, December* 29*th*, 1970; *Com.* 2252.)

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