Dihydrobenzofurans in which $J_{cis\text{-}2,3} > J_{trans\text{-}2,3}$: Confirmation Using *X*-Ray Diffraction Analysis

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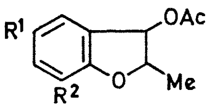
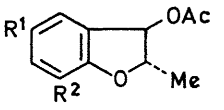
Summary The validity of the Karplus equation for the assignment of stereochemistry in some substituted 3-acetoxy-2-methyl-2,3-dihydrobenzofurans was confirmed by *X*-ray diffraction analysis.

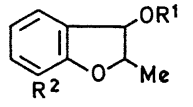
APPLICATION of the Karplus equation for the assignment of *cis–trans* stereochemistry has recently been reported to be invalid in some substituted 2,3-dihydrobenzofurans.



(I) $R^1 = NO_2, R^2 = H$
(III) $R^1 = H, R^2 = NO_2$



(II) $R^1 = NO_2, R^2 = H$
(IV) $R^1 = H, R^2 = NO_2$



(V) $R^1 = Ac, R^2 = NMe_2$
(VI) $R^1 = H, R^2 = NMe_2$
(VII) $R^1 = H, R^2 = NMe_3I$

In these examples a series of 3-hydroxy (or acetoxy)-2-isopropyl-2,3-dihydrobenzofurans were shown to have $trans_{2,3}$ coupling of 6 Hz and $cis_{2,3}$ coupling of 4 Hz.[1] During the preparation of some similar dihydrobenzofurans as potential cholinergic agents, it was necessary to assign *cis–trans* stereochemistry to the isomers. In view of the reported exception to the Karplus equation, additional studies on structure validation were essential.

The *cis–trans* isomers† of 5-nitro- and 7-nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofurans (I—IV) were prepared by nitration of the *cis–trans* mixture of 3-acetoxy-2-methyl-2,3-dihydrobenzofuran; separation of the isomers was accomplished by chromatography and crystallization. The 7-nitro-isomer (III) was reduced to the dimethylamino-derivative, (V) the acetyl group saponified to give (VI), and the resulting amino-alcohol (VI) converted into *cis*-7-dimethylamino-3-hydroxy-2-methyl-2,3-dihydrobenzofuran methiodide (VII). *X*-Ray diffraction analyses of (VII) showed the 2-methyl and 3-hydroxy-groups to be *cis*. Though the hydrogens were not located in this analysis, from the angles of the other substituents at C-2 and C-3 a 19° torsion angle for the hydrogens on C-2 and C-3 of (VII) is a reasonable approximation.

The *cis*-isomers (I), (III), (V), (VI), and (VII) showed $J_{2,3}$ 6 Hz and the *trans*-isomers (II) and (IV) gave a coupling constant, $J_{2,3}$ 2 Hz. This agrees with the assignments made on the basis of the Karplus equation.[2]

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† The n.m.r., i.r., and elemental analysis of all compounds in this paper support the assigned structures.

[1] L. H. Zalkow and M. Ghosal, *J. Org. Chem.*, 1969, **34**, 1646; *Chem. Comm.*, 1967, 922.

[2] L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, 1969, 2nd edn., p. 281.