Isolation and Identification of the Cis–Trans Stereoisomers of Substituted 3-Hydroxy- (or 3-Acetoxy-) 2-methyl-2,3-dihydrobenzofurans. Dihydrobenzofurans Which Obey the Karplus Equation[1]

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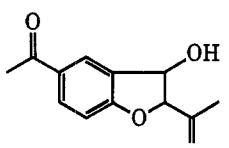
The cis-trans stereoisomers of 5-nitro- and 7-nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofurans (**4a–d**) were separated by a combination of column chromatography and fractional crystallization. *cis*-7-Nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofuran (**4c**) was converted to the dimethylamino isomer **5** by catalytic reduction of the nitro group in methanol–formaldehyde. Hydrolysis of the acetyl and quaternization of the amino alcohol **6** gave *cis*-7-dimethylamino-3-hydroxy-2-methyl-2,3-dihydrobenzofuran methiodide (**7**). The stereoisomers of **4** having $J_{2,3}$ = 2 Hz were assigned trans stereochemistry and the stereoisomers having $J_{2,3}$ = 6 Hz were assigned cis stereochemistry. These assignments were confirmed by determining the X-ray diffraction patterns of the *cis*-MeI salt **7**. The X-ray diffraction results confirm the validity of the Karplus equation in predicting the stereochemistry of these substituted 2,3-dihydrobenzofurans.

Recently, Zalkow and Ghosal[2,3] observed that 1,2-trans coupling was greater than cis coupling in the nmr spectra of 2-isopropyl-3-hydroxy- (or acetoxy-) dihydrobenzofurans ($J_{trans\text{-}2,3} > J_{cis\text{-}2,3}$). The failure of the Karplus equation in these systems was attributed to the stereochemical dependence of the electronegativity effect in the cis series. It was proposed that $J_{cis\text{-}2,3}$ is lowered due to a steric interaction of the 2-isopropyl and 3-hydroxy substituents of dihydrotoxol (**2**). As the C-2 and C-3 substituents bend away from each other, the angle between the 3-hydroxy and C-2 proton approaches 180°, the angle of maximum electronegativity effect and minimum $J_{2,3}$.[4] The authors



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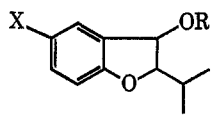
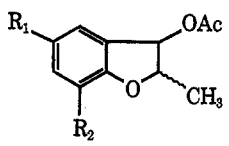


2, X = Ac; R = H
3, X = Br; R = Ac

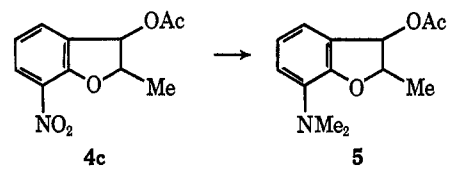


4a (*cis*), $R_1 = NO_2$; $R_2 = H$
b (*trans*), $R_1 = NO_2$; $R_2 = H$
c (*cis*), $R_1 = H$; $R_2 = NO_2$
d (*trans*), $R_1 = H$; $R_2 = NO_2$

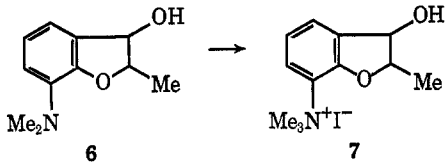
conclude that the assignment of stereochemistry based solely on the size of the coupling constants can be misleading in systems such as 2,3-dihydrobenzofurans.

Hayward and coworkers[5] have assigned the stereochemistry of 2,3-dialkyldihydrobenzofurans on the basis of mode of synthesis. The relative magnitude of the coupling constants in this series, $J_{cis\text{-}2,3} > J_{trans\text{-}2,3}$, was as predicted by the Karplus equation and, as the authors note, is not comparable to the models of Zalkow and coworkers since the 3 substituent, being alkyl, would not be expected to have the same "electronegativity effect" as the 3 oxygen.

We wish to report the results of studies on the assignment of cis–trans stereochemistry in 5- and 7-substituted 3-acetoxy- (or hydroxy-) 2-methyldihydrobenzofurans, models similar to those reported in the work of Zalkow and coworkers. The reaction conditions used to synthesize the 2-methyl-2,3-dihydrobenzofurans (**4**) were similar to those reported[3] in the stereospecific synthesis of **2** and **3**. However, the product obtained in the 2-methyl series was a mixture of equal amounts of the cis and trans isomers.[6] The separation of the cis and trans isomers of **4** was accomplished by a combination of column chromatography and fractional crystallization. Each series contained one isomer with $J_{2,3}$ = 2 Hz and one isomer with $J_{2,3}$ = 6 Hz. The initial assignments, assuming the validity of the Karplus equation for series **4**, should give the 2,3-cis isomer for $J_{2,3}$ = 6 Hz (**4a** and **4c**) and the 2,3-trans isomer for $J_{2,3}$ = 2 Hz (**4b** and **4d**). However, from the exceptions of Zalkow and Ghosal[2,3] this assumption is subject to question.



4c **5**



6 **7**

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(2) L. H. Zalkow and M. Ghosal, *ibid.*, 922 (1967).

(3) L. H. Zalkow and M. Ghosal, *J. Org. Chem.*, **34**, 1646 (1969).

(4) H. Booth, *Tetrahedron Lett.*, 411 (1965).

(5) (a) E. C. Hayward, D. S. Tarbell, and L. D. Colebrook, *J. Org. Chem.*, **33**, 399 (1968); (b) K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 516 (1963).

(6) L. J. Powers and M. P. Mertes, *J. Med. Chem.*, **14**, 361 (1971).

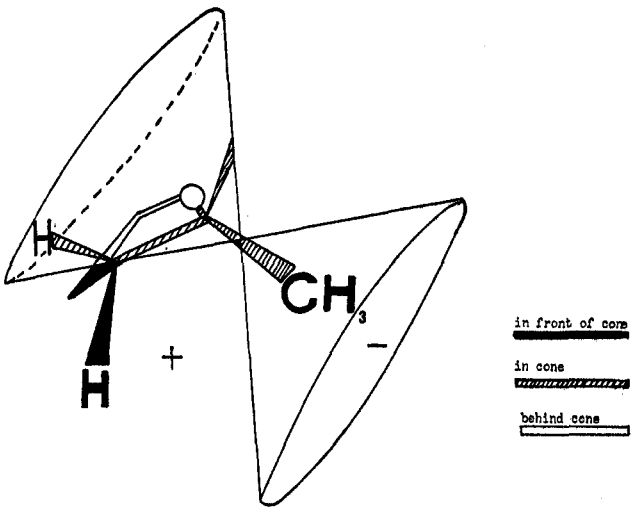

Figure 1.—The anisotropic shielding (+) of the cis C-3 proton and the anisotropic deshielding (−) of the trans C-3 proton by the methyl–C-2 bond in 2-methyl-2,3-dihydrobenzofurans.

Factors that can be considered for structural assignment are the relative magnitude of the coupling constants and the expected changes that would occur in comparing the 2-methyl series (**4**) with the 2-isopropyl series (**2** and **3**). If, as Zalkow and Ghosal[2,3] suggest, the lowering of the coupling constant in the cis series (**2** and **3**) is due to a steric interaction of the C-2 and C-3 substituents, it would seem logical that **3**, having the bulkier 2-isopropyl substituent, would have a greater steric interaction between the C-2 and C-3 substituents, a greater dihedral angle, and hence a lower coupling constant than **4a** and **4c**. In addition, the electronegativity effect exaggerated by an antiplanar orientation would diminish the expected coupling constant.[5b] Thus, these factors must operate to give a value of $J_{\text{cis-2,3}}$ of 3.5 Hz for **2** and **3**, a rather strong effect when compared to a $J_{\text{cis-2,3}}$ of 6 Hz for series **4**.

The reported trans coupling constants for **2** and **3** are 5–6 Hz, high values considering ring distortion should be minimal and the dihedral angle should approach 120°;[5b] the respective trans coupling of 2 Hz is noted in series **4**.

The most striking differences between the nmr spectra of the cis and trans isomers of **4**, other than the values of $J_{2,3}$, are the different values for the chemical shift of the C-3 proton. The C-3 proton of the trans isomers (**4b** and **4d**) is about δ 0.3 upfield from the corresponding C-3 protons of the cis isomers (**4a** and **4c**). This difference in chemical shift was examined by varying temperature nmr studies for a steric interaction of the 2-methyl group and the 3-acetoxy group of the cis isomer which might restrict the free rotation of the acetoxy substituent. No change in the chemical shift of the C-3 proton in the cis series (**4a** and **4c**) was observed in the range −27 to 100°. Since this difference in chemical shift is apparently not a conformational effect, a reasonable explanation is that the difference is due to the proximity of the methyl group to the C-3 proton in the trans stereoisomer (in which the C-2 methyl group and C-3 proton are cis). The basis of such a shielding interaction is the known anisotropic effect of the C–C single bond.[7] As shown in Figure 1, the C-3 proton in the trans stereoisomer of the 2-methyl-3-acetoxy-2,3-dehydrobenzofurans is in a shielding region while the C-3 proton of the cis stereoisomer is in a deshielding region.

(7) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 117.

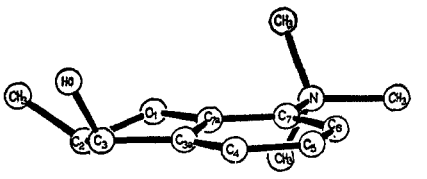

Figure 2.—X-Ray crystal structure of *cis*-7-trimethylammonium 3-hydroxy-2-methyl-2,3-dihydrobenzofuran iodide (**7**).

The mass spectra of the series **4** contain some interesting relationships. The greatest difference between the mass spectra of the cis isomers (**4a** and **4c**) and those of the trans isomers (**4b** and **4d**) is in the relative abundances of the peaks at *m/e* 177 and 178 (loss of CH_3COOH and CH_3COO, respectively) as well as the peaks at *m/e* 131 and 132 (loss of NO_2 and CH_3COOH or CH_3COO). It appears that the trans isomers **4b** and **4d** ($J_{2,3}$ = 2 Hz) have a greater tendency to lose a AcOH fragment relative to the loss of a AcO fragment than do the cis isomers **4a** and **4c** (Table I). This can be explained by assuming that the trans isomers would be in a favorable configuration to undergo a McLafferty[8] rearrangement with the abstraction of the C-2 proton. In the case of the cis isomers **4a** and **4c**, the abstraction would seem to be less favorable as the proton is located on the side of the ring opposite the acetoxy group.

TABLE I

THE RELATIVE PROBABILITY OF THE LOSS OF A CH_3COOH AND CH_3COO FRAGMENT IN THE $J_{2,3}$ = 2 Hz AND $J_{2,3}$ = 6 Hz ISOMERS OF 5-NITRO-3-ACETOXY-2-METHYL-2,3-DIHYDROBENZOFURAN AND 7-NITRO-3-ACETOXY-2-METHYL-2,3-DIHYDROBENZOFURAN

	$J_{2,3}$ = 2 Hz		$J_{2,3}$ = 6 Hz	
	4b	**4d**	**4a**	**4c**
$\frac{m/e\ 177}{m/e\ 178}$	5.1	7.6	3.6	3.9
$\frac{m/e\ 131}{m/e\ 132}$	1.7	1.3	1.1	0.8

In order to prepare a derivative for X-ray crystallographic confirmation of the assigned stereochemistry, the cis nitro acetate **4c** was converted to the methiodide salt **7** and the X-ray diffraction pattern of this salt was determined. The nitro acetate **4c** was converted to the Me_2N analog **5** by a modification of the reductive alkylation procedure of Martell and Boothe.[9] Alkaline hydrolysis of **5** gave *cis*-5-dimethylamino-3-hydroxy-2-methyldihydrobenzofuran (**6**). Conversion of **6** to the methiodide **7** was accomplished in the usual manner. The nmr spectra of the intermediates showed the usual pattern with regard to the C_2 and C_3 protons ($J_{\text{cis-2,3}}$ = 6 Hz).

X-Ray diffraction analysis of compound **7** confirmed cis stereochemistry (Figure 2). The torsion angle, about the 2,3 positions as obtained from the crystal

(8) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1966, Chapter 8.

(9) M. J. Martell, Jr., and J. H. Boothe, *J. Med. Chem.*, **10**, 44 (1967).

structure determination, is shown in Figure 3. Though the hydrogens were not located in this analysis, a 19° angle is a reasonable approximation for their spatial distribution.

The results of this research and that of Hayward and coworkers[5] indicate that in the absence of steric crowding the stereochemistry of 2,3-dihydrobenzofuran systems can be assigned on the assumption that $J_{cis\text{-}2,3} > J_{trans\text{-}2,3}$.

Experimental Section[10]

Isolation and Purification of the Stereoisomers of 5-Nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofuran (4a and 4b) and 7-Nitro-3-acetoxy-2-methyl-2,3-dihydrobenzofuran (4c and 4d).—The crude reaction mixture from the nitration of 3-acetoxy-2-methyl-2,3-dihydrobenzofuran[6] (mixture of stereoisomers) with nitric acid in acetic anhydride was chromatographed as previously described.[6] Three major fractions collected from the silica column contained the nitro acetates **4**. Evaporation of the solvent from the first fraction gave the pure *trans*-5-nitro acetate **4b** as a yellow oil in 13% yield: bp 138° (0.2 mm); ir (CCl_4) 1740 (C=O), 1520 and 1355 (NO_2); nmr ($CDCl_3$) δ 1.46 (d, 3, J = 6 Hz, $CHCH_3$), 2.12 (s, 3, $OCOCH_3$), 4.97 (octet, 1, J = 2 and 6 Hz, $CHCH_3$), 5.94 (d, 1, J = 2 Hz, CHOAc), 7.0 (m, 1, aromatic H-7), 8.3 (m, 2, aromatic H-4 and H-6).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.72; H, 4.59; N, 5.94.

The second fraction contained (in 32% yield) a mixture of the *cis*- and *trans*-5-nitro isomers. Crystallization from MeOH followed by recrystallization from C_6H_{12} gave the pure *cis*-5-nitro acetate **4a**: mp 95–97°; ir (KBr) 1736 (C=O), 1508 and 1340 (NO_2); nmr ($CDCl_3$) δ 1.52 (d, 3, J = 6 Hz, $CHCH_3$), 2.10 (s, 3, $OCOCH_3$), 4.95 (quintet, 1, J = 6 Hz, $CHCH_3$), 6.25 (d, 1, J = 6 Hz, CHOAc), 6.90 (d, 1, J = 9 Hz, aromatic H-7), 8.25 (m, 2, aromatic H-4 and H-6).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.59; H, 4.87; N, 5.98.

The third fraction contained a mixture (in 35% yield) of the *cis*- and *trans*-7-nitro acetates. Crystallization from CCl_4 gave the pure *cis*-7-nitro acetate **4c**: mp 129.5–130.5°; ir (KBr) 1732 (C=O), 1525 and 1345 (NO_2); nmr ($CDCl_3$) δ 1.62 (d, 3, J = 6 Hz, $CHCH_3$), 2.10 (s, 3, $OCOCH_3$), 5.03 (quintet, 1, J = 6 Hz, $CHCH_3$), 6.27 (d, 1, J = 6 Hz, CHOAc), 7.05 (t, 1, J = 8 Hz, aromatic H-5), 7.74 (m, 1, aromatic H-4), 8.10 (m, 1, aromatic H-6).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.80; H, 4.65; N, 6.03.

The CCl_4 was removed from the mother liquor and the residual oil was crystallized from MeOH to give the *trans*-7-nitro acetate **4d**: mp 82.5–83.5°; ir (KBr) 1730 (C=O), 1525 and 1340 (NO_2); nmr ($CDCl_3$) δ 1.54 (d, 3, J = 6 Hz, $CHCH_3$), 2.11 (s, 3, $OCOCH_3$), 5.09 (octet, 1, J = 6 and 2 Hz, $CHCH_3$), 5.98 (d, 1, J = 2 Hz, CHOAc), 7.08 (t, 1, J = 8 Hz, aromatic H-5), 7.79 (m, 1, aromatic H-4), 8.17 (m, 1, aromatic H-6).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.39; H, 4.79; N, 6.11.

***cis*-7-Dimethylamino-3-acetoxy-2-methyl-2,3-dihydrobenzofuran (5).**—The nitro acetate **4c** (1.5 g, 6.3 mmol) in a minimum amount (10–20 ml) of 2-methoxyethanol was added to a suspension of 10% Pd/C (1.0 g) and CH_2O (9 ml of a 37% aqueous solution) in MeOH (50 ml). The reaction mixture was stirred at 25° under a H_2 atmosphere (1 atm) until 774 ml (31.5 mmol) had been absorbed. The reaction mixture was filtered, concentrated to ~30 ml, and poured into $CHCl_3$ (100 ml). The $CHCl_3$ solution was washed with 5% $NaHCO_3$ (three 40-ml portions) and dried ($MgSO_4$), and the solvent was removed to give a yellow residual oil. An aliquot (200 mg) of the oil was chromatographed on a preparative tlc plate (10% EtOAc–Skelly B). The major band (uv visualization, R_f *ca.* 0.4–0.5) was removed and extracted with Et_2O. The solvent was evaporated and the residual oil was dissolved in anhydrous Et_2O and dried ($MgSO_4$). Dry HCl was passed into the solution to give the hydrochloride salt of **5** as a gum which solidified on standing. The solid was recrystallized from Me_2CO–EtOAc, mp 145.5–146.5°.

Anal. Calcd for $C_{13}H_{18}ClNO_3$: C, 57.45; H, 6.69; N, 5.15. Found: C, 57.64; H, 6.72; N, 5.37.

***cis*-7-Dimethylamino-3-hydroxy-2-methyl-2,3-dihydrobenzofuran (6).**—The amino acetate **5** (1.5 g, 6.3 mmol) was dissolved in MeOH (20 ml), and NH_4OH (10 ml) was added. The reaction mixture was stirred at 55° for 2 hr, cooled, and poured into H_2O (50 ml). The solution was extracted with $CHCl_3$ (three 50-ml portions) and the combined extracts were dried ($MgSO_4$). Evaporation of the solvent gave a dark residual oil which was chromatographed over 100 g of Woelm Al_2O_3 (activity grade I, neutral, 0.5% MeOH–C_6H_6). The fractions containing the product (on the basis of tlc) were combined and the solvent was removed to give a light yellow oil. Conversion of the residue to the HCl salt in Et_2O and recrystallization from Me_2CO–EtOAc gave **6**, mp 142–143° (62%).

Anal. Calcd for $C_{11}H_{16}ClNO_2$: C, 57.51; H, 7.01; N, 6.10. Found: C, 57.57; H, 7.02; N, 6.06.

The methiodide salt **7** was prepared by dissolving **6** in absolute EtOH (10 ml), and CH_3I (1.0 ml) was added. The solution was refluxed for 30 min and then allowed to cool to room temperature. The salt which crystallized was analytically pure (70% yield): mp 191–192° nmr (D_2O) δ 1.58 (d, 3, J = 6 Hz, CCH_3), 3.72 (s, 9, NCH_3), 4.96 (quintet, 1, J = 6 Hz, $CHCH_3$), 5.28 (d, 1, J = 6 Hz, CHOAc), 7.0–7.3 (m, 1, aromatic H-5), and 7.5–7.8 (m, 2, aromatic, H-4 and H-6).

Anal. Calcd for $C_{12}H_{18}INO_2$: C, 42.99; H, 5.42; N, 4.18. Found: C, 42.99; H, 5.42; N, 4.07.

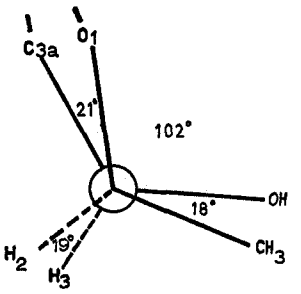

Figure 3.—Torsion angles from X-ray crystal structure of 7-trimethylammonium 3-hydroxy-2-methyl-2,3-dihydrobenzofuran iodide (**7**). Hydrogens are represented in presumed conformation.

Registry No.—**4a**, 26819-61-4; **4b**, 26819-62-5; **4c**, 26819-63-6; **4d**, 26921-99-3; **5** HCl, 28506-57-2; **6** HCl, 28506-58-3; **7**, 26819-65-8.

(10) All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind., or by Mrs. H. Kristiansen at the University of Kansas. Spectra were recorded on a Beckman IR-10, a Varian A-60A, a Varian HA 100, or a Finnigan 1015 mass spectrometer.