

On Vicinal H-H Coupling Constants in 3-Hydroxy-2,3-dihydrobenzofuran Derivatives (1)

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Zalkow and Ghosal have reported (3) for 2-isopropyl-3-hydroxy-2,3-dihydrobenzofuran derivatives of structure I, that $J_{2,3}$ is 4 Hz in the *cis* and 6 in the *trans* series. This finding was unexpected on the basis of the Karplus equation (4) as well as considerable experimental evidence on 5-membered rings (5), and was ascribed to selective diminution of J_{cis} by an electronegativity effect in accord with observations on 6-membered rings (6). The effect was attributed to the oxygen functions in the heterocycle and at C₃. Subsequently, Tarbell noted that this hypothesis does not apply to 2,3-dialkyl-2,3-dihydrobenzofurans, for which $J_{cis} > J_{trans}$, as predicted (7). Consequently, the effect was attributed specifically to the presence of oxygen functions at C₃ (7,8). We now report that 2-phenyl-3-hydroxy-2,3-dihydrobenzofuran derivatives IIa-c exhibit $J_{cis} > J_{trans}$, and also, a selective lowering of J_{trans} in the more electronegative acyl derivatives, findings which appear to contradict Zalkow's hypothesis.

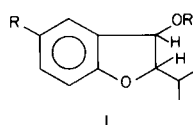
The isomeric alcohols IIa are formed on irradiation of *o*-benzyloxybenzaldehyde (9,10). One of the isomers was obtained crystalline, m.p. 126-127°, by column chromatography; the other was isolated as an oil by preparative glc, and analyzed as the crystalline 3,5-dinitrobenzoate derivative, m.p. 118-119° dec. Both provided 2-phenylbenzofuran on acid catalyzed dehydration. The previous *cis* assignment to the crystalline isomer is herein confirmed by nmr spectral data, presented in Table I, on the alcohols IIa, their acetates IIb, and 3,5-dinitrobenzoates IIc.

TABLE I

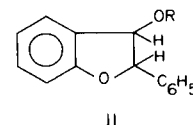
Compound	NMR Spectra of the Products (a)	
	τ (multiplicity) (J, Hz)	
	2H, 3H (b)	OR
IIa, <i>cis</i>	4.52, 4.84 (AB) (6.2)	8.6 (s) (c)
<i>trans</i>	4.53, 4.82 (AX) (3.8)	7.5 (s) (c)
IIb, <i>cis</i>	3.64, 4.39 (AX) (6.5)	8.47 (s)
<i>trans</i>	3.97, 4.41 (AX) (2.1)	7.96 (s)
IIc, <i>cis</i>	3.35, 4.15 (AX) (6.5)	1.37 (d) (2.0) (d)
		0.94 (t) (2.0) (e)
<i>trans</i>	3.54, 4.17 (AX) (2.0)	0.83 (s)

(a) Obtained in deuteriochloroform on a Varian A-60 Spectrometer. (b) Individual assignments were not made. (c) 10% solution. (d) *ortho*-Hs. (e) *para*-H.

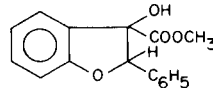
STRUCTURES



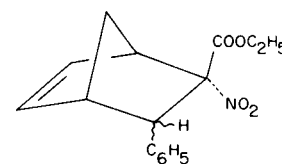
- a) R = Br, R' = H
 b) R = Br, R' = COCH₃
 c) R = COCH₃, R' = H
 d) R = R' = COCH₃



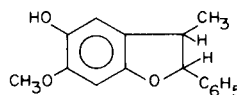
- a) R = H
 b) R = COCH₃
 c) R = COC₆H₃(3,5-diNO₂)



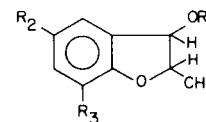
III



IV



V



VI

- R₁ = H or COCH₃
 R₂ = H or NO₂
 R₃ = H, NO₂, NMe₂, or NMe₃

First, the hydroxyl resonance of the crystalline isomer appears at higher field relative to that of the oil by one ppm (both in 10% solution), which may be attributed to a shielding effect by the adjacent *cis*-phenyl group. This effect, which is well-documented by studies on a series of norbornanols, has been ascribed to OH- π hydrogen bonding by Kleinfelter (11).

Secondly, the methyl hydrogens of the corresponding *cis*-acetate resonate at abnormally high field at τ 8.47, clearly indicative of residence in the shielding cone of the adjacent phenyl group. The difference in chemical shifts between the methyl resonances of the isomeric acetates is one half ppm. This effect has also been observed on the carbomethoxy resonances of the isomeric dihydrobenzofurans III (10), which is a closely analogous system, as

well as on the carboethoxy resonances of the isomeric norbornene derivatives of structure IV (12).

The spectra of the isomeric 3,5-dinitrobenzoates (3,5-DNBs) IIc uniquely substantiate the assignments. The aromatic 3,5-DNB hydrogens of the *trans* isomer appear as a singlet at τ 0.83. However, in the *cis* isomer, the *ortho*-hydrogens (a doublet) are centered at τ 1.37, which reflects shielding of one half ppm relative to the *trans* isomer, whereas the *para*-hydrogen (a triplet) is centered at τ 0.94. This pattern nicely conforms to the expected spatial relationship between these hydrogens and the shielding cone of the adjacent phenyl group. The same behavior has been noted with the isomeric 3,5-DNBs of structure III (13); and Kleinfelter has observed analogous results with phenylnorbornyl *p*-nitrobenzoates and tosylates (14).

Thus, our stereochemical assignments are based on these pronounced shielding effects, which we ascribe to a *cis* relationship of the C_3 -substituents with the C_2 -phenyl group in compounds II. This conclusion is structurally reasonable (15) and in accord with observations on the isomeric 2-phenyl-3-methyl-2,3-dihydrobenzofuran derivatives V, wherein the C_3 -methyl resonance appears at τ 8.63 in the *trans* isomer, obtusafuran, as compared to 9.26 in the *cis*. The latter stereochemical assignments were established by base-catalyzed isomerization of *cis* V, derived from the corresponding benzofuran by catalytic hydrogenation, into the *trans* isomer (16).

The results indicate that isopropyl and phenyl substituents at C_2 exert significantly different influences on $J_{2,3}$ in the 3-hydroxy-2,3-dihydrobenzofuran system. We find that $J_{2,3}$ is 6.2 Hz for *cis* IIa and 3.8 for the *trans* isomer; whereas Zalkow and Ghosal report coupling constants of 6 Hz for the *trans* and 4 for the *cis* derivatives in the corresponding 2-isopropyl derivatives I (3,8). Recently, Mertes and Powers have utilized X-ray diffraction analysis (17) to determine that 2-methyl-3-hydroxy (and acetoxy)-2,3-dihydrobenzofuran derivatives VI exhibit $J_{2,3}$ of 6 Hz in the *cis* ($R_1 = \text{H}$ or COCH_3) and 2 Hz in the *trans* isomers ($R_1 = \text{COCH}_3$), in close correspondence with our findings on the 2-phenyl derivatives II. Thus, the coupling constants of the 2-isopropyl derivatives I (3,8) are unique in this series of 3-hydroxy-2,3-dihydrobenzofurans, which clearly limits applicability of the electronegativity effect in these systems. On the other hand, the findings that $J_{trans} > J_{cis}$ in the 2-isopropyl case and that $J_{cis} = J_{trans}$ in the case of isomers V (16), indicate that caution must be exercised in utilizing the relative magnitude of these coupling constants in assigning stereochemistry of 2,3-dihydrobenzofurans.

EXPERIMENTAL (18)

cis- and *trans*-2-Phenyl-3-hydroxy-2,3-dihydrobenzofurans (IIa).

Irradiation of *o*-benzyloxybenzaldehyde (1-2% solutions in *t*-butyl alcohol) was carried out with a Hanovia 450-W medium pressure lamp and Pyrex filter, as previously described (9). The crude photo-product (in benzene) was applied to a column of Mallinckrodt SilicAr (200-325 mesh). Elution with a 9:1 benzene-ether mixture (v/v) effected a partial separation of the isomers, which was monitored by gas-liquid chromatography (glc) with a column of 3% (w/w) Versamid 900 (available from Varian Aerograph) on acid-washed Chromosorb W (available from Hewlett-Packard). The early fractions were rich in the *cis* isomer, which was purified by crystallization from benzene-hexane mixtures. The gross structure of this isomer, m.p. 126-127°, was secured by its spectral properties, and dehydration to 2-phenylbenzofuran, as previously described (9).

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.3; H, 5.7. Found: C, 79.5; H, 5.8. Molecular weight, Calcd.: 212. Found: 212 (mass spec.).

The *trans* isomer could not be induced to crystallize. However, a pure sample was obtained by preparative glc and utilized for spectral determinations and dehydration to 2-phenylbenzofuran. Elemental analysis was conducted on the crystalline 3,5-dinitrobenzoate derivative (see below).

Dehydration of *trans* IIa to 2-Phenylbenzofuran.

An ether solution (6 ml.) of *trans* IIa (62 mg.), thionyl chloride (0.2 ml.), and pyridine (0.4 ml.) was allowed to stand for 3 days, after which time it was poured onto ice-water and extracted with ether. The combined ether layers were washed, in turn, with dilute aqueous solutions of hydrochloric acid and sodium bicarbonate, dried over solid sodium sulfate, and concentrated to afford a solid mass. 2-Phenylbenzofuran (25 mg.), m.p. 120-121°, identical with authentic material (19) was obtained on recrystallization from 95% ethanol.

cis- and *trans*-2-Phenyl-3-acetoxy-2,3-dihydrobenzofurans (IIb).

A pyridine solution (2 ml.) of *cis* IIa (36 mg.) and acetyl chloride (0.1 ml.) was heated for 30 minutes at 85° (oil bath), allowed to stand overnight at room temperature, poured onto ice-water, and extracted with benzene. The benzene layers were washed, dried, and concentrated, as described for the above dehydration, and the crude acetate was distilled in a sublimation apparatus at 40° (0.1 mm.) to yield a pale yellow oil (35 mg.), which crystallized on standing. Several recrystallizations from hexane provided a pure sample of *cis* acetate IIb, m.p. 62-63°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.6. Found: C, 75.2; H, 5.5.

The *trans* acetate IIb, similarly prepared from *trans* IIa, could not be induced to crystallize. However, its identity was insured by a comparison of its spectral properties with those of the corresponding *cis* isomer.

cis- and *trans*-2-Phenyl-3-[3,5-dinitrobenzoyloxy]-2,3-dihydrobenzofurans (IIc).

A pyridine solution (5 ml.) of *cis* IIa (100 mg.) and 3,5-dinitrobenzoyl chloride (230 mg.), freshly crystallized from heptane, was allowed to stand overnight at room temperature and was, subsequently, warmed on a steam bath with swirling for 5 minutes. After work-up, as described for the acetates, the crude product was obtained crystalline on trituration with ether and was recrystallized from benzene-hexane to afford *cis*-3,5-dinitrobenzoate IIc

(120 mg.), m.p. 155-156°.

The *trans*-3,5-dinitrobenzoate IIc, m.p. 118-119°, was obtained similarly from *trans* IIa.

Anal. Calcd. for C₂₁H₁₄N₂O₇: C, 62.1; H, 3.5; N, 6.9. Found for *cis* IIc: C, 62.2; H, 3.4; N, 6.9; Found for *trans* IIc: C, 62.0; H, 3.6; N, 7.0.

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(1) Acknowledgment is made to the donors of the Petroleum Research Foundation, administered by the American Chemical Society for partial support of this research.

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(15) Reversal of these assignments would require selective shielding of the C₃-substituents which are *trans* to the C₂-phenyl group. However, since the C₂-phenyl is most favorably situated in an almost perpendicular relationship with the dihydrobenzofuran ring, as indicated by space-filling molecular models, this would require, on the average, a closer proximity of the C₂-phenyl with the *trans*-substituent at C₃ than the *cis*, a situation which is considered highly unrealistic. The possibility that the two aryl moieties in combination selectively shield the *trans*-C₃-substituent is also considered unreasonable.

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Received June 15, 1970

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