# Chemical and Nuclear Magnetic Resonance Studies
# of 3,3-Diphenyltetrahydrofuran Derivatives (1)

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Pyrolytic cyclization of α- and β-methadol methiodides afforded *cis* and *trans* isomers of 2-ethyl-3,3-diphenyl-5-methyltetrahydrofuran, respectively. Catalytic hydrogenation of 2-ethylidene-3,3-diphenyl-5-methyltetrahydrofuran yielded the *cis* and *trans* isomers in a 2:1 ratio. The nmr spectra of these and structurally related compounds have been analyzed in terms of a half-chair conformation for 2-ethyl-5-methyl, 2-ethyl, and 5-methyl derivatives. An envelope conformation has been suggested for the compounds containing a double bond at C-2.

In connection with a study (3) on the stereochemical determination of methadol diastereomers (Ia, Ib), we have investigated the nmr spectra (4) of isomeric tetrahydrofuran (THF) derivatives (IIIa, IIIb) arising from the pyrolysis of the corresponding methiodides (IIa, IIb) and from the catalytic hydrogenation of ethylidene compound IV.
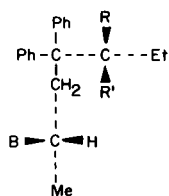

la R = H, R' = OH, B = NMe$_2$
lb R = OH, R' = H, B = NMe$_2$
lla R = H, R' = OH, B = ÑMe$_3$ I⁻
llb R = OH, R' = H, B = ÑMe$_3$ I⁻
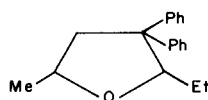
IIIa *cis*-Et:Me
IIIb *trans*-Et:Me

Easton, *et al.* (5) have reported that pyrolysis of racemic methadone methiodide (V) afforded compound IV. Evidence subsequently was obtained that cyclization proceeded *via* an $S_N 2$ inversion rather than through an alkene intermediate by using optically active V (6). Other examples (7) involving stereospecific cyclization under Hoffmann elimination conditions also support the idea that the formation of IV is associated with inversion at the asymmetric center.
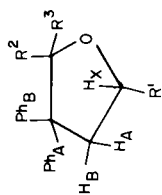

IV

V
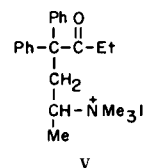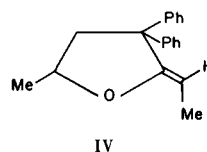
The stereospecific nature of the cyclization reaction suggested that pyrolysis of racemic methadol methiodide diastereomers should proceed stereospecifically to yield THF derivatives whose stereochemistries can be deduced from the known (3) relative configurations of IIa and IIb. Accordingly, pyrolysis of racemic IIa and IIb afforded IIIa and IIIb, respectively. It is noteworthy that a single isomer was produced in each case, thus confirming the stereospecificity of the reaction.

Additional evidence corroborating the preceding assignments was obtained from catalytic hydrogenation of IV, where a mixture of IIIa and IIIb was produced in a 2:1 ratio (3). A Stuart-Briegleb model of IV reveals that the face of the molecule opposite to that possessing the 5-methyl group is less hindered and consequently should be more accessible to the hydrogenation catalyst. The preponderance of the *cis* isomer (IIIa) therefore is consistent with this observation.

Chemical Shifts of Aromatic Protons.

The chemical shift data of IIIa, IIIb and several structurally related compounds are compiled in Table I. The spectrum of IIIa showed two resonances of equal

TABLE I

Chemical Shifts for Protons in Substituted 3,3-Diphenyltetrahydrofuran Derivatives

Compound	R^1	R^2	R^3	Ph$_A$	Ph$_B$	H$_A$	H$_B$	H$_X$	R^1	R^2	R^3
								Ppm (a)			
IIIa	CH$_3$	H	C$_2$H$_5$	7.31 s (b)	7.24 m	2.49 q	2.33 q	4.0 m	1.39 d	4.55 m	1.0 m
IIIb	CH$_3$	C$_2$H$_5$	H	7.30 m	7.21 s	2.16 q	3.13 q	4.5 m	1.18 d	1.0 s	4.5 m
VIII(c)	H	H	C$_2$H$_5$	7.35 s	7.23 m	2.9 m	2.3 m	4.0 m	4.0 m	4.55 m	1.0 m
VII(c)	CH$_3$	H	H	7.22 s / 7.18 s		2.24 q	2.67 q	4.2 m	1.25 d	4.57 d	4.17 d
IV(d)	CH$_3$	=CH-CH$_3$		7.22 s / 7.11 s		2.39 (f)	2.48 (f)	4.0 m	1.33 d	1.65 d (g) / 3.88 q (h)	
IX(e)	CH$_3$	=NH		7.30 s / 7.20 s		2.57 q	2.81 q	4.3 m	1.38 d	6.84 s (=NH)	
X(e)	CH$_3$	=O		7.28 s / 7.23 s		2.54 q	3.03 q	4.4 m	1.34 d	---	

(a) The ppm values for all protons displaying first order spin-spin coupling were calculated according to the method of E. Garbisch, *J. Chem. Ed.*, **45**, 402 (1968). (b) The symbols s, d, q and m indicate that the absorption is seen as a singlet, doublet, quartet or multiplet, respectively. (c) N. R. Easton, C. A. Lukach, V. B. Fish and P. N. Craig, *J. Am. Chem. Soc.*, **75**, 4731 (1953). (d) N. R. Easton, C. A. Lukach, S. J. Nelson and V. B. Fish, *ibid.*, **80**, 2519 (1958). (e) F. Wilson, *J. Chem. Soc.*, 1993 (1948). (f) H$_A$ and H$_B$ appear as an abnormal AB portion of an ABX pattern. (g) Methyl resonance. (h) Vinyl proton resonance.

TABLE II

Coupling Constants for Protons
in Substituted 3,3-Diphenyltetrahydrofurans

Compound	J_{AB} cps	J_{AX} cps	J_{BX} cps
IIIa (a)	12.0	10.2	5.8
IIIb	13.0	6.0	8.0
VII (b)	12.0	8.5	6.3
IV (c)	12.2 (d)	10.7 (d)	4.5 (d)
IX	12.3	10.6	4.1
X	12.9	10.1	4.3

(a) J_{MeX} = 6.0-6.5 cps for all compounds. (b) J_{yz} = 8.5 cps; J_{BZ} = 1.0 cps. (c) For $CH_3CH=$, J_{MeH} = 7 cps. (d) Calculated according to the method of E. Garbisch, *J. Chem. Ed.*, **45**, 402 (1968).

area in the aromatic region; a narrow band at 7.31 ppm and a multiplet centered at 7.24 ppm. Generally, protons attached to unhindered, alkyl-substituted benzenes display identical or very similar chemical shifts (8). The fact that the protons on one of the phenyl groups appear as a multiplet may be interpreted as a consequence of steric factors. Examination of a Stuart-Briegleb model of IIIa reveals that the ethyl group hinders the rotation of Ph_A. The probable conformation of the phenyl groups are as shown in projection formula VIa.

VIa   VIb
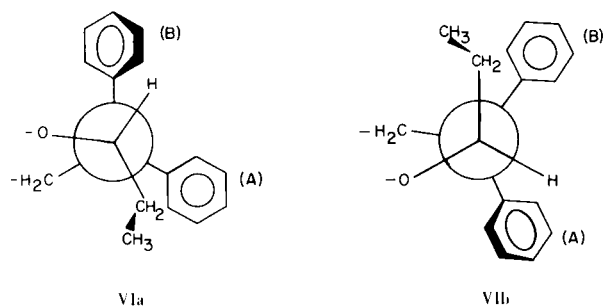
The *ortho* protons of Ph_A lie in the shielding zones of Ph_B and the ethyl group. Consequently, the chemical shift of the ortho protons differ from other protons on the aromatic ring and Ph_A is seen as a multiplet. Similarly, the spectrum of the *trans* isomer (IIIb) also shows a narrow band and a multiplet. In this case the multiplet is assigned to pH_B since it is *cis* to the ethyl group and thus is sterically hindered

(see projection formula VIb). Further evidence implicating the vicinal ethyl group as a cause of the aromatic multiplicity was obtained from the nmr spectra of VII and VIII. Compound VII, which does not contain the ethyl group, displays two singlets, each integrating for an equal number of protons. On the other hand, the compound (VIII) possessing an ethyl group and no methyl group contained aromatic resonances which are analogous to those displayed by IIIa and IIIb. Moreover, molecular models suggest that sp^2 hydridization at the C-2 position (compounds IV, IX and X) will not hinder rotation of the phenyl groups. The fact that the spectra of these compounds possess two sharp aromatic peaks is consistent with this interpretation.

VII R = Me, R' = H   IX R = NH
VIII R = H, R' = Et   X R = O

Chemical Shifts of Ethyl and Ethylidene Groups.

In compounds IIIa, IIIb, and VIII, the methylene protons attached to the ethyl group resonate in the vicinity of 1 ppm. Generally, in the absence of anisotropic effects, protons of this type would be expected to absorb near 2 ppm (9). Molecular models reveal that a minimum amount of steric hindrance occurs when the methylene protons are located in the shielding zone (10) of the aromatic ring as depicted in formulas VIa and VIb.

Of particular interest is the configuration of the ethylidene group in IV. If the methyl group were *trans* to the ring oxygen, one would expect these protons to be highly shielded, since it would be above the plane of one of the phenyl rings. However, the chemical shift (1.65 ppm) for this group is in the normal range (9) for a methyl group attached to a double bond, while the olefinic proton resonance (3.88 ppm) is seen at unusually high field. The fact that the phenyl groups obviously are shielding the olefinic proton and not the methyl group, signifies that this group is *cis* to the ring oxygen.

Chemical Shifts of H_A and H_B.

As a consequence of the conformational restraint imposed upon the aromatic ring that is *cis* to the ethyl substituent, the C-4 proton which is also *cis* to the aforementioned groups should lie approximately in the plane of the constrained phenyl ring and thus experience a paramagnetic shift (10). However, the C-4 proton which bears a *trans* relationship should lie in the periphery of the

shielding zone of the less hindered phenyl ring (see conformational formulas XI and XII). On this basis, the lower field absorption has been assigned to the C-4 proton which is cis to the ethyl substituent. Thus, in compounds IIIa and VIII, H_A is located downfield relative to H_B and, for the same reason, H_B in the trans isomer (IIIb) is assigned to the downfield quartet. It can be noted that the difference in chemical shift between H_A and H_B is

considerably greater in IIIb (when compared to IIIa). This is attributed to the 5-methyl group which shields H_A (11). In the cis isomer (IIIa), the net effect would then be that the deshielding of H_A by Ph_A is partially offset by the shielding of the 5-methyl group. In IIIb, however, H_B is deshielded by Ph_B, while H_A is shielded by the methyl group, thus giving rise to the large chemical shift difference between H_A and H_B. The fact that the compound lacking the 5-methyl group (VIII) has a chemical shift difference (Δ ppm = 0.6) for the C-4 protons which lies between those found for IIIa (Δ ppm = 0.16) and IIIb (Δ ppm = 0.94), lends additional support for the assignment of these protons.

The anisotropic influence of the phenyl groups on the chemical shifts of H_A and H_B might be expected to be less important in compounds (IV, VII, IX, X) that do not contain the ethyl substituent, inasmuch as the aromatic rings are not hindered to the same extent as in IIIa, IIIb, and VIII. The shielding effect of the 5-methyl group therefore should be of primary importance and H_A consequently should be located upfield relative to H_B. This indeed has been found to be the case. Additional evidence based on coupling constants presented in the latter portion of the discussion supports this assignment.

Chemical Shifts of C-2 and C-5 Protons.

The C-2 and C-5 protons in IIIa were assigned to the multiplets centered at 4.55 and 4.0 ppm, respectively, and were verified by decoupling experiments. It appears likely that this substantial chemical shift difference can be in part explained by conformation XIa where Ph_B is oriented such that it shields H_X while deshielding the C-2 proton. In view of the similar chemical shifts for protons in IIIa and those in VIII, the same assignment was made in the latter.


XIa

cis

XIb

XIIa

XIIb
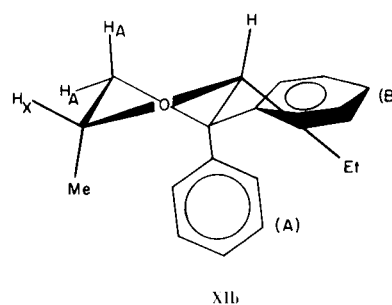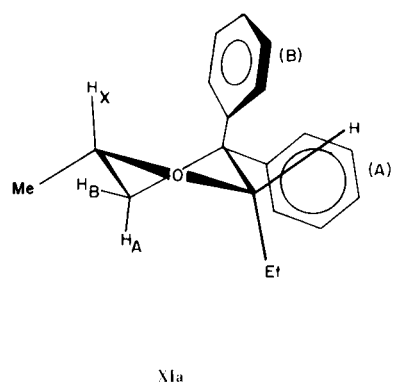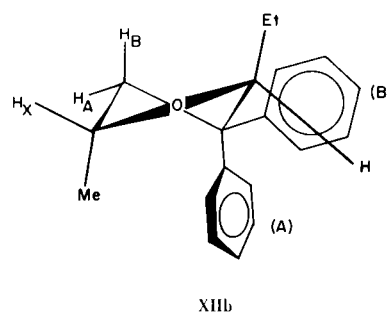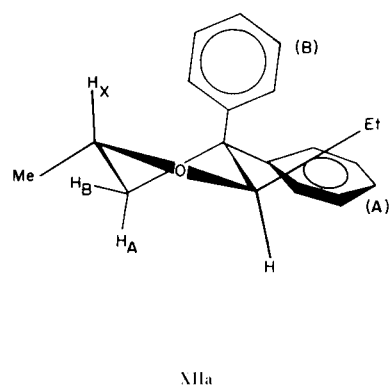
trans

In the *trans* isomer (IIIb) the C-2 and C-5 protons both appear as multiplets centered at approximately 4.5 ppm. The downfield shift for H_X (when compared to IIIa) is attributed to deshielding by Ph_B as depicted in conformational representation XII.

Compound VII shows two doublets which are assigned to the two protons located at C-2. A probable conformation of this molecule is illustrated by formula XIII where it can be seen that one of the rings, the methyl group, and H_Z are in a *quasi*-equatorial conformation. Some deshielding and/or shielding of the C-2 protons may arise from the vicinal phenyl groups.

XIII
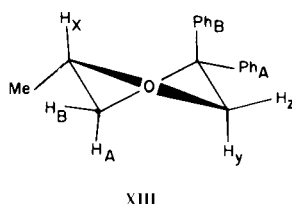
However, an assignment on this basis is difficult because of the relatively free rotation of these groups. A substituent which may play a more predictable role is the methyl group which conceivably may deshield (12) H_Z. The fact that the quartet corresponding to H_B and the doublet assigned to H_Z are both split by 1 cps indicates the presence of mutual long range coupling (13). This suggests that these protons are in a *quasi*-equatorial conformation and provides additional support for the assignment of the lower field doublet to H_Z. The H_X absorption for VIII and for the compounds (IV, IX, X) containing an sp^2 carbon atom show absorptions for this proton in the range of 4.0-4.4 ppm.

Chemical Shift of the 5-Methyl Group.

The difference in chemical shift for the 5-methyl group in IIIa and IIIb represents approximately 0.2 ppm. This most likely is related to the difference in orientation of Ph_A and Ph_B which was described earlier to explain chemical shifts for other protons. The 5-methyl group in IIIa is held in the deshielding zone of Ph_A, while in IIIb it is located in the shielding region (see XI and XII). In VII, the methyl absorption is of an intermediate value, which is what would be expected if there were little restriction in the rotation of Ph_A and Ph_B.

Compounds (IV, IX, X) possessing a double bond at C-2 show the 5-methyl absorption at 1.3-1.4 ppm. The shift to lower field (when compared to H_X in VII) might be due to increased inductive deshielding and to the paramagnetic anisotropy of the double bond.

Coupling Constants.

The coupling constants listed in Table II were determined in order to obtain additional information on the conformational preferences for these compounds. In our interpretation of the data, it was assumed that the most stable conformation in compounds IIIa, IIIb, VII and VIII approximates the half-chair geometry, since existing evidence suggests this to be the case for tetrahydrofuran and pyrrolidine (14). Two pseudorotated half-chair conformations of IIIa are depicted by XIa and XIb. The conformational equilibrium should favor XIa if gauche ethyl-diphenyl and *quasi*-diaxial 5-Me:Ph interactions in XIb are considered to exert a formidable destabilizing influence. The dihedral angles for H_AH_X and for H_BH_X in XIa have been estimated from Dreiding models to be 160° and 30°. This corresponds to calculated (15) values for J_{AX} and J_{BX} of 9.5 and 6 cps, respectively. Conformation XIb has been estimated to have dihedral angles for H_AH_X and H_BH_X and 100° and 20°, which corresponds to calculated (15) coupling constants of 1 and 7 cps, respectively. While these values are approximations (16) only, the close agreement with the observed coupling constants implicates XIa as the preponderant contributor. The estimated coupling constants for XIIa and XIIb are identical to XIa and XIb, respectively, because they bear the same dihedral relationship. In this case, however, the observed coupling constants are roughly equivalent to the average of both conformers. Conformation XIIa possesses a gauche ethyl-diphenyl interaction, whereas XIIb contains Et:Ph and *quasi*-diaxial 5-Me:Ph interactions. It is conceivable that the additional Et:Ph interaction in XIIa compensates for the *quasi*-diaxial interaction in XIIb so that both conformers possess comparable energies.

The coupling constants for VII are consistent with conformation XIII as the major contributor. This is reasonable in view of the favorable *quasi*-equatorial orientations of Ph_A and the methyl group.

The compounds (IV, IX, X) containing an sp^2 carbon atom all have very similar coupling constants. The difference, $\Delta J = J_{AX}-J_{BX}$, is greater than that observed for diphenyltetrahydrofurans lacking a double bond. The coupling can be explained on the basis of a conformation in which atoms attached to the 3-,4-, and 5-positions of the tetrahydrofuran ring are partially staggered. A

XIV
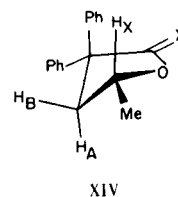
probable conformation for these compounds is the envelope form (XIV), since partial sp^2 character between the ring oxygen and C-2 would be expected to maintain atoms 1,2,3 and 5 in a single plane. Recently, Johnson, et al. (17) have interpreted the nmr spectra of a series of substituted butyrolactones in terms of an envelope conformation.

EXPERIMENTAL

Nmr spectra were obtained with a Varian Associates A-60 spectrometer. Tetramethylsilane (1%) was employed as an internal reference standard in deuteriochloroform at a solute concentration of 15% (w/v). Chemical shifts are considered to be accurate to ±0.02 ppm. The spin-spin coupling constants were determined at a 100 cps. sweep width and are within ±0.2 of the mean value reported. The probe temperature was 38 ± 1°. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside. New York. Melting points were determined on a Thomas-Hoover apparatus and are corrected.

cis-2-Ethyl-3,3-diphenyl-5-methyltetrahydrofuran.

Racemic α-methadol methiodide (18) (1.09 g., 0.0024 mole) was heated with a free flame in a Claisen flask under 15 mm. pressure. The distillate was dissolved in ether, washed with 1 N hydrochloric acid, and then with water. The solvent was removed *in vacuo* and the residue was crystallized from 95% ethanol to yield 0.18 g. (28%) of product, m.p. 90-92° (lit. (18) 89-90°).

(±)-β-Methadol Methiodide.

A mixture of (±)-β-methadol (19) (2.0 g., 0.0065 mole) and excess methyl iodide in absolute ethanol was refluxed for six hours. The reaction mixture was then refrigerated and the crystalline product (2.77 g.) was filtered from the mother liquor. Recrystallization from acetone afforded crystals, m.p. 189-191°.

Anal. Calcd. for C$_{22}$H$_{32}$INO: C, 58.27; H, 7.11; N, 3.09. Found: C, 58.21; H, 7.17; N, 3.34.

trans-2-Ethyl-3,3-diphenyl-5-methyltetrahydrofuran.

Racemic β-methadol methiodide (1.04 g., 0.0023 mole) was pyrolyzed under conditions identical to those employed for the *cis*-isomer. The oily product was dissolved in ether and extracted with 1 N hydrochloric acid followed by washing with water. The ether solvent was then removed *in vacuo* and the residue chromatographed on neutral alumina with cyclohexane. Recrystallization from ethanol afforded 0.12 g. (19% yield) of product, m.p. 61-63°.

Anal. Calcd. for C$_{19}$H$_{22}$O: C, 85.67; H, 8.33. Found: C, 85.65; H, 8.47.

Catalytic Hydrogenation of 2-Ethylidene-3,3-diphenyl-5-methyltetrahydrofuran.

A mixture of 0.5 g. (0.0019 mole) of IV and 0.3 g. of 10% palladium-on-carbon was placed in 30 ml. of absolute ethanol and shaken at an initial hydrogen pressure of 57 psi until the theoretical amount of hydrogen was absorbed. The mixture was filtered and

the solvent removed *in vacuo* to yield 0.52 g. of crude product. The ratio of chromatographed products (IIIa:IIIb) was found to be 2:1 by examination of the nmr peak height ratios of the 5-methyl substituent (20).

Acknowledgment.

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