Carbon-13 and Proton Magnetic Resonance Spectra of 2,4-Disubstituted 3,3-Diphenyltetrahydrofurans Derived From Isomethadone and Isomethadol

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Proton and carbon-13 nmr spectra for *cis*- and *trans*-2-ethyl-3,3-diphenyl-4-methyltetrahydrofurans and 2-ethylidene-3,3-diphenyl-4-methyltetrahydrofuran, derived from the pyrolysis of the quaternary ammonium salts of the diastereomeric isomethadols and isomethadone, respectively, are reported. ^1H and ^{13}C chemical shifts and ^1H-^1H coupling constants have been assigned in each case. The isomeric teterahydrofurans have been analyzed in terms of a half-chair conformation, and an envelope conformation for the ethylidene derivative.

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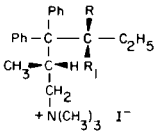
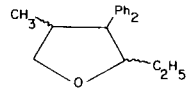
The thermal decomposition of quaternary ammonium salts of amino alcohols has been reported to yield cyclic ethers rather than olefins (1). A number of examples leading to the production of epoxides or larger cyclic ethers have been cited, although in several of these the reaction occurred in poor yields and gave a mixture of products. This report deals with the stereospecific decomposition of the isomethadol methiodide diastereomers (**1** and **2**) and the conformational analysis of the tetrahydrofuran products (**3** and **4**) using proton (^1H) and carbon-13 (^{13}C) nmr.



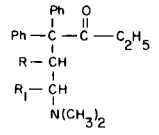
1: R=H; R_1=OH

2: R=OH; R_1=H



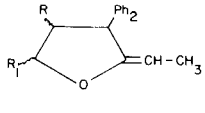
3: cis-C_2H_5:CH_3

4: trans-C_2H_5:CH_3



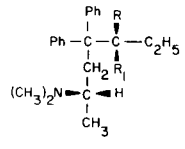
5: R=H; R_1=CH_3

6: R=CH_3; R_1=H



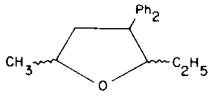
7: R=H; R_1=CH_3

8: R=CH_3; R_1=H



9: R=H; R_1=OH

10: R=OH; R_1=H



11: cis-C_2H_5:CH_3

12: trans-C_2H_5:CH_3

Easton, *et al.* (2), have reported that pyrolysis of racemic methadone (**5**) and isomethadone (**6**) methiodides afforded the tetrahydrofurans, **7** and **8**, respectively. Evidence subsequently was obtained that cyclization proceeded via an S_N2 inversion rather than through an alkene intermediate by using optically active **5** and **6** (3). Other examples (1) involving stereospecific cyclization under Hofmann elimination conditions also support the idea that formation of **7** is associated with inversion at the asymmetric center.

The stereospecific nature of the cyclization reaction prompted Portoghese and Williams (4) to investigate the pyrolysis of racemic methadol methiodide diastereomers. The results of the study revealed that the α-diastereomer (**9**) stereospecifically produced the *cis*-tetrahydrofuran (**11**) while the β-diastereomer (**10**) produced the *trans*-tetrahydrofuran (**12**). They were able to deduce the stereochemistries of the tetrahydrofurans (**11** and **12**) from the known relative configurations of **9** and **10**.

Using these studies as a basis, we proceeded to pyrolyze the isomethadol methiodide diastereomers (**1** and **2**), and to examine the structure of the tetrahydrofuran products. The stereochemistries of the tetrahydrofurans (**3** and **4**) were then deduced from the corresponding known relative configurations of **1** and **2** (5). In each case, only a single isomer was produced thus confirming the stereospecificity of the reaction.

^1H-Nmr Analysis.

^1H-^1H Coupling Constants.

The conformation of the 5-membered tetrahydrofuran ring is usually discussed in terms of an envelope or half-chair shape. These forms undergo rapid pseudorotation,

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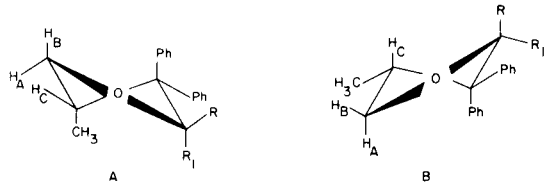
Figure 1



A B

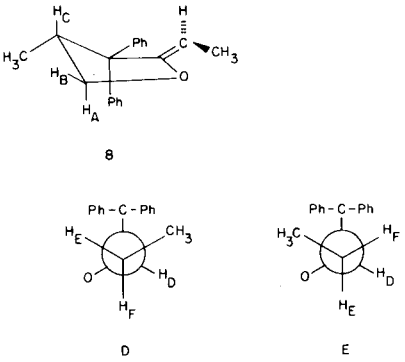
3: R=H, R_1=C_2H_5

4: R=C_2H_5, R_1=H

but it is generally agreed that the half-chair is the favored conformation (6). However, for the tetrahydrofurans reported here, the presence of bulky groups on adjacent carbons imposes steric constraints that reduce the mobility of the ring system into two pseudo-rotated half-chair conformations depicted by A and B (Figure 1). The H_ACCH_C and H_BCCH_C dihedral angles were estimated from Drieding models to be between 90-100° and 30-20° respectively, corresponding to calculated vicinal coupling constants of $J_{H_AH_C}$ = 0-0.4 Hz and $J_{H_BH_C}$ = 9.6-11.3 Hz. Similar estimates for conformer B gave dihedral angles of 140-150° and 20-30°, corresponding to calculated vicinal coupling constants of $J_{H_AH_C}$ = 7.5-9.5 Hz and $J_{H_BH_C}$ = 11.3-9.6 Hz. The calculations were based on the Karplus relationship (7): $J_{vic} = k\cos^2\Phi$, in which Φ is the dihedral angle and k is a constant whose value depends on the substituents on the C-C group (8). The values of k for $0° \leq \Theta \leq 90°$ and $90° \leq \Theta \leq 180°$ in this O-$CH_AH_BCH_C$-C system were calculated by using corresponding values for J_{gauche} (Θ = 60°) = 3.2 Hz and J_{trans} (Θ = 180°) = 12.7 Hz, which were in turn calculated from empirical relationships described by Abraham and Gatti (8). These relationships which relate ^1H-^1H vicinal coupling constants with substituent electronegativities have been shown to give good results (9,10).

The calculated J_{gauche} and J_{trans} values used in our calculations are consistent with values obtained experimentally from the model compound *trans*-2,3-dimethyl-1,4-dioxan (11). The observed $J_{H_AH_C}$ and $J_{H_BH_C}$ in both **3** and **4** (Table 1) agree with the expected limits for conformer B, and differ greatly from the set of values expected for conformer A. Conformer B, therefore, appears to be the preferred conformation contributor for **3** and **4**. The coupling constants observed in **8** are also consistent with conformer B being the major contributor. Because of the exocyclic double bond, the ethylidene derivative **8** is expected to adopt an envelope conformation (4), in which atoms 1,2,3, and 5 are maintained in the same plane. Such a conformation has been attributed to some δ-butyrolactone analogs in which the ring atoms have the same hyridization as in compound **8** (12). The H_AH_C and H_BH_C dihedral angles in the envelope conformation are apparently very similar to those in the pseudorotated half-chair conformation described above as is evidenced by the similarity of the vicinal H_A, H_B, and H_C coupling constants (Table 1) in these two groups of compounds.

Figure 2



8

C D E

Information on the conformation of the 2-ethyl substituent in **3** and **4** was obtained from the vicinal coupling constants of the C-2 methine (H_D), and the two ethyl methylene protons (H_E,H_F) (Table 1). The ethyl group can exist in three possible conformations (**C,D,E**) (Figure 2), obtained by rotation around the CH-CH_2CH_3 bond. The large $J_{H_DH_F}$ and small $J_{H_DH_E}$ values observed in the spectra of both compounds indicate that conformer **C** is the predominant conformer. This predominance is slightly more prevalent in isomer **3**. Assignment of the downfield multiplet to H_F and the upfield multiplet to H_E in compound **3** is consistent with the expected preferential deshielding effect that the ether oxygen will exercise on the H_F proton which is *gauche* to it over the H_E proton which is *trans*. The preferred conformer **C** has the CH_3 of

Table 1

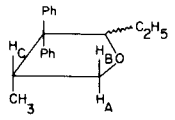
^1H-^1H-Coupling Constants for 2,4-Disubstituted 3,3-Diphenyltetrahydrofurans (a)

Compound No.	$J_{H_AH_B}$	$J_{H_AH_C}$	$J_{H_BH_C}$	$J_{H_DH_E}$	$J_{H_DH_F}$
3 *(cis)*	8.1	10.0	8.5	2.7	10.5
4 *(trans)*	8.1	9.8	8.1	3.6	8.4
8 (b)	8.0	10.6	8.0	—	—

(a) Coupling constants are in Hz, and are within ± 0.2 Hz of the mean value reported. (b) For CH_3CH = 7 Hz.

Table 2

^{1}H-Chemical Shifts for 2,4-Disubstituted-3,3-Diphenyltetrahydrofurans



Compound No.	2-Ethyl	4-Methyl	3,3-Diphenyl	2-H	H_A	H_B	H_C
3 *(cis)*	1.08 m (3H) 1.68 m (1H) 2.03 m (1H)	0.57 d	7.2 m	3.86 m	3.50 m	4.02 m	2.99 m
4 *(trans)*	1.0 m (5H)	0.57 d	7.2 m	4.56 m	3.43 m	4.02 m	2.86 m
8	1.82 d (3H) 4.32 q (1H	0.58 d	7.2 m	—	3.44 m	3.97 m	3.04 m

Table 3

^{13}C-Chemical Shifts (a) in 2,4-Disubstituted-3,3-diphenyltetrahydrofurans

Compound No.	C-2	C-3	C-4	C-5	(C-2)*C*	CH_2CH_3	(C-4)CH_3	(C=CH)CH_3	Aromatic Protons
3	91.1	59.9	41.4	71.7	22.5	12.0 (b)	12.0 (b)	—	143.5 (C-1′), 140.6 (C-1′′), 131.4, 128.4, 128.2, 127.3, 126.7, 126.0
4	88.7	60.7	37.1	72.7	26.9	10.9 (c)	12.9 (c)	—	144.4 (C-1′, C-1′′), 129.9, 129.1, 128.0, 127.5, 126.3, 126.1
8	161.6	60.4	39.6	72.1	94.7	—	11.1	10.1	143.4 (C-1′), 141.6 (C-1′′), 130.4, 128.7, 128.1, 127.3, 126.7, 126.6

(a) Spectral assignments were made by analogy. Chemical shifts are considered accurate to ± 0.05 ppm. (b) Only one peak was observed for these two carbons when the spectrum was obtained in deuteriochloroform solutions. The frequencies were resolved (δ = 11.8, 11.9 ppm) when the solvent was changed to DMSO-d_6. (c) Some uncertainty still exists about these two assignments.

the ethyl group pointing away from the tetrahydrofuran ring and *trans* to the bulky CPh_2.

^{1}H Chemical Shifts.

The stereochemistry of the isomeric tetrahydrofurans (**3** and **4**) was also confirmed from examination of the ^{1}H chemical shifts (Table 2). The major distinguishing spectral difference between **3** and **4** is the chemical shift of the methylene protons in the 2-ethyl substituent. These protons show resonances centered at 1.69 (1H) and 2.03 (1H) ppm in the *cis* isomer (**3**), whereas in the *trans* isomer (4), the two protons show a dramatic upfield shift and merge with the methyl protons to give a single 5H peak centered at 1.00 ppm. This upfield shift for both of the methylene protons in **4** is most probably a result of the anisotropic shielding by one of the neighboring phenyl rings. A molecular model of **4** in the half-chair conformation shows that when the ethyl group is in a quasi-axial orientation, both methylene protons are lying within the shielding zone of the *cis*-phenyl ring (Ph_B). When the ethyl group is quasi-equatorial, it is not subject to this effect. The measured chemical shifts are, therefore, compatible only with a quasi-axial ethyl group in **4**. On the other hand, in isomer **3** a quasi-equatorial ethyl group having the ring oxygen and one of the phenyl rings *gauche* is preferred, as indicated by the absence of any dramatic shielding in the ethyl protons. In this conformation, the methylene protons of the ethyl substituent experience different shielding and deshielding influences from the adjacent phenyl rings and the ether oxygen, and thus appear as separate ^{1}H multiplets.

H_A was assigned the higher field position since other studies (4) have shown that a tetrahydrofuran ring proton

cis to an adjacent methyl group is shielded by this methyl group.

^{1}H chemical shift measurements also provided us with information on the stereochemistry of the ethylidene group in **8**. In this compound, the ethylidene methyl protons have a chemical shift (δ = 1.80 ppm) in the normal range for an allylic methyl group, while the olefinic proton resonance (δ = 4.32 ppm) occurs at a considerably higher field than expected indicating shielding from the neighboring phenyl rings. The fact that the phenyl groups are shielding the olefinic proton and not the methyl group is evidence that the ethylidene group is *cis* with the ring oxygen.

^{13}C Chemical Shifts.

^{13}C chemical shift data (Table 3) provided additional confirmation for the previous conformational assignments for the two tetrahydrofuran isomers (**3,4**) and their ethylidene analog (**8**). It was thus observed that the C-2 and C-4 carbons in **3** and **4** differ, respectively, by 2.4 and 4.3 ppm, with the *trans* isomer (**4**) absorbing at higher fields. This observation is in accord with a quasi-axial ethyl group assignment for **4**, since axial substituents in saturated cyclic compounds are generally known to have a shielding effect on the α and γ-carbons when compared to their corresponding equatorial isomers (13). The shielding effect exercised by the quasi-axial methylene group on the C-4 carbon can be attributed (13) to steric polarization arising from non-bonded interactions of the closely neighboring atoms in these two groups that are in a *gauche* configuration with each other. This shielding is generally known as the γ-effect. The absence of such an interaction by C-4 in **3** is evidence that the methylene group in this isomer is in a quasi-equatorial configuration. The upfield shifts observed in **4** are somewhat smaller than those observed in cyclohexane derivatives. However, these shifts are considerably larger than those in the cyclopentanes indicating that the two molecules under consideration exist in conformations that are more puckered than the normal cyclopentane envelope conformation.

Chemical shifts for the methylene carbons of the 2-ethyl groups, in **3** and **4**, differ by 4.4 ppm in the opposite direction. The methylene carbon frequency is thus further upfield in the *cis* isomer (**3**) and is consistent with a conformation in which the ethyl group is in a quasi-equatorial prositon and *gauche* to both phenyl rings. In this conformation the methylene group in addition to experiencing two γ-*gauche* effects from the C-1′ and C-1′′ of the phenyl rings, is considerably more crowded sterically than the corresponding quasi-axial methylene carbon (14). It is therefore expected to absorb further upfield. The γ-*gauche* effect is also experienced by the two C-1′ and C-1′′ phenyl carbons in **3** as indicated by their smaller chemical shifts when compared to those of **4**.

The methyl carbon at C-4 has very similar chemical shifts in the tetrahydrofuran isomers (**3,4**), as well as in their ethylidene analog (**8**), indicating that it maintains the same quasi-equatorial conformation in all three compounds.

EXPERIMENTAL

The proton nmr spectra were obtained at 220 MHz using 0.4*M* deuterated benzene solutions with tetramethylsilane as internal standard, at ambient temperature of 23°. Coupling constants and chemical shift values were extracted directly from the spectra using first order analysis. Proton decoupled natural abundance carbon-13 nmr spectra were obtained at 15.1 MHz and 30° using 0.75*M* deuterated chloroform solutions with tetramethylsilane as an internal standard. Melting points were obtained using a Mel-Temp apparatus and are uncorrected.

β-(±)-Isomethadol Methiodide (**3**).

A mixture of *β*-(±)-isomethadol (5.0 g., 0.016 mole) and excess methyl iodide in 50 ml. of anhydrous ethyl acetate was refluxed for six hours. The reaction mixture was refrigerated overnight, and the crystalline precipitate was collected, yield 7 g. (96%). Recrystallization from acetone afforded a white product, m.p. 221-223°.

Anal. Calcd. for $C_{22}H_{23}INO$: C, 58.27; H, 7.11; N, 3.09. Found: C, 58.41; H, 6.99; N, 3.38.

trans-(±)-2-Ethyl-3,3-diphenyl-4-methyltetrahydrofuran (**4**).

The methiodide of *β*-(±)-isomethadol (4.0 g., 0.089 mole) was heated with a free flame in a Claisen flask under 15 mm pressure. The distillate was dissolved in ether, washed with dilute hydrochloric acid, and then water. The ether was removed *in vacuo*, and the oily residue was chromatographed on neutral alumina with cyclohexane. The solvent was stripped under reduced pressure to afford a waxy solid that was crystallized from 95% ethanol to yield 1.5 g. (26%) of product, m.p. 60-61°.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.67; H, 8.33. Found: C, 85.76; H, 8.15.

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