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STEREOCHEMISTRY OF SEVEN-MEMBERED HETEROCYCLES. COMMUNICATION 14.* SYNTHESIS AND THREE-DIMENSIONAL STRUCTURE OF 4-METHYL-1,3-DIOXA-5,6-BENZOCYCLOHEPTENES

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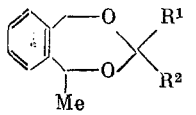
UDC 542.91:541.63:547.89

It has been established that 1,3-dioxa-5,6-benzocycloheptenes in solution are represented by the chair (Ch) and twist (Tw) conformations [2-6]. The realization of these forms and the unfavorability of the boat conformation are in agreement with calculated data [7]. A quantitative analysis of the position of the conformational equilibrium, carried out by means of ^{13}C NMR [3, 8] and IR spectroscopy [6], made it possible to determine the influence of substituents at C^2. The accumulated quantitative information can be used to determine the conformational properties of substituents at $C^4(C^7)$ [9, 10].

Here we are reporting on an investigation of the three-dimensional structure of 4-methyl-1,3-dioxa-5,6-dibenzocycloheptenes. For this work, we synthesized acetals on the basis of 1-hydroxymethyl-2-(α-hydroxyethyl)benzene (I)-(IV)



(I)—(V)

$R^1 = R^2 = H$(I); $R^1 = H$, $R^2 = Me$(II); $R^1 = H$, $R^2 = Ph$(III); $R^1 = H$, $R^2 = C(Me)_3$ (IVa)-cis, (IVb)-trans; R^1, $R^2 = (CH_2)_5$(V).

We analyzed the structures of these compounds by the dipole moment (DM) method; and in the case of (IV), we also used ^{13}C NMR spectrometry. ^1H and ^{13}C NMR spectra confirming the structures of the products are presented in Tables 1 and 2.

In principle, the acetals (II)-(IV) can be obtained in the form of two geometric isomers; however, we were able to register the two isomers only in the case of (IV). According to the ^{13}C NMR spectra, in the reaction mixture obtained by condensation of the original glycol with pivalic aldehyde, the minor form is observed in amounts of 5-10%. In order to resolve the question of the three-dimensional structures of the epimers (IVa) and (IVb), we brought in data previously obtained on the ^{13}C NMR of the chair conformations of 2-tert-butyl-1,3-dioxa-5,6-benzocycloheptene (VI) and its diastereomeric 4,7-dimethyl derivatives (VII) and (VIII) [1, 9]. We have indicated in Diagram 1 the chemical shifts (CS) of the C^2 carbons of the acetal (VI) and the methyl-substituted derivatives.

A diagnostic sign of the presence of the axial methyl in the d, l-isomer (VIII) is the 89.64 ppm upfield shift of the C^2 carbon signal relative to the signal for the meso isomer (VII) [1, 9]. An analogous C^2 CS trend can be seen for the isomers of (IV), so that we can assign the dominant isomer (IVa) to the cis form, and the minor isomer, with a greater upfield CS, to the trans form with an axial methyl at C^4. We should consider that the chair conformation of the isomers of (IV) has been established quite reliably, since the diastereomers (VII)

*For Communication 13, see [1].

A. M. Butlerov Chemical Institute. V. I. Ul'yanov-Lenin Kazan' State University. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 10, pp. 2259-2265, October, 1984. Original article submitted July 8, 1983.

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TABLE 1. ^{1}H NMR Spectra of Acetals (I)-(V) (δ in ppm; J in Hz; Δν in Hz)

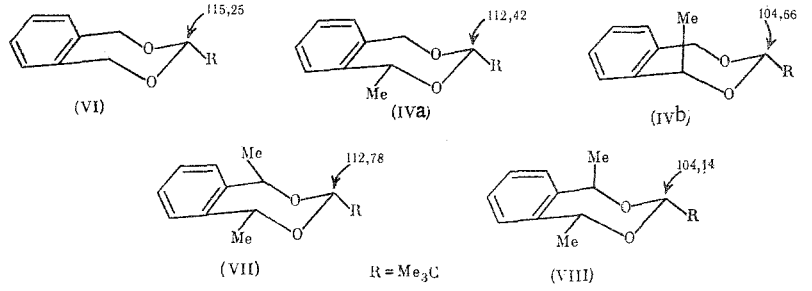
Compound	H^2	H^4	H^7	4-Me	Other signals
(I)	4,87 AB (J=−5,0, Δν=10,9)	4,85 q (J=7,0)	4,70 s	1,52 d (J=7,0)	–
(II)	4,97 q (J=5,0)	4,78 q (J=7,0)	4,63 AB (J=−14,0, Δν=17,0)	1,44d (J=7,0)	1,21d (CH_3, J=5,0)
(III)	5,83 s	5,11 q (J=7,0)	4,68 AB (J=−14,0, Δν=26,5)	1,62 d (J=7,0)	–
(IVa)	4,40 s	4,80 q (J=7,0)	4,71 AB (J=−14,0, Δν=14,3)	1,51d (J=7,0)	0,84s ($(CH_3)_3$)
(V)	–	5,07q (J=7,0)	4,70 AB (J=−14,0, Δν=76,5)	1,50d (J=7,0)	1,62m ($(CH_2)_5$)

TABLE 2. ^{13}C NMR Spectra of Acetals (I)-(IV) and (VI) (δ in ppm)

Compound	C^5	C^6	C^8—C^{11}	C^2	C^4	C^7	Other signals
(I)	143,17	138,88	126,98, 126, 79, 126,43, 125,29	95,20	75,12	70,93	19,94 (Me)
(II)	142,87	138,91	127,63, 127,05, 126,72, 124,71	103,13	75,38	69,17	21,24, 19,94 (Me)
(III)	142,52	138,91 *	127,86, 127,18, 126,85, 126,66, 124,97†	103,26	74,96	67,87	139,30 *, 127,57, 126,40 (2-Ph), 20,07 (Me)
(IVa)	143,26	138,03	128,45, 127,37, 126,95, 124,71	112,42	76,97	71,19	35,77 (C), 24,98 (Me_3C), 19,98 (Me)
(IVb)	141,70	137,35	127,11, 126,79, 125,78	104.66	72,75	72,03	35,90 (C), 25,21 (Me_3C), 19,39 (Me)
(VI)	139,82	139,82	127,15	115,25	73,33	73,33	36,03 (C), 25,11 (Me_3C)

*The possibility of the reverse assignment of signals cannot be eliminated.
†One of the signals of C^p of the 2-Ph group.

Diagram 1



and (VIII), and also the isomeric 4-phenyl derivatives with a tert-butyl substituent at the C^2, have the chair conformation [1, 9, 10]. This is also indicated by the spectral data.

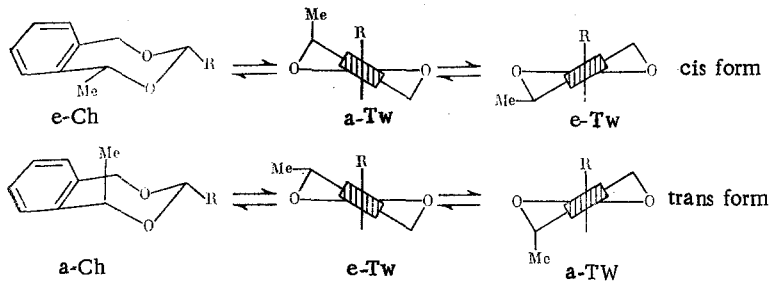
The spectral information obtained for (IVa) and (IVb) provides a means for determining the stereospecific influence of the 4-Me group on the CS of the C^2 and C^4-C^7 carbons, and for determining the so-called α-, β-, γ-, and δ-effects [11]. It is known that in order to evaluate these effects, it is necessary to compare the CS of (IV) with those for the related acetal (VI). Thus, substitution of an H atom on the benzyl carbon (VI) by an equatorial Me is expressed in a downfield shift of C^4 (α_e 3.63 ppm); in the case of an axial methyl (IVb), we observe an upfield shift (α_a −0.58 ppm). We find α-effects of the Me that are the same in sign but somewhat greater in magnitude for the C^2 carbons of 1,3-dioxanes, namely 5.06 and −1.02 ppm; for the C^4 in the six-membered ring, α_e is 5.76, and α_a 0.92 ppm [12].

The influence of the 4-Me on the C^2 CS (γ-effect) is considered to be stereochemically and conformationally important. In the 1,3-dioxane series, the γ_e-effect of the Me group is small (−0.42 ppm [12]); for the cis isomer (IVa) it is quite large, −2.83 ppm. Such a difference in the magnitudes of the γ_e-effects in six-membered and seven-membered rings is undoubtedly due to nonidentical torsion angles $CH_3C^4OC^2$, which has already been discussed for 2-R substituents [3, 13].

Axial substituents, as a rule, give upfield shifts that are greater in magnitude. An axial Me at the C^4 of 1,3-dioxanes, for example, shifts the signal of the acetal carbon by −7.12 ppm; the magnitude of γ_a^{Me} for substitution at C^2 is still greater, −7.76 ppm [12]. In the seven-membered ring, the γ_a effect of the Me substituent is extremely large, −10.59 ppm. Also stereospecific is the effect of 4-Me on the chemical shift of the C^7 carbon. In both isomers, the δ effect is upfield — δ_e = −2.14 and δ_a = −1.30 ppm — which is similar to the effects of the 4-Ph group, −1.36 and +0.39 ppm, respectively [10]. The chemical shifts of the C^5 and C^6 carbons of the acetal (IV), in the β and γ positions relative to the 4-Me, also depend on the configuration of the 4-Me group: β_e is equal to 3.44, γ_e −1.79, β_a + 1.88, and γ_a −2.47 ppm.

The cis isomer dominates in the mixture (IV) because it is more energetically favorable than the trans form. The axial Me group experiences unfavorable syn-axial contacts, particularly close from those with the proton at C^2. It is not impossible that the chair form of the trans isomer is deformed in the direction of a flexible form, similar to (VIII) (see [1]).

It is known that the reaction of formation of phthalylacetals is usually completed in 0.5 h [4, 5, 9, 10]; the synthesis of (I)-(IV) was continued for 60-90 min, so as to ensure the dominance (in those cases in which the formation of isomers is possible) of the more thermodynamically favorable structures. Since the condensation of the original glycol with acetaldehyde and benzaldehyde was accompanied by a greater amount of tar formation, it was impossible to register by spectroscopic means the minor configurational form. There is not enough evidence to assign the configurations of (II) and (III) on the basis of NMR data obtained at ~20°, since the spectral parameters are averaged values. Both the cis and trans isomers can coexist in solution in the form of a mixture of conformers, the chair forms being represented only by the equatorial substituent at C^2 [4]



The conformational equilibrium for the cis isomers is most likely a two-component equilibrium, owing to the considerable stress in the a-Tw form, where there is syn-axial repulsion R—Me. This statement is supported by our preliminary data on the structure of r-2-p-chlorophenyl-cis-4-cis-7-dimethyl-1,3-dioxa-5,6-benzocycloheptene, the conformational equilibrium of which is shifted anancomerically in the direction of the chair. The absence of the alternative twist form is due specifically to its unfavorability, as a result of analogous Me—Ar repulsion. Both flexible forms of the trans isomers of (II) and (III) are more accessible, even through the a-Tw conformer includes additional repulsion of the Me substituent with the H atom. The relative stability of the chair forms a-Ch and e-Ch is evidently slightly different from that in the isomers of the acetal (IV).

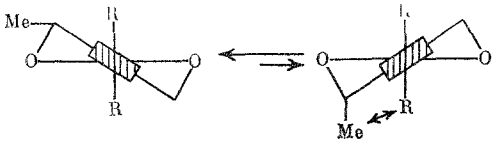
From the above discussion of the possibility of seeking the configurational form for (II) and (III) that is energetically more favorable, it becomes clear that the a-Ch form is more highly stressed in comparison with e-Ch; however, the flexible conformations of both isomers are energetically comparable. Consequently, this sort of approach does not give us any grounds for rigorous differentiation of the isomers with respect to energy stability.

The dipole moment method is capable of solving simultaneously the configurational and conformational problems for (II) and (III). Traditionally, the dipole moment (DM) method

includes a comparison of theoretically calculated values with experimentally determined values, and/or the involvement of conformationally rigid structures. In the present situation, we selected as models the conformationally inhomogeneous 2-methyl- and 2-phenyl-1,3-dioxa-5,6-benzocycloheptenes (IX) and (X) [3-6], assuming that the introduction of the 4-Me group into the molecules of (IX) and (X) would not affect the theoretical values of the DM of the e-Ch and Tw forms. The DM of (II) and (III) is 1.69 and 1.42 D; for the models (IX) and (X), the values are 1.84 D [5] and 1.51 D [10], respectively. A pair comparison of the experimental values of the DM of (IX) vs (II), and (X) vs (III), indicates a slight drop when the change is made to the 4-Me derivative (drops of 8% and 6%, respectively), i.e., a very slight shift in the position of the equilibrium toward the Tw forms. Such a situation can be realized only in the case in which (II) and (III) are cis isomers. We can advance two arguments in favor of this conclusion. In the first place, the presence of an axial Me in the chair form of the trans isomers whould shift the conformational equilibrium in the direction of the flexible conformers, the DM of which is ~0.3-0.4 D [4, 5, 9, 10]. In the second place, even in the rigid chair, the replacement of equatorial biaxial Me leads to an appreciable change in the DM, from 2.15 to 1.40 D, which we observe for the diastereomeric (VII) and (VIII) [9].

The acetal (I) is a compound that is extremely complex in terms of conformation, since for this compound in solution, it is necessary in principle to account for four conformational forms (two chairs and two flexible conformations), and this complicates the analysis of the conformational composition. Nonetheless, when we compare its DM of 1.46 D with that of the model phthalylformal, 1.78 D [5], we can follow a certain shift in the position of the equilibrium in the direction of the Tw forms in comparison with the related methylal.

It has been noted repeatedly [2, 4, 6, 10, 14-16] that 2,2-dialkyl-substituted 1,3-dioxa-5-cycloheptenes are realized in the twist conformation because of the unfavorability of the chair forms, where short syn-axial contacts are traced. No exception is the spiroketal (V), 8-methyl-7,12-dioxaspiro[5,6]benz[9,10]-9-dodecene, the DM of which, 0.39 D, is practically equal to the DM of the related 8-phenyl derivative, 0.42 D [10]. Also similar for these ketals are the nonequivalences of the benzyl protons, 76.5 and 76.7 Hz, which are very characteristic for the flexible form [2, 17].* Of the two flexible forms of the seven-membered ring of (V), the conformation with the pseudoequatorial position of the Me is far more favorable, since in the *a*-Tw conformation, there is steric repulsion of the Me group



R, R = $(CH_2)_5$

with the substituent at the acetal carbon. For this reason, we should speak of an anancomeric equilibrium.

Let us consider the conformational consequences of introducing a 4-Me group into the molecule of 2-R-1,3-dioxa-5,6-benzocycloheptenes. The conformational specifics of the Me cannot be followed in the epimers of (IV), since the related acetal (VI) is also realized in the chair conformation; and in all compounds, the decisive factor stabilizing the chair form is the bulky anancomerizing substituent at the C^2. The tert-butyl group also "masks" the conformational characteristics of the Me. Analogously, the flexible conformation of the seven-membered ring in the ketal (V) is determined not by the Me substituent, but by the spiro fragment. In contrast, even in the twist form, the Me group is uniquely capable of being situated in a conformation that is free of steric overloading.

The conformationally nonrigid acetals (II) and (III) are the most informative in this respect, since they offer the possibility of analyzing trends in the change of position of the conformational equilibrium in the paris (IX) vs (II) and (X) vs (III). The situation is such that the shift in the direction of the twist form lies essentially within the limits of accuracy of the DM method. This does not mean, however, that the Me substituent is analogous

*The difference between the chemical shifts of the benzyl protons of the 8-phenyl derivative [10] should be considered as erroneous.

TABLE 3

Compound	mp, °C, and bp, °C (p, mm Hg)	Found, %		Empirical formula	Calculated, %	
		C	H		C	H
(I)	40–42 70–71 (10^{-2})	73,40	7,39	$C_{10}H_{12}O_2$	73,17	7,32
(II)	61,5–62 70–72 (10^{-2})	74,11	7,78	$C_{11}H_{14}O_2$	74,16	7,86
(III)	68–69,5 133–135 (10^{-3})	79,49	6,77	$C_{16}H_{16}O_2$	80,00	6,67
(IVa) *	20–23 150–152 (2)	75,97	9,10	$C_{14}H_{20}O_2$	76,36	9,09
(V)	37–39 120–122 (10^{-2})	77,21	8,71	$C_{15}H_{20}O_2$	77,59	8,62

*Configurational purity 90-95%.

TABLE 4

Compound	α	ν	P_{or}	μ, D
(I)	3,30	0,76	43,461	1,46
(II)	3,94	0,80	58,371	1,69
(III)	2,34	0,68	41,199	1,42
(V)	0,60	0,45	3,104	0,39

to an H atom in the conformational sense. Even in the case of completely identical positions of the conformational equilibrium of the acetals (II) vs (IX) and (III) vs (X), we must consider that the magnitudes of ΔG (the difference in free energies of the forms) will be far from identical, and that they differ by RT ln 2 (~400 cal/mole), whereupon, ΔG (II) < ΔG (IX) and ΔG (III) < ΔG (X). This can be attributed to the population composition of the conformational equilibrium: For the 2-R-substituted acetals (IX) and (X), in the one chair form there are two flexible conformations, but for the cis isomers (II) and (III), only one conformation. The estimated value of 400 cal/mole should logically be considered as the conformational energy of the 4-Me group e-Ch–e-Tw [6], under the condition of similarity of conformational energies of 2-Me and Ph in both series of acetals, and under the further conditions of additivity of the conformational energies of the substituents at C^2 and C^4. A more rigorous value of $\Delta G^{Me}_{e-K-e-Tw}$ can be determined by investigating dynamic ^{13}C NMR spectra of (II) and (III), with a subsequent comparison with data on the 2-R derivatives [3, 8]. In equal measure, in order to determine ΔG of the Me group e-Ch–a-Ch, quantitative data will be needed on the epimerization of the isomers (IVa) and (IVb).

EXPERIMENTAL

1-Hydroxy-methyl-2(α-hydroxyethyl)benzene. A solution of 9.5 g of o-acetyl benzoic acid in 100 ml of absolute ether was added dropwise with stirring to 3.5 g of $LiAlH_4$ in 500 ml of ether, and the mixture was worked up in accordance with [18]. After driving off the solvent, obtained a thick, pale yellow oil that crystallized upon standing; mp 65-66° (ether–hexane, 1:1), yield 7.2 g (82%) (compare [19], where an oil was obtained, and [20], where a boiling point of 115-118° at 0.05 mm was reported).

Compounds (I)-(V) were obtained by condensation of the glycol with carbonyl compounds in benzene in accordance with [4]; after distillation, the products were crystallized from EtOH, yields 60-90%; the constants are listed in Table 3.

The dipole moments were determined in accordance with [21], in CCl_4 at 25°. The coefficients of the calculational equations are given in Table 4. The NMR spectra were recorded in a Varian HA-100 instrument, the ^{13}C NMR spectra in a Bruker WH-90 instrument, with CCl_4 solvent, TMS internal standard. The chemical shifts of the C^4 and C^6 carbons of (I) and (IV) were assigned by means of a procedure of partial decoupling from the protons; the signals of C^5 and C^6 were assigned by bringing in the data of [22].

The authors wish to express their appreciation to P. P. Chernov for taking the ^{13}C NMR spectra.

CONCLUSIONS

1. On the basis of data obtained by the dipole moment method, cis-2-methyl(or phenyl)-4-methyl-1,3-dioxa-5,6-benzocycloheptenes have an equilibrium of chair and twist forms that is close in quantitative respects to the related 2-R-phthalyacetals; the spiroketal of cyclohexanone is realized in the e-Tw form; the methylal is conformationally inhomogeneous.

2. The isomeric 2-tert-butyl-4-methyl-1,3-dioxa-5,6-benzocycloheptenes, according to ^{13}C NMR data, are realized in chair conformations. An analysis has been made of the influence of the 4-methyl group on the chemical shifts of the carbon atoms of the seven-membered ring.

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