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STRUCTURE AND CONFORMATION OF HETEROCYCLES. II. (1) THE 1,4,5,8-TETRAOXADECALIN VS. BI(DIOXOLAN-2-YL) ISOMERIC SYSTEMS.

Benzion Fuchs

Department of Chemistry, Tel-Aviv University, Tel-Aviv, Israel

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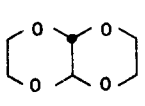
When ethylene glycol is condensed with an α-diketone (R-CO-CO-R) in an acid catalyzed reaction, a mixture of two isomers is usually obtained (2). Interestingly enough, the structural assignments of the parent compounds (R=H), isomers A and B, were a matter of dispute over a period of more than thirty years (2-4). Thus, they underwent a series of changes: A=1, B=2 (2); A=1, B=3 (3); A=2; B=3 (4a). In fact, no systematic and general method of identification and differentiation has so far been put forward for the entire series.

We are currently concerned with the conformational analysis of 1,4,5,8-tetraoxadecalins (1,5). The prerequisite of any conformational study should obviously be sound structural assignments of the systems under scrutiny. We report here the results of our own efforts towards establishing a methodical and unequivocal approach for identifying and differentiating between the isomeric systems. We considered it adequate to base it on physical methods and to seek corroboration by chemical correlation within the series. Synthesis of various known (3), as well as new pairs of isomeric products were performed starting from the corresponding 1,2-diketones; the new compounds gave correct elemental analyses. We regard our results as being conclusive in showing that we deal with the title structures 2 and 3 and in differentiating between them.

Since we found IR spectral analysis to be inconclusive in differentiating 2 from 3 (6), we turned to NMR and mass spectral studies and found these methods to be of diagnostic value.

The relevant feature in the NMR spectra of the two systems is the absorption of the methylene protons around δ=4 ppm (Table 1) (7,8). In the bi(dioxolan-2-yl) derivatives it appears as a relatively sharp multiplet (sometimes even as a singlet) with half-width $w_{1/2}$=7Hz, whereas the peripheral methylene protons in the 1,4,5,8-tetraoxadecalins absorb as well resolved AA'BB' systems (4a) with a half-width $w_{1/2}$=50Hz. This behavior is in accord with similar results



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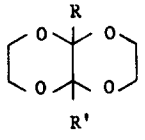

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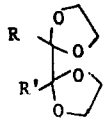

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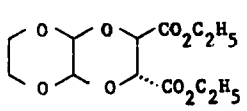

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R = R' = H, CH_3, CH_2Br, CH_2D, C_6H_5

obtained on dioxolane derivatives, when compared to 1,4-dioxanes (5,8,9) and is apparently due to the increased mobility of the five membered ring vs the six-membered one. It is noteworthy that the bi(dioxolanyl) multiplet is usually centered at lower field than the one of the corresponding tetraoxadecalin, the difference ranging between 0.1-0.3 ppm. It is to be mentioned that all these observations, as well as those described below, are of a general character and no exception has been found so far among the compounds studied, including those having cyclic substituents (R-R') e.g. tetraoxapropellanes (1b) or different groups (R≠R') (10) in the angular positions (but not necessarily peripherally substituted ones).

Mass spectrometry provides another criterion for differentation in the series (Table 2) (7). The molecular peak which appears in the tetraoxadecalins, is virtually absent in the corresponding bi(dioxolanyl) derivatives. The behavior of the latter is well understood from the accumulated knowledge on the entire class of ethylene ketals (11). In our case, a cleavage of the central bond leads to the most abundant ion of m/e=M/2. Interestingly enough, the tetraoxadecalins also exhibit the $M/2^+$ ion as the peak of highest relative abundance. This seemingly contradictory observation can find its rationale in two possible reasonable rearrangements leading to a cation identical to that obtained from the bi(dioxolanyl) compounds on electron impact (see Scheme).

The choice between the two pathways was made possible by securing the 2,3-substituted tetraoxadecalin 4, (12) and its mass spectrum. Obviously, if pathway I obtains, an un- and/or disubstituted dioxolanyl ion should occur in high abundance whereas rearrangement II should yield a monosubstituted dioxolanyl ion. Our results, so far, indicate (Table 2) that rearrangement I largely prevails, although other fragmentation modes obtain as well. Definitive assignments, though, are deferred until additional results will be available. At any rate, one feels compelled to assert that the occurrence of this interesting rearrangement is not an isolated phenomenon and could show up in other analogous heterocycles, demanding great care in cases where one might be tempted to use the $M/2^+$ ion as a criterion for rejection of the heterodecalin structure(13).

Chemical correlation between members of the series was undertaken with the aim of supporting the said assignments. Strangely enough, no chemical interconversion between compounds in the series has been described so far, to the best of our knowledge, in spite of considerable synthetic work performed (2,12). As a first instance, Li Al H_4 reduction of the di(bromomethyl) derivatives 2 and 3 ($R=CH_2Br$) in boiling THF, yielded the corresponding dimethyl derivatives 2 and 3 ($R=R'=CH_3$). Many other attempts to use the CH_2Br group as a target for chemical attack failed obviously due to both the neopentylic site and the geminal C-O bonds. Finally, our assignments are given strong endorsement both by the temperature dependent NMR study (1a) and by the X-ray analysis of cis-9,10-di (bromomethyl)-1,4,5,8-tetraoxadecalin (5) and thus provide a closed cycle for the di(bromomethyl) and the dimethyl angularly substituted derivatives.

Further applications of these methods are currently being carried out and will be reported shortly.

Table 1: $O-CH_2-CH_2-O$ NMR spectra of various isomers 2 and 3[a].

δ, ppm ($w_{1/2}$, Hz)[b]

R = R'	H	CH_3	CH_2D	CH_2Br	C_6H_5
2	3.83(51)	3.83(60)	3.86(48)	3.93(56)	not available
3	3.98(6)	3.99(7)	4.01(7)	4.15(7)	3.76(5) (singlet)

a) Taken at 100 Mc on ca. 10% $CDCl_3$ solutions with TMS as internal standard.

b) δ stands for the center of the AA'BB' pattern and $w_{1/2}$ for its width at half height.

Table 2: Mass spectra of various isomers 2 and 3[a].

m/e (%)

R = R'	H		CH_3		Ph	CH_2Br			
	2	3[b]	2	3	3	2	3	4	
	147(2)	86(5)	174(3)	114(3)	150(11)	330	168(5)	290(3)	88(7)
	146(19)	74(4)	114(2)	101(2)	149(100)*	332 (2)	167(100)*	216(21)	87(10)
	86(3)	73(100)*	112(2)	88(7)	105(22)	334	166(5)	174(4)	86(28)
	74(4)	58(2)	88(3)	87(100)*	77(13)	251(4)	165(96)*	173(3)	82(23)
	73(100)*	45(45)	87(34)*	45(4)		253(4)	123(28)	171(4)	77(7)
	61(3)	43(11)	86(5)	44(8)		168(5)	121(30)	145(8)*	76(4)
	60(8)	42(10)	73(4)	43(98)		167(100)*	95(9)	143(8)	75(3)
	58(3)		61(3)			166(4)	93(9)	128(23)	74(6)
	47(4)		56(2)			165(97)*	87(10)	127(57)	73(100)
	45(35)		45(3)			163(3)	86(55)	126(36)	71(33)
	44(5)		44(5)			123(56)	45(6)	117(7)	70(7)
	43(9)		43(100)			122(4)	43(15)	115(6)	69(6)
	42(2)		41(11)			121(61)	42(29)	105(5)	65(6)
						120(3)		103(5)	63(7)
						95(14)		102(5)	61(5)
						93(15)		101(23)	50-60(4-10)
						89(5)		100(24)	45(88)
						87(22)		99(75)	44(29)
						86(3)		91(41)	43(36)
						73(2)		89(7)	42(16)
						45(21)			
						44(3)			
						43(39)			
						42(24)			

a) Taken on an Atlas CH4 and/or Perkin Elmer RMU-6 mass spectrometer. Relative abundances down to 2% are given. The ion $M/_2^+$ is indicated by an asterik.

b) At extremely high sensitivities, the molecular peak of this compound is detectable, albeit of $\Sigma_{40} < 0.001$.

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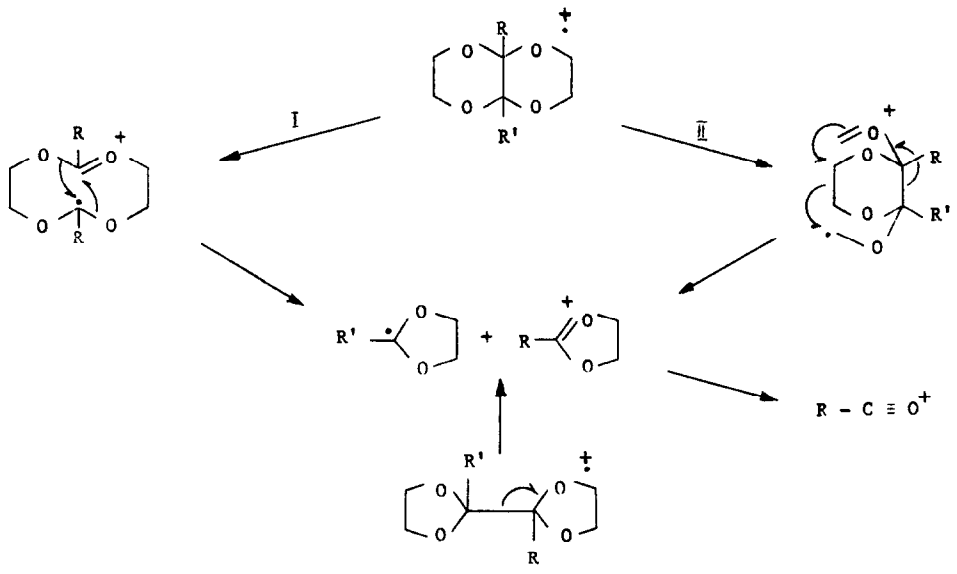
SCHEME



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