Tetrahedron Letters No. 6, pp 467 - 468, 1976. Pergamon Press. Printed in Great Britain.

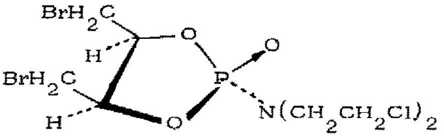
DETERMINATION OF THE Z AND E ISOMERS OF DIOXAPHOSPHOLANES BY ASIS

P. Sohár*, J. Kuszmann and É. Gilicze

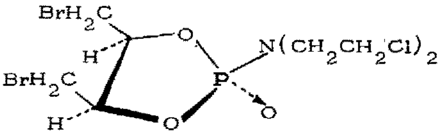
Research Institute for Pharmaceutical Chemistry, 1352 Budapest, POB 82, Hungary

(Received in UK 10 November 1975; accepted for publication 24 December 1975)

Recently Zon described[1] the synthesis and configurational stability of diastereomeric cyclophosphamide derivatives. Now we wish to report on the determination of Z and E configurations of similar phosphamide derivatives, carrying a 4,5-disubstituted, five-membered 1,3,2-dioxaphospholane ring[2] (1 and 2) instead of the flexible six-membered ring, investigated by Zon[1].



1



2

For determining the configuration the aromatic solvent induced shifts (ASIS, review by László[3]) were studied. In the ^{1}H nmr spectra of 1 and 2 the signals of the methylene groups, that is the A_2B_2 multiplet of the two identical N-CH$_2$-CH$_2$-Cl groups and the A part of the $A_2A'_2XX'$ spectrum[4] of the -CH(CH$_2$Br)-CH(CH$_2$Br)- group overlap. The signal of the methyne (X) protons appears separately. From the 14 lines of the symmetric A_2B_2 multiplet 10 can be identified, whereas the other 4 overlap with the absorption of the bromomethyl groups in CDCl$_3$ as well as in C$_6$D$_6$ solution. Accordingly only the chemical shifts of the latter protons can not be determined exactly from the spectra /table/.

It is well-known, that solvation of molecules by benzene occurs preferentially at their positively polarized sites. Therefore the shift difference observed in CDCl$_3$ and benzene, resp. should be greater for those protons, being sterically further away from the negatively polarized parts of the molecules. Since in 1 and 2 the oxygen of the dative bond from the phosphorus atom represents the strongest negative pole, a more significant ASIS effect should be detectable on the methyne protons of that isomer (1) in which these protons are on the other side of the phospholane ring ("trans" relation) compared to the other compound (2), where these protons are situated on the same side ("cis"). Similarly, in the case of the N-CH_2-groups[5] a stronger ASIS effect should prevail in isomer 1, where this group is "trans" related to the bromomethyl groups. For the chloromethyl groups no significant shift difference can be expected because of the negative character of the chloro atoms. The bromomethyl groups however should be more shifted in isomer 2 according to their "trans" arrangement with the P-O bond.

T A B L E

Chemical shifts (δ_{TMS}=0 ppm) and shift differences ($\Delta\delta = \delta_{CDCl_3} - \delta_{C_6D_6}$ ppm) of compounds 1 and 2

	Z-isomer (1) mp. 97-98°C			E-isomer (2) mp. 123-124°C		
	δ_{CDCl_3}	$\delta_{C_6D_6}$	$\Delta\delta$	δ_{CDCl_3}	$\delta_{C_6D_6}$	$\Delta\delta$
CH_2Br (4H)	3.70	3.08	0.62	3.65	2.95	0.70
NCH_2 (4H)	3.33	2.80	0.53	3.38	3.20	0.18
CH_2Cl (4H)	3.65	3.10	0.45	3.65	3.20	0.45
CH (2H)	4.85	3.95	0.90	5.03	4.40	0.63

The experimental data proved unambiguously the Z configuration of compound 1 (mp. 97-98°C) and the E configuration of isomer 2 (mp. 123-124°C).

NOTES AND REFERENCES

1/ G. Zon, Tetrahedron Letters 3139 (1975).

2/ J. Kuszmann and L. Vargha, Carbohyd. Res. 3, 38 (1966).

3/ P. László, Solvent effects and NMR. In "Progress in NMR Spectroscopy"; Ed.: J.W. Emsley, J. Feeney, L.H. Sutcliffe, Pergamon Press 3, 231 (1967).

4/ The diastereotopic protons of the bromomethyl groups are practically isochromous ($\delta A \approx \delta B$), therefore an $A_2A'_2XX'$ spin system prevails instead of the theoretical AA'BB'XX' system.

5/ The N-CH_2- group is readily solvolized because of the positively polarized N atom.