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THE PREPARATION OF SOME $CH_2\overset{\oplus}{N}Me_3$-SUBSTITUTED BICYCLO [3,2,1]OCTANES. THE ROTAMERIC BEHAVIOUR OF THE $CH_2\overset{\oplus}{N}Me_3$- SUBSTITUENT.

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The conformations of cis-2-CH_2X-4-Me-3,6,8-trioxa-bicyclo[3,2,1]octane (X=Cl,$\overset{+}{N}Me_3$) and cis-2-$CH_2\overset{+}{N}Me_3$-4-Me-3,8-dioxa-6-aza-bicyclo[3,2,1]octane are investigated by ^1H-NMR spectroscopy. As a result of the imposed conformation of the five membered ring-moiety, the orientation of the side-chain is that with the C_2-N^+ and adjacent O_3-C_2 bonds in an antiperiplanar relationship. This situation corroborates a previously proposed parallelity effect between p-O and C-$N^{\oplus}$.

We have found earlier[1] a pronounced rotameric preference of a $CH_2\overset{\oplus}{N}Me_3$ side-chain with respect to an adjacent C-O bond, during a comparative study of 2-CF_3-4-$CH_2\overset{+}{N}Me_3$-1,3-dioxolanes and 2-CH_3-4-$CH_2\overset{+}{N}Me_3$-1,3-dioxolanes. Two types of rotamers could be distinguished. Type I (fig.1) is characterized by an antiperiplanar relationship between the $C_{4'}$-N^+ and C_4-O_3-bonds ; whereas in type II they stay gauche. We found[1] the latter situation to be the favoured one, if parallelity between the $C_{4'}-N^+$ bond and an oxygen p-orbital is possible. Thus in 5-$\overset{\oplus}{N}Me_3$-1,3-dioxane, the axial position is favoured (Type II) over the equatorial (Type I) for at least 2 kcal/mole.[1,2] This parallelity is compromised in 2-CH_3-1,3-dioxolanes because of the tendency for flattening of the ring and as a result, the side-chain in these compounds prefer a type I-conformation. The conformation in 2-CF_3-1,3-dioxolanes on the contrary is characterized by a lifted-out oxygen atom, and as a result they are type II-compounds.[3] We have also investigated[1] 4-$CH_2\overset{+}{N}Me_3$-1,3-dioxanes. Molecular models disclose that $C_{4'}-N/C_2-O_3$-parallelity is possible in the fundamental chair form of these substances and they indeed were found to belong to the type II-compounds.[1]

Type I Type II

Figure 1

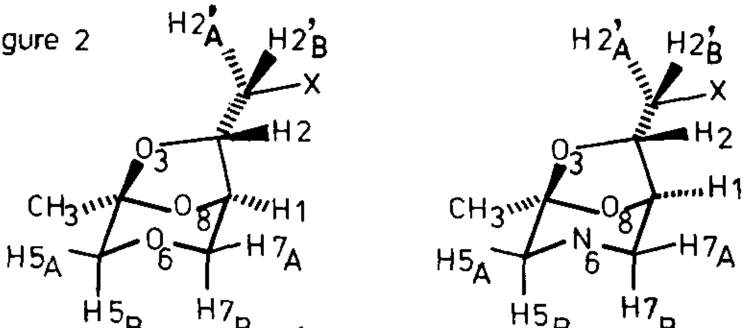
We now wish to report about the orientation of the $CH_2\overset{+}{N}Me_3$-group in cis-2-$CH_2\overset{+}{N}Me_3$-4-Me-3,6,8-trioxabicyclo[3,2,1]octane (1) and in cis-2-$CH_2\overset{+}{N}Me_3$-4-Me-3,8-dioxa-6-aza-bicyclo[3,2,1]octane (2) as a further check of this parallelity effect.

(1) was prepared using trans-1,4-dichloro-2-butene as the starting material. The alkene was hydroxylated with $KMnO_4$ and so

formed threo-1,4-dichloro-2,3-butanediol was then condensed with ethyl pyruvate under azeotropic removal of water, yielding 2-Me-2-COOEt-trans-4,5-di-CH_2Cl-1,3-dioxolane (B.p. 85°C/0.03 mm). After $LiAlH_4$-reduction of the ester-function the bicyclic compound was obtained by an SNi-reaction. From the synthesis, it is clear, that the 2-CH_3-group stands cis with respect to the remaining CH_2Cl-group. The latter is transformed in the $CH_2\overset{+}{N}Me_3$-group following usual procedures.[1]

The molecule combines a 1,4-dioxane-structure together with a 1,3-dioxolane structure (fig.2) and is rigid. A $^3J(1,2) = 0$ indicates a torsion angle of ∿ 90° between these two protons. The 1,4-dioxane ring adopts a chair-conformation. Indeed, $^3J(1,7A)$ = $^3J(1,7B)$ *and both are very small (1.3 Hz)*, thus excluding the occurence of a boat conformation. The small value of the $^3J(1,7)$ shows, that one of the oxygen p-orbitals from the dioxane ring has a net equatorial character.[4,5]

Figure 2



1 2

As a result of the chair dioxane ring, there is a unique conformation imposed on the dioxolane moiety, e.g. an almost pure envelope with O_8 as the top ($\tau(C_2\text{-}C_3) < 30°$, hence $^3J(1,2) = 0$). It follows that with this fixed conformation, no parallelity is allowed between the $C_{2'}$-N^+ bond and the p-orbitals of the O_3-atom, and we therefore expect[1] the side-chain to be oriented as in cis-2-Me-4-$CH_2\overset{+}{N}Me_3$-1,3-dioxolane (type I). Indeed, we find $H_{2'A}$ (proton with the large $^3J(2,2') = 9.5$ Hz) upfield ($\delta = 3.52$) from $H_{2'B}$ (proton with a $^3J(2,2') = 1.5$ Hz, $\delta = 3.63$); moreover, shift-values and coupling constants of the side-chain protons in our bicyclic compound are very similar to those of cis-2-Me-4-$CH_2\overset{+}{N}Me_3$-1,3-dioxolane[3] ($\delta = 3.52$ to 3.57 versus $\delta = 3.63$ to 3.62 with resp. $^3J = 9.50$ to 10.0 Hz and $^3J = 1.5$ to 1.9 Hz). As was already ascertained in all dioxolanes and dioxanes previously studied,[1] the CH_2Cl-side chain in the precursor (1 ; X=Cl) prefers also a type I-conformation (cf. Table).

Exact assignment of H_5-protons may be done from long-range considerations. Long-range coupling is usually most pronounced when a planar zig-zag path can be traced along the bonds in going from one proton to the other. This is the so-called M-rule.[6]

For the 2-$CH_2\overset{+}{N}Me_3$-compound a $^4J(7,5) \sim 0.5$ Hz is found on the H_5-proton at $\delta = 3.60$, therefore this proton is assigned the equatorial partner (H_{5A}). The proton at $\delta = 3.66$ is then the axial one.

For the 2-CH_2Cl-compound the proton at $\delta = 3.37$ shows a small $^4J \sim 0.5$ Hz and can therefore be assigned as H_{5A} (cf. fig.2). H_{5B} is then the axial proton at $\delta = 3.39$. The lowest field signal of the H_7-proton shows the same long-range of ~ 0.5 Hz, thus, H_{7A} (equatorial) becomes $\delta = 3.75$, H_{7B} (axial proton), $\delta = 3.55$.

The conformational behaviour of cis-2-$CH_2\overset{+}{N}Me_3$-4-Me-3,8-dioxa-6-aza-bicyclo[3,2,1]octane (2) is very similar to 1. The compound can be considered as a combination of a morpholine with a 1,3-

dioxolane moiety. It has been synthetised starting from trans-1,4-dichloro-2-butene which was hydroxylated with $KMnO_4$ to the same threo-1,4-diCl-2,3-butanediol as reported for **1**. This was then condensed with α-chloroacetone and the resulting 2-Me-2,4,5-tri-CH_2Cl-1,3-dioxolane was closed using Me_2NH (m.p. 240°C). It is clear that only 2,4-cis-standing CH_2Cl-groups can react with Me_2NH with ring closure, thus the remaining CH_2Cl-group stands cis to the 2-CH_3 group. It was subsequently transformed to the $CH_2N^+Me_3$ by classical procedures.

The H_1-proton being partially hidden in the ^1H-NMR-spectrum of **2** it was not possible to determine exactly $^3J(1,2)$, although it can be stated that this value is certainly less than 2.0 Hz. Other values (Table) are very similar to those for **1** (e.g. J(1,7) ∿ 1.0 Hz and 2.0 Hz) and the same conclusions may be drawn.

For both groups of the H_5 and H_7 protons, the lower field protons are now the equatorial ones (H_{5A} at $\delta = 2.88$, H_{5B} at $\delta = 2.28$; H_{7A} at $\delta = 2.99$, and H_{7B} at $\delta = 2.49$. H_{5A} as well as H_{7A} possess the $^4J(5A,7A) = 0.8$ Hz long-range coupling.

It is interesting to note, that in cis-2-CH_2NMe_2-4-Me-3,8-dioxa-6-aza-bicyclo[3,2,1]octane (**2** ; X=NMe_2) the CH_2NMe_2-side chain's orientation is mainly of type II, the proton with the largest ^3J-value being situated downfield from the other one. An exact explanation for the latter behaviour cannot yet be given, but the reason must be an other one than for the $CH_2\overset{+}{N}Me_3$-compounds.

All ^1H-NMR-parameters are collected in the table. They were obtained at 300 MHz (VARIAN HR-300) and the values were ascertained by comparison with simulated spectra (SIMEQ 16/II program).

Shift-values of bicyclo[3,2,1]octanes.[a]

	Solvent	CH_3	H_1	H_2	$H_{2'A}$	$H_{2'B}$	H_{5A}	H_{5B}	H_{7A}	H_{7B}
I	CS_2	1.62	4.22	4.38	3.22	3.43	3.37	3.39	3.75	3.55
II	D_2O	1.50	4.43	5.02	3.52	3.63	3.60	3.66	3.90	3.84
III	CCl_4	1.30	4.13	4.13	2.23	2.11	2.60	1.98	2.61	2.28
IV	D_2O	1.56	4.46	..	3.48	3.58	2.88	2.28	2.99	2.49

J-values in Hz of bicyclo[3,2,1]octanes.[a]

	$^2J(2'A,2'B)$	$^3J(2,2'A)$	$^3J(2,2'B)$	$^3J(1,2)$	$^2J(7A,7B)$	$^3J(1,7A)$	$^3J(1,7B)$	$^2J(5A,5B)$	$^4J(5A,7A)$
I	-10.5	10.3	4.10	∿0	-11.4	1.30	1.30	-11.3	∿-0.5
II	-13.7	9.50	1.50	∿0	-11.9	1.20	1.20	-11.8	∿-0.5
III	-12.1	9.80	3.90	∿0	-10.8	1.80	1.90	-10.5	-0.8
IV	-13.6	11.7	2.30	max. 2.0	-12.6	∿1.0	2.00	-12.0	-0.8

[a] See figure 2. I = **1**(X = Cl) ; II = **1**($X = \overset{\oplus}{N}Me_3$) ; III = **2**($X = NMe_2$) and IV = **2**($X = \overset{\oplus}{N}Me_3$).

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