CONFORMATION STUDIES OF ISOMERIC 1-ACYLOXY-2-(4-METHOXYBENZYL)-CYCLOHEXANES BY ^{1}H NMR SPECTROSCOPY

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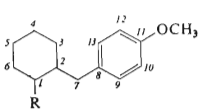
The conformation of the cyclohexane ring and the *p*-methoxybenzyl substituent in the series of isomeric 1-acyloxy-2-(4-methoxybenzyl)cyclohexanes was studied by means of ^{1}H NMR spectroscopy. In all the substances investigated the cyclohexane ring assumes chair conformation. *trans*-Isomers have both substituents in equatorial positions, while in *cis*-isomers the *p*-methoxybenzyl group is always equatorial and the hydroxy or acetoxy group axial.

Recently we published[1] some results of the investigation of juvenogen substances which are potentially utilizable as modern systemic "pro-pesticides". The knowledge of the spacial arrangement of these substances in solution may be important for the elucidation of the mechanism of biological effect. Therefore we now prepared four pairs of model substances, *I* – *VIII*, with *cis*- or *trans*-1,2-disubstituted cyclohexane ring and studied, by means of ^{1}H NMR, the effect on them of the relative configuration of substituents and of their volume on conformation of *1*) cyclohexane ring, *2*) *p*-methoxybenzyl substituent.

The ^{1}H NMR spectra of compounds *I* – *VIII* in hexadeuteriodimethyl sulfoxide were not completely interpretable. The hydrogens in positions 2 and 6 of the cyclohexane ring formed a complex multiplet of overlapping signals in the δ 1·00–2·00 region. The ^{1}H NMR parameters of other assignable signals are given in Table I.



I, R = *cis*-OH
II, R = *cis*-OCOCH$_3$
III, R = *cis*-OCOCH(CH$_3$)$_2$
IV, R = *cis*-OCOC(CH$_3$)$_3$

V, R = *trans*-OH
VI, R = *trans*-OCOCH$_3$
VII, R = *trans*-OCOCH(CH$_3$)$_2$
VIII, R = *trans*-OCOC(CH$_3$)$_3$

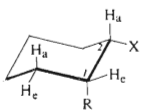
TABLE I

^{1}H NMR Parameters of compounds *I*— *VIII* in hexadeuteriodimethyl sulfoxide

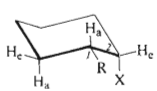
Parameter	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
δH-1	3·60	4·70	4·70	4·68	3·02	4·41	4·43	4·42
	(W = 9·0)[a]	(W = 9·0)	(W = 8·2)	(W = 8·2)	(W = 22·0)[a]	(W = 23·8)	(W = 23·6)	(W = 23·6)
δH-7	2·60	2·46	2·45	2·44	3·07	2·74	2·73	2·74
δH-7′	2·35	2·38	2·38	2·38	2·15	2·22	2·21	2·20
$J_{2,7}$	6·8	7·6	7·3	6·9	3·2	4·0	3·8	3·6
$J_{2,7'}$	7·6	7·8	7·9	8·0	9·5	8·8	8·8	9·2
$J_{7,7'}$	−13·5	−13·8	−13·6	−13·6	−13·5	−13·6	−13·8	−13·7
δH-10,12	6·81	6·82	6·82	6·82	6·82	6·83	6·83	6·83
δH-9,13	7·08	7·03	7·01	7·01	7·05	7·03	7·02	7·02
δOCH_3	3·71	3·71	3·71	3·71	3·71	3·71	3·71	3·71
δ Other H	4·21	2·06	2·59[b]	1·22	4·56	1·99	2·51[c]	1·17
	(OH)	(OAc)	(CHCO)	(CH_3)	(OH)	(OAc)	(CHCO)	(CH_3)

[a] After the addition of CD_3COOD; [b] 1·16 and 1·15 (CH_3); [c] 1·11 and 1·14 (CH_3).

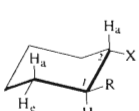
A complete NMR analysis of the ring conformation or an extraction of the coupling constant values of hydrogens H-1 and H-2 is impossible, owing to the overlapping of the proton signals in position 2 and 6. Hence, the only criterion available is the width of the H-1 multiplet, corresponding approximately to the sum of its interaction with three neighbouring hydrogens ($J_{1,2}$, $J_{1,6}$ and $J_{1,6'}$). For *cis*-isomers *I–IV* we found the widths of the multiplets of hydrogen H-1 within the 8·2–9·0 Hz interval, that is within a range not exceeding the experimental error. The multiplet width shows that hydrogen H-1 must be equatorial (with two $^3J_{eq,eq}$ and one $^3J_{eq,ax}$ with typical values about 3 Hz) and, therefore, the OH or O-acyl group in position 1 must be axial, while the benzyl substituent in 2-position must be equatorial in the preferred chair conformation *A*. The proportion of the chair form *B* with an opposite orientation of substituents should lead to an increase in the width of the multiplet H-1 (in this case H-1 is axial), which is evidently very low in substances *I–IV*. A stabilization of the form *A* in *I–III* with a more voluminous benzyl substituent in the equatorial position may be expected. It is interesting, that the



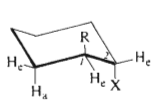
A



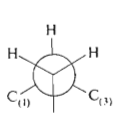
B



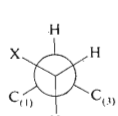
C



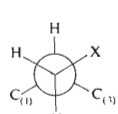
D



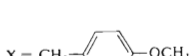
E



F



G



axial pivaloyloxy substituent in derivative *IV* does not lead to a widening of the signal H-1 either, which would indicate a more distinct proportion of the form *B*.

For the *trans* isomers *V*–*VIII* we found the multiplet widths of H-1 again within a narrow range, 22·0–23·8 Hz. This shows that H-1 assumes an axial position (with two $^3J_{ax,ax}$ about 10 Hz and one $^3J_{ax,eq}$ about 3 Hz) and the preferred conformation of the molecule is *C*, with both substituents in equatorial positions. For energy reasons the conformation *D* with axial substituents is evidently highly instable and the proportion of it is negligible.

The information on the orientation of *p*-methoxybenzyl around the $C_{(2)}$—$C_{(7)}$ bond is included in the coupling constants $J_{2,7}$ and $J_{2,7'}$. If considering, as is usual, only three staggered rotamers *E*, *F*, and *G* as statistically important, we may calculate from the experimentally found values $J_{2,7}$ and $J_{2,7'}$ and from the assumed values for $^3J_{gauche}$ and $^3J_{trans}$ constants the relative populations of rotamers *E*, *F* and *G*. The forms *F* and *G* are unambiguously distinguishable only if the signals of H-7 and H-7′ can be assigned unambiguously. When using Pachler's values[2] for coupling constans $^3J_{trans}$ = 13·6 and $^3J_{gauche}$ = 2·6 Hz (proposed for the same purpose in phenylalanine and further amino acids) we obtained the populations presented in Table II. In *cis*-isomers *I*–*IV* rotamer *E* (0·08–0·17) is least populated, evidently in consequence of the steric interaction of *p*-methoxyphenyl with the OH or the acyloxy group. The other two rotamers where the interaction of the substituents disappears, are represented much more distinctly and not too differently, *i.e.* *F* (0·38 to 0·45) and *G* (0·45–0·49), the assignement of which, however, is merely tentative (on the basis of the greater distance between the substituents in *G*). No systematic effect of the increasing volume of the substituent R was observable.

In *trans*-isomers *V*–*VIII* the situation is different. The rotamer *F* (0·05–0·13) is least populated and the rotamer *G* (0·56–0·63) is most populated, in which, according to models, the interaction of substituents is strongest (in *F*) and weakest (in *G*), which was also used for their mutual assignement. A medium population was calculated for rotamer *E* (0·31–0·33), again in agreement with an analysis

TABLE II

Calculated rotamer populations of *p*-methoxybenzyl group in compounds *I*–*VIII*

Rotamer	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
E	0·17	0·08	0·09	0·12	0·32	0·31	0·33	0·31
F	0·38	0·45	0·43	0·39	0·05	0·13	0·11	0·09
G	0·45	0·47	0·48	0·49	0·63	0·56	0·56	0·60

of models. In *trans*-isomers a systematic effect of the increasing volume of the substituent R has not been observed either.

EXPERIMENTAL

The course of the reaction and the purity of the substances *I*—*VIII* prepared were checked by thin-layer chromatography. The products obtained were purified on preparative thin-layer plates (20 × 20 cm) with "Kieselgel 60 PF_{254}" (Merck. Darmstadt) or by column chromatograohy on silica gel (Herrmann, Koeln/Ehrenfeld). The ^1H NMR spectra were measured on a Varian XL-200 spectrometer (200 MHz) in hexadeuteriodimethyl sulfoxide, using tetramethylsilane as internal reference. The coupling constants $J_{2,7}$ and $J_{2,7'}$ were obtained by analysis of the multiplet of hydrogens H-7 and H-7' as AB-parts of an ABX system.

2-(4-Methoxybenzyl)-1-cyclohexanol (*I*, *V*)

2-(4-Methoxybenzyl)-1-cyclohexanone[3] (6·9 mmol) was reduced with lithium aluminium hydride (14 mmol) in ether (25 ml). After the decomposition of the mixture by a procedure decribed earlier[4] and chromatographic separation of both isomers on a fifty-fold amount of silica gel with ether–light petroleum 1 : 3, 597 mg (39%) of *cis*-isomer *I* were obtained, with m.p. 62—62·5°C and 900 mg (59%) of *trans*-isomer *V* with m.p. 57—58°C. The mass spectra of compounds *I* and *V*: $m/z = 220$ (M^+), 202, 159, 121 (base peak). The evaluation of the ^1H NMR spectra of compounds *I* and *V* is given in Table I. For $C_{14}H_{20}O_2$ (220·3) calculated: 76·32% C, 9·15% H: found: for *I* 76·30% C, 9·11% H; for *V* 76·33% C, 9·12% H.

Preparation of Compounds *II*—*IV* and *VI*—*VIII*

Pyridine (0·3 ml) was added to a solution of *I* or *V* (0·227 mmol) in benzene (2 ml) and a solution of corresponding acyl chloride (0·26 mmol) in benzene (1 ml) was added to it dropwise and under stirring. The mixture was allowed to stand for 2 to 6 h at room temperature and then poured onto ice (5 ml), acidified with hydrochloric acid to pH 5·5 to 6 and extracted with benzene (40 ml). After evaporation of benzene the crude product was purified on preparative thin-layer plates and individual esters were obtained as pure compounds in liquid state. Their structures were determined on the basis of their ^1H NMR spectra (the results of these measurements are shown in Table I) and mass spectra: *II* and *VI*: $m/z = 262$ (M^+), 202, 159, 121 (base peak), 59, 43; *III* and *VII*: $m/z = 290$ (M^+), 202, 159, 121 (base peak), 87, 71; *IV* and *VIII*: $m/z = 304$ (M^+), 202, 159, 112 (base peak), 101, 85. For $C_{16}H_{22}O_3$ (262·3) calculated: 73·25% C, 8·45% H; found; for *II* 73·21% C, 8·47% H; for *VI* 73·19% C, 8·45% H. For $C_{18}H_{26}O_2$ (290·4) calculated: 74·44% C 9·02% H; found: for *III* 74·39% C, 9·05% H; for *VII* 74·40% C, 9·04% H. For $C_{19}H_{28}O_3$ (304·4) calculated: 74·96% C, 9·27% H, found: for *IV* 74·98% C, 9·27% H; for *VIII* 74·94% C, 9·31% H.

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