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Stereochemistry of Seven-membered Heterocycles: XLIV.* Spatial Structure of 4-R-3,5-Dioxabicyclo[5.1.0]octanes

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Abstract—4-R-3,5-Dioxabicyclo[5.1.0]octanes were prepared in good yields by reduction of the corresponding 8,8-dichloro derivatives in a system Li–*t*-BuOH. According to the data of dynamic ^1H and ^{13}C NMR spectroscopy involving experiments in the NOESY mode the formal (R = H) at –93°C in $(CD_3)_2CO$ exists in nearly equally occupied *chair* forms with *endo*- and *exo*-oriented three-membered ring. The like structure were found in the diastereomeric 4-Me(*t*-Bu)-analogs. The characteristic feature of ^{13}C NMR spectra consists in considerable difference in the chemical shifts of the C^8 atoms ($\Delta\delta$ ~16–17 ppm). The data on epimerization of diastereomers and calculations along AM1 procedure suggest for formal a three-component equilibrium including a *twist*-form.

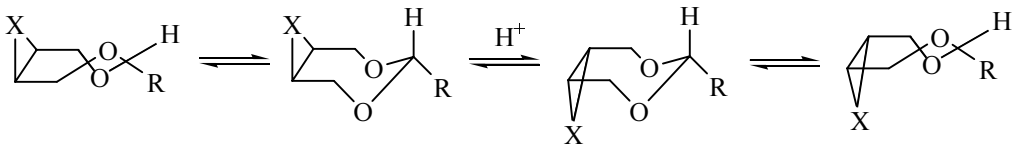
It was shown formerly that dihalo derivatives of 3,5-dioxabicyclo[5.1.0]octane **I** and **II** exist in an equilibrium of *chair*-like and flexible forms [1] (Scheme 1).

For adducts of dichloro- and dibromocyclopropanation the position of conformational and epimerization equilibria is governed by the repulsive interactions involving halogens and oxigens of the acetal fragment and also the bulky R substituent attached to C^4 atom. As show ^{13}C NMR data and semiempirical AM1 calculations for formals **Ia** and **IIa** the most favorable conformation is *exo-chair*. The analogous situation is observed in the diastereomers of the *exo*-series whereas for the *endo*-diastereomers the *chair*-like structure is significantly strained, and the conformational equilibrium is virtually totally shifted to the flexible form In case of identical substitution at the C^4 atom the position of epimerization equilibrium is the same in dichlorides and dibromides, but with growing bulk of the substituent at the acetal carbon the equilibrium is displaced to the *chair* form.

It seemed reasonable to perform the conformational analysis for bicyclic acetals **III** where the sterical contacts involving the cyclopropane moiety and oxygen atom are minimized.

This class compounds were formerly obtained in two ways, either by condensation of *cis*-1,2-dimethylolcyclopropane with paraformaldehyde, isobutyraldehyde [2], and cyclohexanone [3], or by cyclopropanation of 1,3-dioxacyclohept-5-ene by Simmons–Smith reaction [4]. We applied to the synthesis of compounds **III** the known procedure of hydrogenolysis of dichloro derivatives **I** with lithium in the *tert*-butanol. The yields of reaction products **III** were no less than 85% and were higher than those mentioned in [2–4]. The possibility of stereospecific reduction of easily available con-

Scheme 1.



exo **Ia–Ic–IIIa–IIIc** *endo*

X = CCl_2 (**I**), CBr_2 (**II**), CH_2 (**III**); R = H (**a**), Me (**b**), *t*-Bu (**c**).

* For communication XLIII see [1].

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Table 1. Chemical shifts in ^{13}C NMR spectra of compounds **IIIa–IIIc** in acetone-d_6, δ, ppm

Compd. no.	C^4	$C^{2,6}$	$C^{1,7}$	C^8	Substituent at C^4
IIIa[a]	100.99	72.10	18.38	7.78	–
IIIa[b, c]	102.18	75.59	19.60	17.43	–
	100.04	69.50	17.08	0.54	–
exo-**IIIb**[a]	108.55	74.12	19.33	16.18	22.80
exo-**IIIb**[b]	108.17	73.87	18.89	16.26	22.63
endo-**IIIb**[a]	106.81	68.51	17.78	1.29	22.51
endo-**IIIb**[b]	106.61	68.15	17.20	0.48	22.34
exo-**IIIc**[a]	117.70	74.99	19.48	16.74	26.04, 36.64
exo-**IIIc**[b]	116.85	74.30	19.12	16.54	25.71, 36.41
endo-**IIIc**[a]	115.67	69.18	17.81	0.83	25.75, 36.64
endo-**IIIc**[b]	114.95	68.56	17.26	0.40	25.06, 36.41

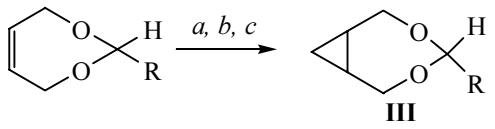
[a] At *T* 25°C.

[b] At *T* –93°C.

[c] Upper line corresponds to signals of the *chair* form with the *exo*-orientation of the cyclopropane ring, the lower line to the respective form with *endo*-orientation.

formationally pure *exo*-dichlorides **I** occurring without epimerization is also very attractive and valuable. Thus we were able to perform the configurational identification of compounds **IIIb** and **IIIc** by chemical means. The alternative isomers were prepared by epimerization (Scheme 2).

Scheme 2.



III

a, $CHCl_3$–50% NaOH–triethylbutylammonium chloride; *b,* epimerization of isomer mixture; *c,* Li–*t*-BuOH.

^{13}C NMR spectroscopy proved to be informative in the stereochemical investigation of seven-membered acetals [1, 5, 6]. The chemical shift of carbon atoms of acetals **IIIa–IIIc** are presented in Table 1. The chemical shifts in the spectra of diastereomeric acetals **IIIb** and **IIIc** are virtually unchanged in the temperature range 25...–93°C, whereas in the spectrum of compound **IIIa** already at the room temperature the exchange broadening of the cyclopropane C^8 resonance appears. In the low-temperature spectrum (Fig. 1) two sets of signals are observed corresponding to the ratio of forms 48/52. Earlier two sets of signals corresponding to the presence of two forms in a ~ 1/1 ratio were observed applying dynamic ^1H NMR spectroscopy to this acetal in acetone-d_6 at –80°C [2].

The maximum difference in the chemical shifts of stereoisomers **III** is observed for C^8 atoms of the methylene groups in the cyclopropane ring (Δδ ~ 16–17 ppm), and therewith the more upfield signal belongs to the *endo*-structures. The conformations of compounds **III** were assigned by analysis of γ-effects of substituents widely used in the conformational analysis [7–9] comparing the latter with those in the series of 1,3-dioxanes **IV** and seven-membered 1,3-dioxa-5,6-benzocycloheptenes **V**.

The values of the γ-effects of substituents for the *chair*-like forms of acetals **IV** and **V**, and also the corresponding values obtained from the low-temperature spectra of diastereomers **III** are given in Table 2 In the table are also shown the values of the dihedral angles RCOC (τ).

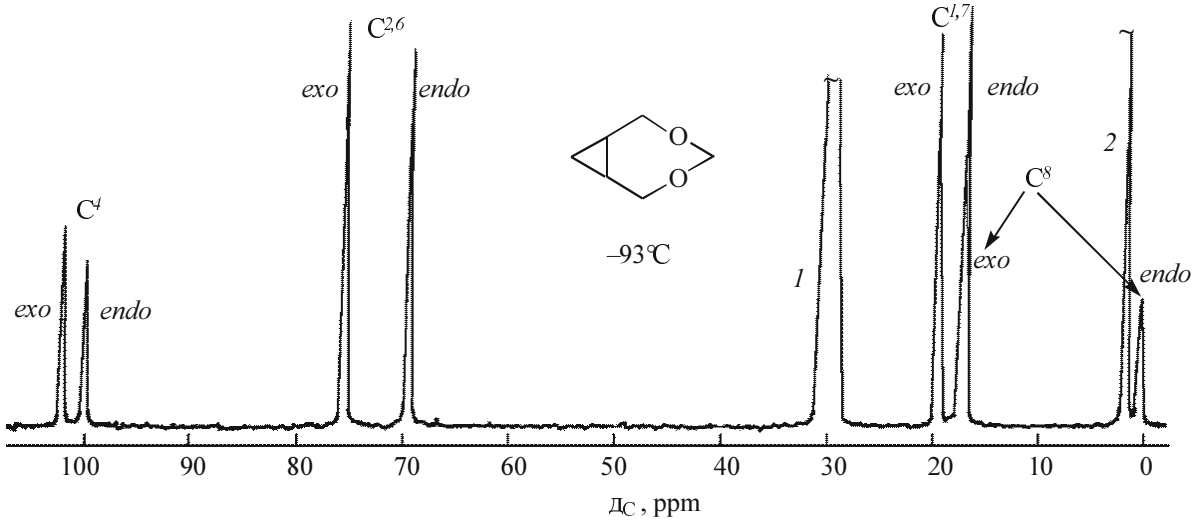


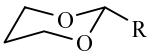
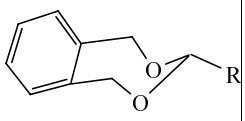
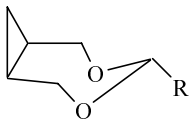
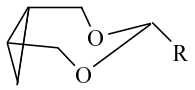
Fig. 1. ^{13}C NMR spectrum of formal **IIIa** at –93°C. Solvent acetone-d_6. *1* is solvent signal, *2* is HMDS signal.

Inasmuch as no data on geometrical characteristics of compounds **III** were available, we calculated by AM1 procedure the τ values for the *chair*-like forms of isomeric bicyclic acetals **III**. The torsion angles were virtually insensitive to the replacement of a methyl group by a *tert*-butyl one. The value calculated for the *exo*-isomer was close to the torsion angles values obtained by X-ray diffraction analysis of the related 8,8-dichloro(dibromo) derivatives [14]. The seven-membered acetals under study differ considerably in both parameters from the corresponding values of 1,3-dioxanes whereas the difference between their isomers is insignificant. The torsion angle in the 1,3-dioxanes at virtually zero γ-effect is H ≈ 80°; the relation of these parameters to each other has been previously analyzed for carbocycles [15] and seven-membered acetals **V** [5]. The latter fact allows attribution of *chair*-like structures to both diastereomeric acetals **IIIb** and **IIIc**. Note that the values of the α-effects in the isomeric *exo*(*endo*)-acetals **IIIb** and **IIIc** amount to 5.99 (6.57) and 14.67 (14.91) respectively and are close to the values determined for compounds from **V** series [6.64 (15.47)].

In order to gain additional information on the structure of compound **IIIa** we measured NOESY spectra on ^{1}H nuclei under conditions of slow exchange. The assignment of proton signals in the ^{1}H NMR spectrum was performed by ^{1}H /^{13}C heterocorrelation procedure. The NOESY experiment at –90°C provided a possibility to establish the exchange route and to analyse the spatial structure of conformers distinguished by the orientation of the cycloprppane ring with respect to the *chair*-like seven-membered skeleton. For instance, in the spectrum of the *exo*-conformer cross-peaks due to NOE were observed between axial protons at $C^{2,6}$ atoms and the *endo*-proton attached to C^8 (Fig. 2).

Cross peaks were found between protons $H^{1,7}$ and both protons $H_e^{2,6}$ and *exo*-H^8 (the interacting protons are marked with arrows). In the heterocyclic part NOE was observed between *syn*-axial protons at atoms C^4 and $C^{2,6}$. In the spectrum of the *endo*-structure where the $H^{1,7}$ protons are located with respect to $H_{a,e}^{2,6}$ protons in the actually skewed conformation the integral intensities of the NOE cross-peaks are close in value. The intense interaction between $H^{1,7}$ and *exo*-H^8 is observed both in the *exo*- and *endo*-conformers. We failed to reveal the interaction between *syn*-axial protons in the latter conformer due to overlapping of the diagonal peaks caused by close chemical shift values of these protons. We do not report the trivial NOE of the geminal protons

Table 2. Values of γ-effects of substituents (δ, ppm) and torsion angles RCOC (τ, deg) of *chair*-like six- and seven-membered acetals **III–V**

Compound	Substituent		τ
	Me	*t*-Bu	
	–0.1[a]	–0.1[b]	179.1[c]
	–1.54[d]	–0.86[d]	166.7[e]
	–1.72	–1.29	165.2[f]
	–1.35	–0.94	159.6

[a] From [10].
[b] From [11].
[c] From [12].
[d] From [5].
[e] From [13].
[f] For 8,8-dibromo analog 164.5 [14].

for both conformers. The proton chemical shifts of conformers **IIIa** are as follows: *exo*-form: 1.87 (*endo*-H^8), 2.02 (*exo*-H^8), 2.43 ($H^{1,7}$), 4.30 ($H_a^{2,6}$), 5.46 (H_a^4), 5.50 ($H_e^{2,6}$), 6.14 (H_e^4); *endo*-form: 1.41 (*exo*-H^8), 1.69 (*endo*-H^8), 2.11 ($H^{1,7}$), 4.86 ($H_a^{2,6}$), 4.92 (H_a^4), 5.24 ($H_e^{2,6}$), 5.98 (H_e^4).

The spatial structure of formal **IIIa** proved to be identical to that of its carboanalog, *cis*-bicyclo[5.1.0]-octane that was regarded as having two *chair* conformation with *exo*- and *endo*-orientation of the three-membered ring [16–18]. This statement is however valid only at temperature below ≈–100°C. Thus the calculation of acetal **IIIa** by AM1 method suggests the presence of three conformers since the difference in heats of

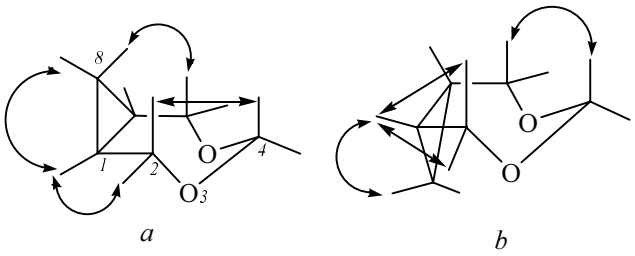


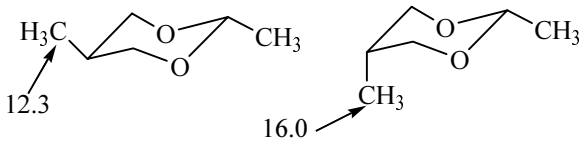
Fig. 2. Interaction of protons (Nuclear Overhauser Effect) in *exo* (*a*) and *endo* (*b*) conformers of acetal **IIIa**.

formation for the *chair*-form with the *endo* (–71.2) and *exo* (–70.3) structure and for *twist*-conformation (–70.3 kcal mol^{-1}) is within 1 kcal mol^{-1}. The preliminary comparison of the Raman spectra [19] obtained from a crystal and a melt of acetal **IIIa** allows to presume the three-component equilibrium.

To consider the conformational state of diastereomers **IIIb** and **IIIc** substituted at C^4 atom we carried out their epimerization (CCl_4, 25°C). The prevalence of *endo*-epimers [54/46 (**IIIb**) and 65/35 (**IIIc**)] in the equilibrium was established with the use of ^{13}C NMR spectroscopy, and the ΔG^0_R values were 0.1 and 0.37 kcal mol^{-1} respectively. It should be noted that formerly determined [2, 20] epimerization constants of 4-isopropyl-substituted isomers (1.22 in $CDCl_3$ at 25°C and 1.2 in boiling benzene), and that found for acetal **IIIb** are of close values.

A proper interpretation of the data on epimerization requires quantitative information on the conformational characteristics of pure *endo*- and *exo*-diastereomers at room temperature. We yet have no proofs of the conformational homogeneity of the diastereomer. Therefor the obtained thermodynamical parameters are just apparent, and their sufficiently close values cannot be a warranty of the conformational similarity of isomeric acetals **IIIb** and **IIIc.**

We would note in conclusion the considerable difference in the chemical shifts of the methyl groups attached to C^5 atom in the isomers of 2,5-dimethyl-1,3-dioxanes **VI** [10] ($\Delta\delta$ –3.7 ppm) and of C^8 atoms in the bicyclic compounds **III** ($\Delta\delta \sim 16$–17 ppm). In the latter, as already mentioned [1], the cyclopropane ring plays the role of a certain substituent..



VI

It is presumable that the observed effect of the acetal oxygen atoms on the chemical shifts of the test carbons located in the *gauche*- and *anti*-positions governs the specific features of electronic interactions involving the cyclopropane fragment and the heteroatoms.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on a spectrometer Varian Unity-300 equipped with a variable temperature probe B-VT-1000 at operating frequencies 300 and 75.43 MHz respectively from solutions of compounds in $(CD_3)_2CO$, internal reference HMDS. The ^1H NMR spectra were measured in a pulse mode at the use of 10– 15-degree pulses, intervals between pulses *dl* 1–2 s; sweep width *sw* 15 ppm; number of scans *nt* from 10 to 100. In the two-dimensional experiments in the NOESY-mode the interval between the successive pulses was three times greater that the average longitudinal relaxation time T_1. The spectra were registered with the use of phase-sensitive procedure for 1024 points of F2 coordinates and 256 points of F1 coordinates applying the exponential filtration along both coordinates. The parameter of mixing time τ_m was chosen equal to 0.2, 0.4, 0.6, and 0.8 s. The ^{13}C NMR spectra were measured in a pulse mode at the use of 20– 30-degree pulses, wide-band decoupling from protons, and digital exponential filtration, *lb* 2–4 Hz. Intervals between pulses were *dl* 1–2 s, *sw* 200 ppm, *nt* from 400 to 1000. Mass spectra were registered on Finnigan MAT-212 instrument at electron impact and direct sample admission into the ion source, ionizing electrons energy 70 eV, the electrons emission current 0.1 mA. The precision measuring of molecular ions masses was performed by peaks superposition method. Semiempirical calculations were carried out by AM1 procedure [21–23] with the use of MOPAC6 software.

4-R-3,5-Dioxabicyclo[5.1.0]octanes IIIa, *exo*-IIIb, *exo*-IIIc. To a solution of 5.5 mmol of 8,8-dichloro-4-R-3,5-dioxabicyclo[5.1.0]octane and 3.24 g of *t*-BuOH in 20 ml of anhydrous ethyl ether was added 0.3 g of lithium, and the mixture was stirred for 3 days. The reaction mixture was filtered, washed with water, dried over magnesium sulfate, and the solvent was distilled off in a vacuum. The yield of the crude reaction product **IIIa** was ≈80%, bp 45–46°C (15 mm Hg.), n_D^{26} 1.4610 {publ.: bp 58°C (18 mm Hg) [4], bp 79–81°C (22 mm Hg) [2]}. Compound *exo*-**IIIb**, bp 75–78°C (17 mm Hg.), n_D^{26} 1.4534. Found, *m/z*: 128.082 $[M]^+$. $C_7H_{12}O_2$. Calculated: *M* 128.084. Compound *exo*-**IIIc**, bp 76–81°C (16 mm Hg), n_D^{26} 1.4510. Found *m/z*: $[M]^+$ 170.131. $C_{10}H_{18}O_2$. Calculated: *M* 170.131.

General procedure of epimerization. To a 10% solution of the isomer mixture in CCl_4 was added a catalytic amount of *p*-toluenesulfonic acid, and the solution was maintained at 25 ± 2°C for 7 days. The completion of the epimerization was monitored by ^{13}C NMR spectroscopy measuring in the samples the isomers ratio by the intensity of signals from the acetal and methylene carbons.

REFERENCES

1. Baryshnikov, R.N., Vafina, R.M.. Fedorenko, V.Yu., Shtyrlin, Yu.G., and Klimovitskii, E.N., *Zh. Org. Khim.,* 2003, vol. 39, p. 1092.
2. Gianni, M.H., Cody, R., Mohan, R.A., Wursthorn, K., Patanode, P., and Kuivila, H.G., *J. Org. Chem*., 1977, vol. 42, p. 365.
3. Gajewski, J.J., Hawkins, C.H., and Jimenez, J.L., *J. Org. Chem*., 1990, vol. 55, p. 674.
4. Pitea, D., Moro, G., and Favini, G., *J. Chem. Soc., Perkin Trans. II*, 1987, p. 313.
5. St-Amour, R. and St-Jacques, M., Canad. *J. Chem*., 1983, vol. 61, p. 109.
6. Klimovitskii, E.N., Timirbaev, M.B., and Arbuzov, B.A., *Zh. Obshch. Khim.,* 1986, vol. 56, p. 144.
7. Werhly, F.W. and Wirthlin, T., *Interpretation of Carbon-13 NMR Spectra,* Heyden L., 1976.
8. Eliel, E.L. and Pietrusiewicz, K.M., *Top.* ^{13}C *NMR Spectrosc*., 1979, p. 172.
9. Wilson, N.K. and Stothers, J.B., *Top. Stereochem*., 1974, p. 1.
10. Pihlaja, K. and Nurmi, T., *Israel J. Chem*., 1980, vol. 20, p. 160.
11. Arbuzov, B.A., Klimovitskii, E.N., Sergeeva, G.N., Remizov, A.B., and Chernov, P.P., *Zh. Obshch. Khim.,* 1983, vol. 53, p. 2770.
12. Hartung, H., Raphtel, I., and Kurnatowski, C., *Cryst. Res. Technol*., 1981, vol. 16, p. 1289.
13. St-Amour, R., Olivier, M.J., St-Jacques, M., and Brisse, F., *Canad. J. Chem.,* 1986, vol. 64, p. 500.
14. Vafina, R.M., Kataeva, O.N., Litvinov, I.A., Sergeeva, G.N., and Klimovitskii, E.N., *Zh. Org. Khim.,* 1993, vol. 29, p. 1885.
15. Lambert, J.B. and Vagenas, A.R., *Org. Magn. Reson*., 1981, vol. 17, p. 265.
16. Todeschini, R. and Favini, G., *J. Molec. Struct*., 1980, vol. 64, p. 47.
17. Favini, G., Pitea, D., Sottocornola, M., and Todeschini, R., *J. Molec. Struct. (Theochem.)*, 1982, vol. 87, p. 53.
18. Brun, P., Casanova, J., Hatem, J., Vincent, E.-J., Waegel, B., and Zahra, J.-P., *C.r*., 1979, vol. 288, p. 201.
19. Sobolev, P.N., *Cand. Sci. (Physicomath.)*, Kazan', 1990.
20. Gianni, M.H., Prezzavento, B., and Shea, K., *J. Org. Chem.,* 1985, vol. 50, p. 1554.
21. Dewar, M.J.S. and Thiel, W., *J. Am. Chem. Soc*., 1977, vol. 99, p. 4899.
22. Stewart, J.J. P., *J. Comput. Chem.,* 1989, vol. 10, p. 209.
23. Stewart, J.J. P., *J. Comput.-Aided, Mol. Des.,* 1990, vol. 4, p. 1.