STEREOCHEMICAL STUDIES. XVIII[1]

Cyclic Aminoalcohols and Related Compounds. IX[1]
Synthesis and NMR Study of Stereoisomeric *cis*-Trimethylene and *cis*- and *trans*-Pentamethylenetetrahydro-1,3-oxazines[2]

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5,6-*cis*-Trimethylene-2-(*p*-nitrophenyl)-tetrahydro-1,3-oxazine (**7**) and 4,5-*cis*-trimethylene-2-(*p*-nitrophenyl)-tetrahydro-1,3-oxazine (**8**) have been prepared by the reaction of *cis*-2-aminomethylcyclopentanol (**1**) and *cis*-2-hydroxymethylcyclopentylamine (**2**) with *p*-nitrobenzaldehyde. 5,6-*cis*- and 5,6-*trans*-Pentamethylene-2-(*p*-nitrophenyl)-tetrahydro-1,3-oxazine (**9**, **10**) and 4,5-*cis*- and 4,5-*trans*-pentamethylene-2-(*p*-nitrophenyl)-tetrahydro-1,3-oxazine (**11**, **12**) were synthesized by the condensation of *cis*- and *trans*-2-aminomethylcycloheptanol (**3**, **4**) and *cis*- and *trans*-2-hydroxymethylcycloheptylamine (**5**, **6**) with *p*-nitrobenzaldehyde. It follows from the NMR spectra of **7**—**12** that in the predominant conformations of the *cis* isomers, both in the trimethylene and pentamethylene series, the hydrogen atoms adjacent to the hetero atoms are equatorial with respect to the hetero ring, *i.e.* conformations **19** and **22** are more probable than **21** and **22**, and conformation **28** and **29** are more probable than **30** and **31** for the *cis*-trimethylene (**7**, **8**) and the *cis*-pentamethylene (**9**, **11**) derivatives, respectively.

Introduction

In an earlier paper of this series [1] the synthesis and NMR study of *cis*- and *trans*-3-*p*-nitrophenyl-1-aza-3-oxa-decalin (**13**, **14**) and *cis*- and *trans*-3-*p*-nitrophenyl-2-aza-4-oxa-decalin (**15**, **16**) were described. As conformational studies on saturated heterocycles are in the foreground of recent research in organic chemistry, it seemed reasonable to synthesize and investigate the related higher and lower homologues of condensed tetrahydrooxazines. In addition to the interest in a study of the conformational relations of these perhydrogenated heterocycles with condensed skeleton, further impulse was given to our work by other factors. Thus the structures of the tetramethylene analogues (**13**—**16**), related to the bicyclic transition state of the N→O acyl migration reaction of the parent 1,3-aminoalcohols, investigated earlier

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[2, 3], had served as incentive for the synthesis and study of the conformations of those compounds; similarly, the analogy of the structures of the tetrahydrooxazines **7** and **8** with the bicyclic transition states of the N→O acyl migration reaction of 1,3-aminoalcohols with cyclopentane skeleton [4, 5] and that of the tetrahydrooxazines **9**—**12** with the transition states of the reaction of cycloheptane derivatives (**3**—**6**) [6], promted us to investigate the compounds dealt with in the present paper.

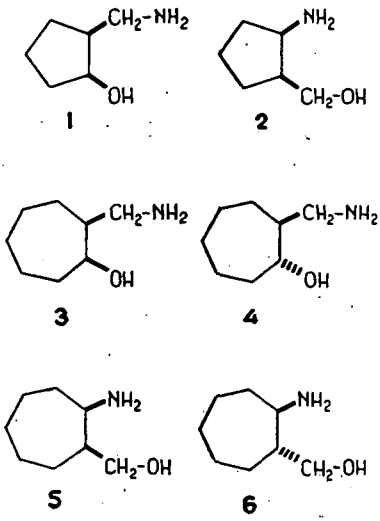

Fig. 1

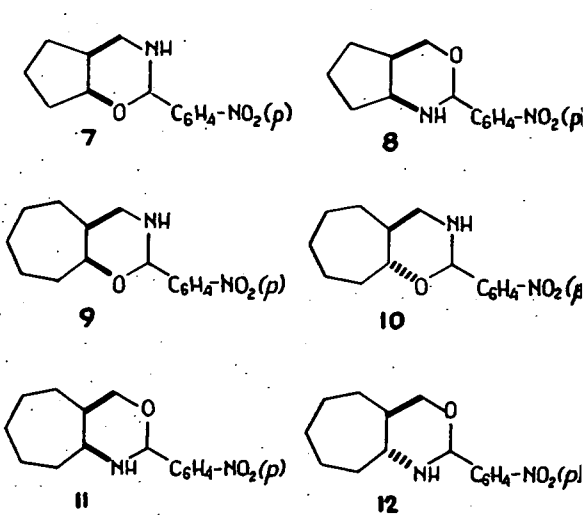

Fig. 2

Synthesis

The stereospecific syntheses of *cis*-2-aminomethylcyclopentanol (**1**) and *cis*-2-hydroxymethylcyclohexylamine (**2**) [5], as well as of *cis*- and *trans*-2-aminomethylcycloheptanol (**3**, **4**) and of *cis*- and *trans*-2-hydroxymethylcycloheptylamine (**5**, **6**) [7] were described earlier. The subject of this communication is the synthesis and NMR study of the isomeric tetrahydrooxazines **7**—**12**.

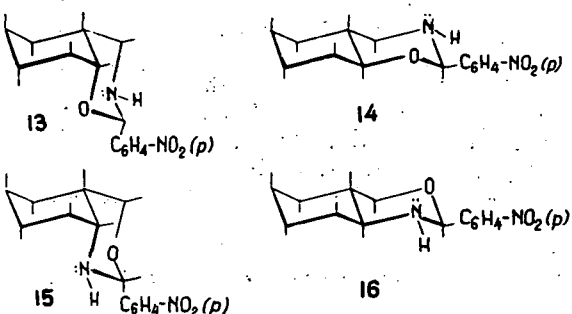

Fig. 3

Table I

Melting points and analyses of tetrahydrooxazine derivatives **7—12**

Compound	M. p. [a.]	Formula (molecular weight)	Analytical data; calculated/found (%) C	H	N	Note
7	80—81 °C	$C_{13}H_{16}O_3N_2$ (248.28)	62.89 63.20	6.49 6.42	11.29 10.95	*b)*
8	84.5—85.5	$C_{13}H_{16}O_3N_2$ (248.28)	62.89 62.55	6.49 6.55		
9	85	$C_{15}H_{20}N_2O_3$ (276.35)	65.20 65.21	7.29 7.12	10.14 10.05	*b)*
10	104	$C_{15}H_{20}N_2O_3$ (276.35)	65.20 65.86	7.29 7.32	10.14 9.89	*d)*
11	108—110	$C_{15}H_{20}N_2O_3$ (276.35)	65.20 65.23	7.29 7.24	10.14 10.10	*b)*
12	74	$C_{15}H_{20}N_2O_3$ (276.35)	65.20 65.20	7.29 7.50	10.14 10.03	*c)*

Note. *a.)* Solvent for recrystallization: petroleum ether, b.p. 45 – 60 °C
b.) Pale yellow needles
c.) Orange crystals
d.) White needles

Compounds **7—12** were prepared from the corresponding aminoalcohols (**1—6**) with *p*-nitrobenzaldehyde, as described [1] for the preparation of the tetramethylene homologues (**13—16**). Melting points and analytical data are summarized in Table I.

Results and discussion

Whereas the conformational analysis of six-membered rings has been succesfully accomplished in many respects both qualitatively and quantitatively, five- and seven--membered rings have been much less studied and understood [8, 9].

For determining the conformational relations of cyclopentane derivatives, calculation methods have been developed [10, 27] and other methods have also been applied [11]. Concerning cycloheptane derivatives, the calculations of HENDRICKSON are of fundamental importance [12—15]. For both systems, owing to the high mobility (pseudorotation), more complex conformational patterns exist than in the case of cyclohexane derivatives.

This also holds for cyclopentane and cycloheptane derivatives condensed with cyclohexane skeleton. Though a number of papers deal with the conformational analysis of *cis*- and *trans*-hydrindane (**18, 17**) [16] and of related perhydrogenated heterocycles [17], the interpretation of the results involves some difficulties. The conformational study of cycloheptane derivatives condensed with cyclohexane skeleton has attracted comparatively little attention [7].

The basic conformations of cyclopentane are the C_s (envelope) and the C_2 (half chair) forms. Taking into account the different energy contents of equatorial and axial positions, a monosubstituted cyclopentane may assume eleven energetically different conformations, five C_2 and six C_s forms [28]. However, on the basis of recent X-ray studies it was concluded that, in the majority of the cases investigated, none of the basic forms represents a minimum of energy [29] but the true geometry is somewhere „in between", being neither C_2 nor C_s.

For cyclopentane derivatives condensed with cyclohexane skeleton the situation is similar. Extensive studies on the conformational relations of steroids [27] have shown that ring D exists only in a few cases in the envelope form (C_s) or as a half chair (C_2); most compounds have their ring D in forms intermediate between the above structures.

Among disubstituted cyclopentane derivatives mainly dihalogenocyclopentanes were investigated, therefore it is difficult to apply the results to other 1,2-difunctional derivatives. However, it is an important result of the investigations that an *aa* ⇌ *ee* equilibrium exists, and the *ee* form predominates in all cases investigated.

Valence-force field calculations [30] provide a very powerful tool for determining torsional and valency angles in condensed cyclopentane derivatives. Calculations show that ring D of androsterone [31] undergoes only small changes during the pseudorotation; this was observed earlier for monosubstituted cyclopentanes, too.

In connection with this observation it is to be mentioned that in *t*-butylcyclopentane derivatives the *t*-butyl group has no holding effect on the cyclopentane ring. BUYS found [11] that in *trans*-1,2-dibromo-4-*t*-butylcyclopentane, the diaxial and diequatorial forms may equilibrate *via* pseudorotation with a very low energy barrier, and the *t*-butyl group remains equatorial during the process. The diaxial form is predominating in the equilibrium.

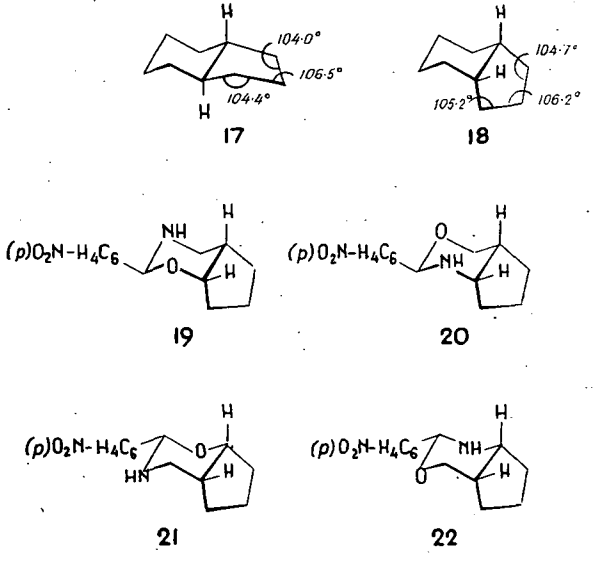

Fig. 4

Similar conclusions can be drawn from our results obtained in the solvolysis of N-benzoyl-O-mesyl derivatives of *trans*-2-amino-4-*t*-butylcyclopentanol isomers [32], where no significant difference was found between the rates of solvolysis of *trans*-2-amino-4-butylcyclopentanol derivatives and of *trans*-2-aminocyclopentanol derivative [33].

There is only a slight difference in the valency angles of the cyclopentane ring of *cis*- and *trans*-hydrindane (**18, 17**); ALLINGER and TRIBLE [16] calculated a 1.1 kcal/mole lower enthalpy for *trans*-hydrindane than for the *cis*-isomer. This small difference arises from the 0.6 kcal/mole higher bending energy of the *trans*-isomer, and on the other hand, from the circumstance that the torsional and van der Waals energies of the *cis*-isomer are higher by 0.6 kcal/mole and 1.1 kcal/mole, respectively, than the corresponding values for the *trans*-isomer.

Though a difference of 1.1 kcal/mole is small in itself, in reactions proceeding through a hydrindane-like transition state, a significant difference in the reactivity of the *cis*- and *trans*-isomers will be found; this equally applies to the cases when the six-membered ring is a carbocycle, as in the N→O acyl migration reaction of *cis*- and *trans*-2-benzamidocyclohexanol [24], and when the carbocycle is five-membered and the heterocycle is six-membered, as in the N→O acyl migration reactions of the N-benzoyl derivatives of *cis*- and *trans*-2-aminomethylcyclopentanol and *cis*- and *trans*-2-hydroxymethylcyclopentylamine [4, 5].

It was found [4, 5] that N→O acyl migration reaction with retention mechanism is readily induced in the N-benzoyl derivatives of *cis*-2-aminomethylcyclopentanol and *cis*-2-hydroxymethylcyclopentylamine, whereas the corresponding *trans*-isomers react only at much higher temperatures and with inversion.

Considerable difference between the reactivity of the *cis*- and *trans*-cyclopentane derivatives was observed also in the oxazine formation reaction, which is discussed in this paper; under the usual conditions [1] cyclic products could be obtained only from the *cis*-aminoalcohols.

For the tetrahydrooxazines (**7, 8**) four conformations (**19—22**) are to be taken into consideration. In consequence of the high δ-values of the hydrogen atoms adjacent to the hetero atom, the hydrogen atoms seem to be equatorial with respect to the hetero ring. Thus conformations **19** and **20** are more probable than **21** and **22**. However, it should be noted that the coupling constants J_{AX} and J_{BX} are small; therefore, though the preferred conformations are similar to those of the cyclohexane homologues (**13, 15**), the conformers will now be obviously less stable.

According to the fundamental papers of HENDRICKSON [12—14], there are four conformations of cycloheptane with nearly equal energy contents (Fig. 5). These are, in the order of increasing energies, the twist-chair (**23**) (0.0 kcal/mole), chair (**24**) (2.16 kcal/mole), twist-boat (**25**) (2.49 kcal/mole) and boat (**26**) (3.02 kcal/mole) conformations. For the above conformations BIXON and LIFESON [34] calculated the values: 0.0, 0.67, 2.64 and 2.40, respectively. ROBERTS *et al.* in a very recent paper [18] give the respective values as 0.0, 1.4, 2.4 and 2.7 kcal/mole.

These authors studied the temperature dependence of the NMR spectra of 4,4-difluoro-1,1-dimethylcycloheptane at low temperatures and found that the molecule existed predominantly in the twist-chair conformation They made a very comprehensive study of the pseudorotation of cyclohexane derivatives, too. As known, the cycloheptane ring is flexible; the conformations are interconvertible *via* pseudorotation.

Though the supposition of a twist-chair form with the lowest energy content seems the most obvious [21], the discussion of a recent paper is based on the chair conformation [22], emphasizing that the differences in the NMR spectra are due to the configurations of the substituents, and not to a preferred conformation of the seven-membered ring.

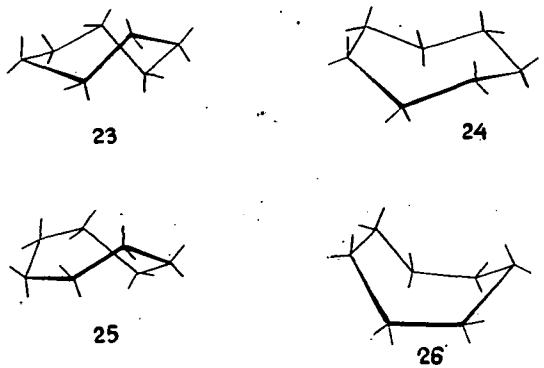

Fig. 5

In the twist-chair conformation three valence orientations, namely equatorial, isoclinal and axial, can be distinguished. The additional strain energy caused by the introduction of an axial methyl group in positions 2, 3 and 4 is 2.5, 3.0 and 1.5 kcal/mole, respectively [14, 23].

The energy contents of 1,2-dimethylcycloheptanes were also studied by isomerization [21]. The data calculated from the temperature dependence of the equilibrium constants ($\Delta H_{cis/trans}=0.7$ kcal/mole and $\Delta S_{cis/trans}=0.5$ e.u.) are consistent with the twist-chair form of cycloheptane. Though alkyl substituents cause some rigidity, the flexibility of the skeleton allows the substituents to occupy equatorial positions as far as possible. However, in 1,2-disubstituted *cis*-cycloheptane derivatives one of the substituents has to be in quasiaxial or isoclinal position. It can be deduced from the calculated data that the substituent in position 1 (isoclinal) is somewhat less favoured than in positions 2*e*, 3*e* or 4*e*.

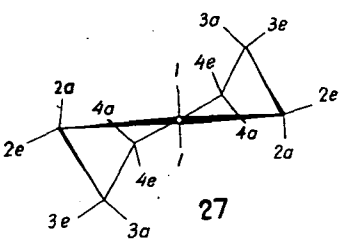

Fig. 6

MANN [21] determined the enthalpy levels of *cis*- and *trans*-dimethylcycloheptanes and of the dimethylcyclohexane isomers. BREDOW *et al.* [35] studied the temperature dependence of the NMR spectrum of 5,5-dimethyl-3,3,7,7-tetradeutero-1,2-dithiacycloheptane. The methylene signals split only at -57 °C, and further details of this part of the spectrum appeared only at -110 °C. These and similar NMR studies furnished valuable data concerning the pseudorotation.

The flexibility of the skeleton is also indicated by the fact that *trans*-cycloheptane-1,2-diol [19] gives an isopropylidene derivative. An early IR study [26] of *cis*- and *trans*-cycloheptane-1,2-diol showed torsional angles of 42° and 51°, respectively, for the OH groups. However, it is to be emphasized that there are only a few papers in the literature on 1,2-disubstituted cycloheptane derivatives evaluating the relative reactivity of *cis*- and *trans*-isomers on experimental basis.

The above circumstances called our attention to the investigation of the rate of hydrolysis of ethyl *cis*- and *trans*-cycloheptanol-2-carboxylate [36] and of the N→O acyl migration reaction of the N-benzoyl derivatives of the aminoalcohols **3**—**6**. Con-

Table II

IR and NMR data of the tetrahydrooxazine derivatives **7—12**

Compound	IR data [a]			NMR data [b]							OCHN
	NH	NO_2		CHO	CHN	A	B	J_{AB}	J_{BX}	J_{AX}	
7	3305	1515	1350	4.2	–	3.39	3.13	15	1	0	5.10
8	3310	1515	1345	–	3.5	*c.)*	*c.)*	*c.)*	*c.)*	*c.)*	5.10
9	3300	1515	1345	4.15	–	3.3	3.1	15	–	–	5.25
10	3300	1510	1340	3.4	–	3.1	2.7	15	10		
11	3300	1510	1350	–	3.4	*c.)*	*c.)*	*c.)*	*c.)*	*c.)*	5.20
12	3310	1515	1345	–	2.6	4.0	3.4	11	11	5	5.05

Note. *a)* ν in cm^{-1}
b) Chemical shifts in δ ppm, coupling constants in Hz units. Solvent: $CDCl_3$
c) The CH_2 signal is a singlet because of the accidental coincidence of C—4 H^A and C—4H^B
d) 20 Hz

densation of **3—6** with urea afforded [7] the pentamethylene-tetrahydrooxazinones. The pentamethylene-tetrahydrooxazines **9—12** are treated in this paper.

NMR data of the *cis*-tetrahydrooxazines **9** and **11** (Table II) showed that among the conformations which are possible in principle (**28**, **29** and **30**, **31**, respectively), **28** and **29** are predominant, where the hetero atom connected to the cyclopheptane skeleton is axial, and the methylene group is equatorial.

These predominating conformations are in accordance with those of the tetramethylene-tetrahydrooxazine derivatives investigated earlier (Fig. 3), where, in the

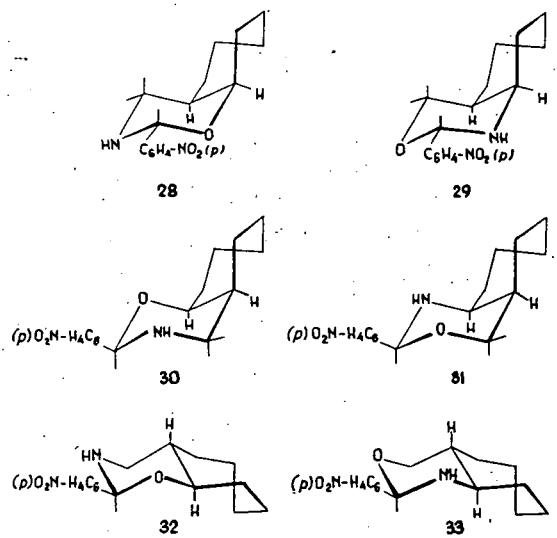

Fig. 7

preferred conformations (**13**, **15**), the hetero atoms connected to the cyclohexane skeleton are also axial. Furthermore, tetrahydrooxazinones condensed with cycloheptane skeleton also show analogous conformations [7].

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References

[1] *Bernáth, G., K. L. Láng, K. Kovács, L. Radics:* Acta Chim. Acad. Sci. Hung. **73**, 81 (1972).
[2] *Bernáth, G., K. Kovács, K. L. Láng:* Tetrahedron Letters **1968**, 2713.
[3] *Bernáth, G., K. Kovács, K. L. Láng:* Acta Chim. Acad. Sci. Hung. **65**, 347 (1970).
[4] *Bernáth, G., K. L. Láng, Gy. Göndös, P. Márai, K. Kovács:* Tetrahedron Letters **1968**, 4441.
[5] *Bernáth, G., K. L. Láng, Gy. Göndös, P. Márai, K. Kovács:* Acta Chim. Acad. Sci. Hung. **74**, 479 (1972).
[6] *Bernáth, G.:* Lecture delivered at a meeting of the Committee for Alkaloid Chemistry of the Hungarian Academy of Sciences, Balatonalmádi, 19 May, 1972. *Cf.:* Bruckner, Gy.: Kémiai Közlemények (Budapest) **38**, 137—185 (1972) and *ibid.* pp. 153—154.
[7] *Bernáth, G., Gy. Göndös, K. Kovács, P. Sohár:* Tetrahedron **29**, 981 (1973).
[8] *Eliel, E. L., N. L. Allinger, S. J. Angyal, G. A. Morisson:* Conformational Analysis, Interscience-Wiley, New York 1965.
[9] *Hanack, M.:* Conformational Theory, Academic Press Inc., New York, 1965.
[10] *Bucourt, R.:* Bull. soc. chim. France **1964**, 2080.
[11] *Buys, H. R.:* Conformational Investigations on Five-Membered Ring Compounds. Thesis. Rijks University, Leiden. Bronder-Offset, Rotterdam, 1968 and references cited therein.
[12] *Hendrickson, J. B.:* J. Amer. Chem. Soc. **83**, 4537 (1961).
[13] *Hendrickson, J. B.:* J. Amer. Chem. Soc. **86**, 4854 (1964).
[14] *Hendrickson, J. B.:* J. Amer. Chem. Soc. **89**, 7036, 7043, 7047 (1967).
[15] *Tochtermann, W.:* Konformative Beweglichkeit von Siebenring-Systemen. In: Fortschritte der Chemischen Forschung—Topics in Current Chemistry. Band 15, Heft 3.: Dynamic Stereochemistry, pp. 378—444. Springer-Verlag Berlin, Heidelberg, New York.
[16] *Allinger, N. L., M. T. Tribble:* Tetrahedron **28**, 1191 (1972), and earlier references cited therein.
[17] *Crabb, T. A., R. F. Newton:* J. C. S. Perkin II **1972**, 1920.
[18] *Glazer, E. S., R. Knorr, C. Ganter, J. D. Roberts:* J. Amer. Chem. Soc. **94**, 6026 (1972).
[19] *Christian, W. R., C. J. Gogek, C. B. Purves:* Can. J. Chem. **29**, 911 (1951).
[20] *Kuhn, L. P.:* J. Amer. Chem. Soc. **76**, 4323 (1954).
[21] *Mann, G., M. Mühlstädt, R. Müller, E. Kern, W. Hadeball:* Tetrahedron **24**, 6941 (1968).
[22] *Baumann, H., H. Möhrle, A. Dieffenbacher:* Tetrahedron **25**, 135 (1969).
[23] *Stoddart, J. F.:* Stereochemistry of Carbohydrates. Wiley-Interscience, New York, 1971. p. 106.
[24] *Fodor, G., É. Fodor-Varga, Á. Furka:* Croatica Chim. Acta **29**, 303 (1957).
[25] *Allinger, N. L., Coke, J. L.:* J. Amer. Chem. Soc. **81**, 4080 (1958).
[26] *Kuhn, L. P.:* J. Amer. Chem. Soc. **76**, 4323 (1954).
[27] *Altona, C.:* Geometry of Five-Membered Rings. In: Conformational Analysis, Scope and Present Limitations (Ed.: G. Chiurdoglu). Acad. Press, New York, London, 1971, p. 1.
[28] *Altona, C., H. R. Buys, E. Havinga:* Rec. Trav. Chim. **85**, 973 (1966).
[29] *Romers, C., C. Altona, H. R. Buys, E. Havinga:* Geometry and Conformational Properties of Some Five- and Six-Membered Heterocyclic Compounds Containing Oxygen or Sulfur. In: Topics in Stereochemistry, Vol. 4. (Eds.: E. L. Eliel, N. L. Allinger), Wiley-Interscience, New York, 1969, p. 39.
[30] *Boyd, R. H.:* J. Chem. Phys. **49**, 2573 (1968).
[31] See: ref. [27] footnote on p. 7.
[32] *Bernáth, G., M. Svoboda:* Tetrahedron **28**, 3475 (1972).

[33] *Bernáth, G.:* to be published.
[34] *Bixon, M., S. Lifson:* Tetrahedron **23**, 769 (1967).
[35] *Bredov, K. von, H. Friebolin, S. Kabuss:* Die konformative Beweglichkeit der gesättigten Siebenringverbindungen. Ringinversion, Version und Pseudorotation des 5,5-Dimethyl-3,3,7,7-tetradeuterium-1,2-dithiacycloheptans. In: Conformational Analysis. Scope and Present Limitations (Ed.: G. Chiurdoglu). Academic Press, New York, London, 1971, p. 51.
[36] *Bernáth, G., Gy. Göndös, P. Sohár, K. L. Láng, L. Gera, A. Pál:* to be published.

СТЕРЕОХИМИЧЕСКИЕ ИССЛЕДОВАНИЯ XVIII. ЦИКЛИЧЕСКИЕ АМИНОСПИРТЫ И РОДСТВЕННЫЕ СОЕДИНЕНИЯ XIX. СИНТЕЗ И ЯМР СПЕКТРОСКОПИЧЕСКОЕ ИЗУЧЕНИЕ *ЦИС-* И *ТРАНС*-ПЕНТАМЕТИЛЕНТЕТРАГИДРО-1,3-ОКСАЗИНОВ

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Получены 5,6-*цис*-триметилен-2-(*п*-нитрофенил)-тетрагидро-1,3-оксазин (**7**) и 4,5-*цис*-триметилен-2-(*п*-нитрофенил)-тетрагидро-1,3-оксазин (**8**) реакцией взаимодействия *цис*-2-аминометилциклопентанола (**1**) с *цис*-2-гидроксиметилциклопентиламином (**2**) и *п*-нитро-бензальдегидом. Получены 5,6-*цис*- и 5,6-*транс*-пентаметилен-2-(*п*-нитрофенил)-тетрагидро-1,3-оксазин (**9**, **10**) и 4,5-*цис*- и 4,5-*транс*-пентаметилен-2-(*п*-нитрофенил)-тетрагидро-1,3-оксазин (**11**, **12**) конденсацией *цис*- и *транс*-2-гидроксиметилциклогептанола (**3**, **4**) и *цис*- и *транс*-2-гидроксиметилциклогептиламином (**5**, **6**) и *п*-нитро-бензальдегидом. На основании ЯМР спектров можно прийти к заключению, что как в ряду триметилена, так и пентаметилена в более стабильной конформации *цис* изомеров атом водорода, присоединяющийся к гетероциклу в соседстве с гетероатомом, находится в экваториальном положении к гетероциклу, т. е. в случае производных *цис*-триметилена (**7**, **8**) конформации **19** и **20** более вероятны, чем **21** и **22**. Далее, в случае производных *цис*-пентаметилена (**9**, **11**), более вероятны конформации **28** и **29**, чем **30** и **31**.