STEREOCHEMICAL STUDIES ON 1,3-DIFUNCTIONAL CYCLOPENTANE, CYCLOHEXANE AND CYCLOHEPTANE DERIVATIVES*

By

G. BERNÁTH, K. L. LÁNG, GY. GÖNDÖS, P. MÁRAI and K. KOVÁCS

Institute of Organic Chemistry, Attila József University Szeged, Hungary

(Received: July 10, 1971)

The authors give a review of their synthetic and stereochemical studies on cyclic 1,3-aminoalcohols.

The stereospecific synthesis of *cis*- and *trans*-2-aminomethylcyclopentanol and *cis*- and *trans*-2-hydroxymethylcyclopentylamine as well as their cyclohexane and cycloheptane analogues are described. Kinetic and preparative studies of the N → O acyl migration reaction of the cyclopentane and cyclohexane derivatives are discussed. The solvolysis and NMR spectroscopical analysis of tetrahydrooxazines prepared from *cis*- and *trans*-2-aminomethylcyclohexanol and *cis*- and *trans*-2-hydroxymethylcyclohexylamine is interpreted. Preparation and investigation of some other derivatives, mainly acid amides, of the above aminoalcohols of pharmacological interest is also discussed.

Introduction

In our investigations in the field of cyclic 1,3-difunctional derivatives [1—13] we aimed at a comparative kinetic study of cyclopentane, cyclohexane and cycloheptane derivatives synthesized in a stereospecific way, by clearing up the dependence of the reaction rate on ring size, configuration and conformation. The first model compounds studied were the *cis*- and *trans*-1,3-aminoalcohols (I—XII) shown in Fig. 1. One functional group and the methylene group bearing the other are attached to the ring in 1,2 position.

By evaluation of the reactions of these 1,3-aminoalcohols and the intermediates of their stereospecific synthesis, — *i.e.* the *cis*- and *trans*-β-aminocarboxylic acids and *cis*- and *trans*-β-hydroxycarboxylic acids and their derivatives — we wished to clear up the reaction mechanism in detail and to obtain data concerning the conformational relations of the bicyclic intermediates. We hoped that the reaction mechanism of these 1,3-difunctional compounds, based on the kinetic and thermodynamic parameters would permit, in some cases, also a deeper insight into the reaction mechanism of the related 1,2-difunctional compounds investigated earlier. Moreover, our stereohomogeneous model compounds and their numerous homologous derivatives seemed promising for a systematic study of the relation between chemical structure, configuration, conformation, and pharmacological effect.

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* This Paper is based on a lecture of the authors presented at the „Symposium on Reaction Mechanism and Synthesis" organised by the Committee of Organic Chemistry of the Hungarian Academy of Sciences, Mátrafüred, 22nd May, 1971.

Normal, medium and large ring compounds have often been used as models for studying the influence of configuration and conformation on reaction rate and reaction mechanism of organic compounds. Monosubstituted as well as 1,1- and 1,2-disubstituted cyclic compounds, among them 1,2-aminoalcohols, have been most widely investigated, whereas a considerably lower number of publications dealing with the reaction mechanism of 1,3-difunctional compounds are available.

An important impulse to stereochemical studies on cyclic aminoalcohols was due to streptamine, one of the decomposition products of streptomycine, which proved to be 1,3-diamino-2,4,5,6-tetrahydroxycyclohexane [15]. To clarify the steric structure of this compound, MCCASLAND *et al.* investigated the configuration of simpler analogues, *cis*- and *trans*-2-aminocyclohexanol. While in 1949 even the configuration of these compounds was dubious, twenty years later more than 40 of the theoretically possible 80 aminocyclitol isomers were known [19].

Numerous reactions of cyclic 1,2-aminoalcohols, mainly of 2-aminocyclopentanol and 2-aminocyclohexanol, even of their medium and large ring homologues were thoroughly investigated [16—18, 47]. Fused ring analogues, such as 2-amino-3-hydroxytetralin [20] and 1-amino-2-hydroxytetralin, 1-amino-2-hydroxytetralin, 1-amino-2-hydroxyindane [21] were prepared and their stereospecific reactions intensively studied. The synthesis of *cis*- and *trans*-6-amino-6,7,8,9-tetrahydro-5H--benzocycloheptanol-5 and their N→O acyl migration reaction were published quite recently [22]. The same can be said about other cyclic 1,2-amino-alcohols [23] with highly condensed skeleton. The investigation of the mentioned 1,2-aminoalcohol derivatives, as ephedrine analogues, is important also from a pharmacological point of view.

Considering the numerous studies on monosubstituted 1,1- and 1,2-disubstituted normal, medium and large ring compounds, it is difficult to understand why investigations on 1,3-difunctional derivatives have received considerably less attention. This can be scarcely explained by the difficulties in synthesizing the 1,3-difunctional compounds, though the stereospecific synthesis of 1,3-aminoalcohols,

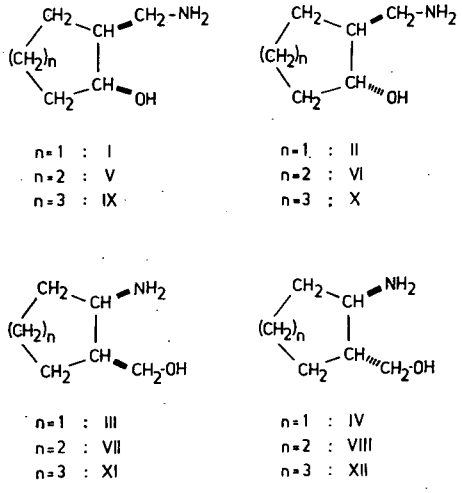


Fig. 1

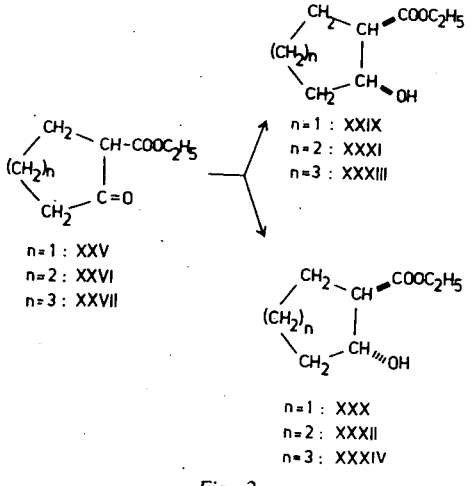


Fig. 2

e.g. of our model compounds is evidently much more difficult and time-consuming than that of the cyclic 1,2-aminoalcohols. It can be stated (see *e.g.* [6]) that, except a few earlier individual papers, no systematic investigations on 1,3-aminoalcohols, especially on the cyclic ones, were published. Our model compounds (I—XII) were not described or, as we pointed out [5], the earlier syntheses were not stereospecific, *i.e.* the compounds regarded as homogeneous proved to be mixtures of the *cis* and *trans* isomers.

Synthesis of model compounds

The stereospecific synthesis of *cis*- and *trans*-2-aminomethylcyclopentanol (I, II) and *cis*- and *trans*-2-hydroxymethylcyclopentylamine (II, IV), as well as of their analogues with cyclohexane and cycloheptane skeleton (V—VIII, IX—XII) was performed by lithium aluminium hydride reduction of the corresponding *cis*- and *trans*-β-hydroxycarboxamides and β-aminocarboxylic acids, respectively (Fig. 3).

Methods for preparing *cis*- and *trans*-2-hydroxycyclopentanecarboxylic acid, *cis*- and *trans*-2-hydroxycyclohexanecarboxylic acid (XLVII, XLVIII), *cis*- and *trans*-2-hydroxycycloheptanecarboxylic acid (XLIX, L) were elaborated by PASCUAL *et al.*, who also determined the configuration of these compounds.

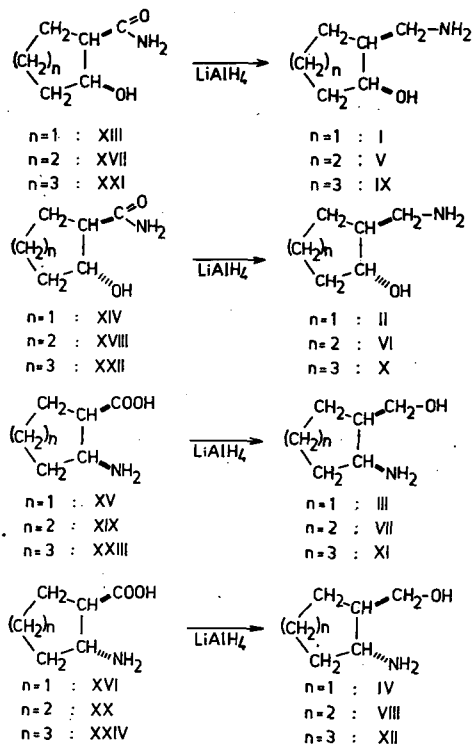


Fig. 3

Reduction of 2-carbethoxycyclopentanon (XXV) [24] in the presence of Adams' PtO_2 catalyst gave *cis*- and *trans*-2-carbethoxycyclopentanol (XXIX, XXX) [25]. The *cis* and *trans* isomers were separated by a tedious fractional crystallization of their 3,5-dinitrobenzoates, then, by hydrolysis, *cis*- and *trans*-2-hydroxycyclopentanecarboxylic acid was obtained. Though recent application of this method is mentioned in literature [26], it does not seem to be convenient for preparing larger quantities, especially of the *trans* isomer obtainable from the mother liquor.

Recently a continuous countercurrent distribution method for the separation of *cis*- and *trans*-2-carbethoxycyclopentanol (XXIX, XXX) was elaborated by MÖHRLE and BAUMANN [27]. Also this method is suitable only for the separation of smaller quantities, like the separation by preparative gas chromatography [92].

PASCUAL *et al.* studied the reduction of 2-carbethoxycyclopentanon (XXV) with different methods. Reduction with sodium borohydride gave mainly *trans*-2-hydroxycyclopentanecarboxylic acid instead of *cis*- and *trans*-2-carbethoxycyclopentanol (XXIX, XXX) [28].

We found that the most convenient method for the preparation of *cis*- and *trans*-2-carbethoxycyclopentanol (XXIX, XXX) was the separation of the isomeric mixture obtained with sodium borohydride or Raney nickel reduction of 2-carbethoxycyclopentanone (XXV) by fractional distillation on a column of high efficiency. Reduction with Raney nickel catalyst in ethanolic solution at 60°C, starting from 120 atm. pressure, yielded 87.3% *cis*- and 12.7% *trans*-2-carbethoxycyclopentanol, according to gas-chromatographic analysis. The sodium borohydride reduction, especially at lower temperatures, gave the *trans* isomer as the main product [11]. This is in good accordance with our earlier results obtained with sodium borohydride reduction of 2-carbethoxy-4-*t*-butylcyclopentanon [14], where the ratio of the isomers containing the hydroxyl and carbethoxyl groups in *trans* position increased with decreasing temperature.

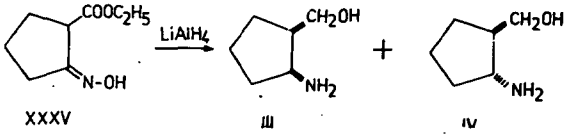


Fig. 4

The reduction of the acid amides (XIII, XIV) obtained from the stereohomogeneous 2-carbethoxycyclopentanols was performed in tetrahydrofurane solution with lithium aluminium hydride at 60°C in 20 hrs and gave *cis*- and *trans*-2-aminomethylcyclopentanol (I, II) with good yield [12].

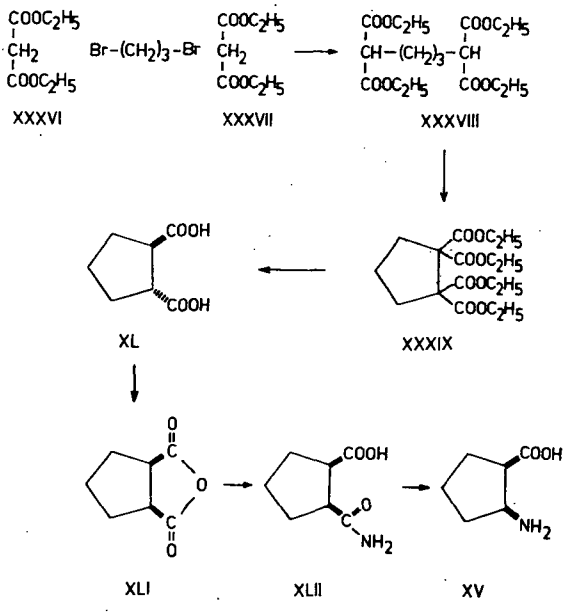


Fig. 5

The preparation of *cis*- and *trans*-2-hydroxymethylcyclopentylamine (III, IV) was achieved with lithium aluminium hydride reduction of *cis*- and *trans*-2-aminocyclopentanecarboxylic acid (XV, XVI) [12]. The synthesis of 2-hydroxymethylcyclopentylamine described by GASSMAN and HECKERT [30] cannot be regarded as stereospecific, because the lithium aluminium hydride reduction of the 2-carbethoxycyclopentanon oxime (XXXV) evidently gives a mixture of the *cis* and *trans* isomers (III, IV) (Fig. 4).

We synthesized *cis*-2-aminocyclopentanecarboxylic acid (XV) applying PERKIN's synthesis [31] modified by BAILEY and SORENSON [32] with some further modifications, as shown in Fig. 5.

Trans-2-aminocyclopentanecarboxylic acid (XVI) can be prepared from 1-cyclopentene-1-carboxylic acid (XLIII) by ammonia addition [33, 34] (Fig. 6). For the preparation of 1-cyclopentene-1-carboxylic acid, we found the dehydration

of *cis*- and *trans*-2-hydroxycyclopentanecarboxylic acid, occurring during the distillation at atmospheric pressure, as the most convenient method.

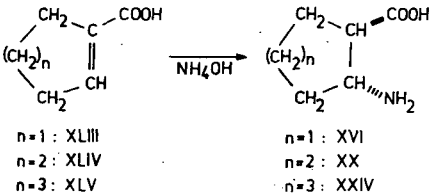


Fig. 6

Cis- and *trans*-2-hydroxycyclohexanecarboxamide (XVII, XVIII) was obtained similarly to the cyclopentane analogues [5]. For preparing *trans*-2-hydroxycyclohexanecarboxylic acid, besides separation by fractional distillation of *cis*- and *trans*-2-carbethoxycyclohexanol (XXXI, XXXII) furnished by sodium borohydride or Raney nickel reduction of 2-carbethoxycyclohexanon (XXV) [36], isomerization of *cis*-2-hydroxycyclohexanecarboxylic acid with 30—40% sodium hydroxide can also be applied [4, 37] (Fig. 7). This alkaline isomerization is also suitable for the preparation of *trans*-2-hydroxycycloheptanecarboxylic acid (L) [38, 39], while it cannot be used to prepare the *trans*-2-hydroxycylcopentanecarboxylic acid because, on heating in alkaline solution, dehydration yielding 1-cyclopentene-1-carboxylic acid (XLIII) takes place [35].

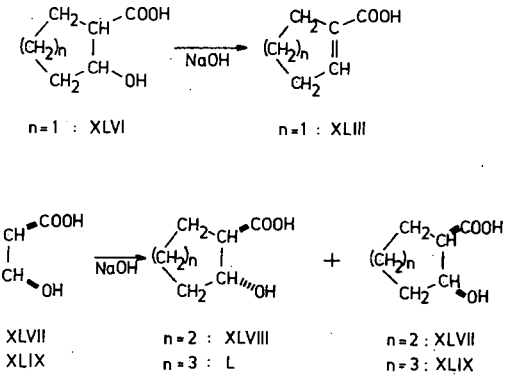


Fig. 7

Cis- and *trans*-2-aminomethylcyclohexanol (V, VI) were earlier described by MOUSSERON *et al.* [40, 41]. They prepared *trans*-2-aminomethylcyclohexanol (VI) *via* *trans*-2-chlorocyclohexanol → 2-cyanocyclohexanol with subsequent reduction by sodium in ethanol. MORICONI and MAZZOCCHI [42] considered *trans* configuration of this compound as questionable. They found the argument used by MOUSSERON *et al.*, namely that the alkaline hydrolysis of the 2-cyanocyclohexanol gives *trans*-2-hydroxycyclohexanecarboxylic acid, was not convincing because in alkaline medium isomerization can take place [37]. MORICONI and MAZZOCCHI synthesized *cis*-2-azabicyclo-(4,2,0)-octane from N,O-ditosyl-*cis*-2-aminocyclohexanemethanol prepared in a stereospecific way. Since the product was identical with that obtained from the ditosylate of the aminoalcohol prepared from 2-cyanocyclohexanol, they considered the configuration of the latter to be proved.

On the base of preparative, IR and NMR spectroscopic evidences, we could unambiguously prove [5] that the *trans*-2-aminomethylcyclohexanol described by MOUSSERON *et al.* was a mixture of the *cis* and *trans* isomers (V, VI). The deficiency of the indirect proof used by MORICONI and MAZZOCCHI can be explained by the circumstance that they obtained the N-tosyl-*cis*-7-azabicyclo-(4,2,0)-octane with a poor yield, which can also be the case starting from a mixture of isomers. It is evident, that the Cl → CN replacement reaction occurs with neighbouring hydroxyl participation, however, even the cleveage of an epoxide ring cannot be considered as a proof

of the configuration [44]. Furthermore, as it is known from experiments of SZÁNTAY and TŐKE [45], the hydroxyl-nitrils can isomerize in alkaline medium.

The *cis*-2-aminomethylcyclohexanol described by MOUSSERON *et al.* did not prove to be stereohomogeneous either. They obtained the *cis* isomer from the N-benzoyl derivative of the above *trans*-2-aminomethylcyclohexanol *via* the oxazoline derivative. MOUSSERON *et al.* gave 172—174°C as m.p. of *cis*-2-aminomethylcyclohexanol hydrochloride, whereas the authentic hydrochloride prepared by us *via* lithium aluminium hydride reduction of *cis*-2-hydroxycyclohexanecarboxamide (XVII) melts at a considerably higher temperature: 182.5—183°C. The stereohomogeneity of our product is proved by IR and NMR spectra.

Cis- and *trans*-2-hydroxymethylcyclohexanol (VII, VIII) were prepared by MORICONI and MAZZOCCHI [42]. We reported [1] on the sysnthesis of these compounds at the same time as the American authors. Though the synthetic pathway was essentially the same, the *trans*-2-hydroxymethylcyclohexylamine hydrochloride described by MORICONI and MAZZOCCHI melted at 140—142°C, whereas the m.p. of our compound was 151.5—152°C. The validity of our data is supported by an earlier publication of MOUSSERON *et al.* [43], who reported the m.p. of the 2-hydroxymethylcyclohexanol hydrochloride (without indicating the configuration), obtained by treatment of 2-hydroxymethylcyclohexylbromide with ammonium hydroxyde, to be 148—150°C. As the m.p. of the *cis*-2-hydroxymethylcyclohexylamine hydrochloride prepared by us is 133—134°C, in accordance with the data given by MORICONI and MAZZOCCHI, it follows that the compound described by MOUSSERON *et al.* [43] (not cited by MORICONI and MAZZOCCHI) must be *trans*-2-hydroxymethylcyclohexylamine hydrochloride contaminated with some *cis* isomer. The essentially lower m.p. found by MORICONI and MAZZOCCHI can be explained by the fact that, instead of purifying the *trans*-2-aminocyclohexanecarboxylic acid (XX) obtained from 1-cyclohexene-1-carboxylic acid (XLIV), they subjected the reaction product immediately to esterification and lithium aluminium hydride reduction.

Cis- and *trans*-2-carbethoxycycloheptanol (XXXIII, XXXIV) used for the preparation of *cis*- and *trans*-2-aminomethylcycloheptanol (IX, X) was obtained by reduction of 2-carbethoxycycloheptanon (XXVII), which can be prepared by condensing cycloheptanone (LI) and diethyl oxalate with sodium ethylate, or by condensation of cycloheptanon and diethyl carbonate with sodium hydride or sodium amide [38, 39]. We performed these reactions under various conditions [11].

Reduction of 2-carbethoxycycloheptanon (XXVII) was performed by PALAU, PASCUAL and RÁFOLS in ethanolic solution in the presence of PtO_2 catalyst or in methanolic solution with sodium borohydride [38]. They did not separate the *cis*- and *trans*-2-carbethoxycycloheptanol, nor did they determine the isomer ratio. As the main product of the catalytic reduction is the *cis* isomer, they obtained the *cis*-2-hydroxycycloheptanecarboxylic acid (XLIX) by fractional crystallization of the acids (XLIX, L) resulting from the hydrolysis of the reduction product. They prepared the *trans* isomer (L) by alkaline isomerization and controlled the stereohomogeneity of both acids by IR spectra.

BHARGAVA, MATHUR and SAHARIA, in a quite recent publication [39], also dealt with the preparation of *cis*- and *trans*-2-hydroxycycloheptanecarboxylic acid, without mentioning the above paper [38] of the Spanish authors. They described the reduction product of 2-carbethoxycycloheptanone (XXVII) with sodium borohydride as stereohomogeneous *cis*-2-carbethoxycycloheptanol, without giving any

proof of the stereohomogeneity. They similarly considered the reaction product of XXVII in ethanolic solution at atmospheric pressure in the presence of W-7 Raney nickel catalyst as a stereohomogeneous *cis* compound.

We found [11] the product obtained by the reduction of the 2-carbethoxycycloheptanone (XXVII) in ethanolic solution, using Raney nickel catalyst at 70°C with 100 atm. starting pressure, to contain *cis*- and *trans*-2-carbethoxycycloheptanol in the ratio 85:15, determined by gas-chromatographic analysis. Reduction with sodium borohydride gave approximately the same ratio, though, according to our experience, the formation of the *trans* isomer in the cyclopentane and cyclohexane analogues by sodium borohydride reduction is more pronounced.

Cis- and *trans*-2-carbethoxycycloheptanol (XXXIII, XXXIV) could also be separated on a column of high efficiency, and hydrolysis of the resulting gas-chromatographically homogeneous esters yielded authentic *cis*- and *trans*-2-hydroxycycloheptanecarboxylic acids (XLIX, L).

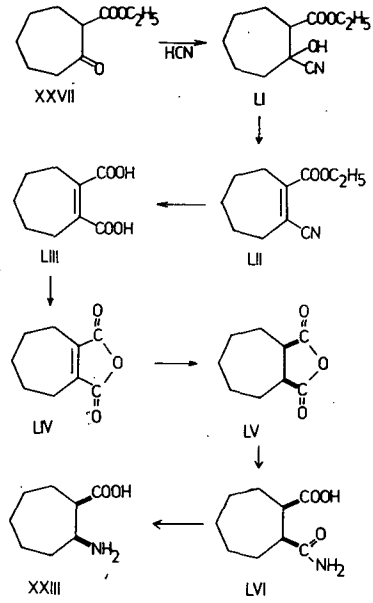


Fig. 8

The preparation of the *trans* amino acid (XXIV) used for the synthesis of the *trans*-2-hydroxymethylcycloheptylamine (XII) was achieved from the corresponding olefinic carboxylic acid (XLV) by ammonia addition (Fig. 6), whereas the *cis*-2-aminocycloheptanecarboxylic acid (XXIII) was obtained starting from 2-carbethoxycycloheptanone (XXVII) (Fig. 8) [46].

N→O *acyl migration reaction of* N-*benzoyl- and p-substituted* N-*benzoyl-derivatives of cis- and trans-2-aminomethylcyclohexanol and cis- and trans-2-hydroxymethylcyclohexylamine*

N→O acyl migration of amino alcohols was reviewed in numerous communications [47—51]. Mechanism, kinetics, stereochemistry, preparative and other application of the process were thoroughly studied. The importance of N→O, O→O, N→N and N→S acyl migration and acyl exchange in biology has also been reviewed [51]. A very comprehensive survey of the acyl migration processes is to be found in the paper of PAVLOVA and RACHINSKII [47], who give a detailed review of the investigations on acyl migration up to 1968, with 228 references.

In contrast to the numerous investigations on the N→O acyl migration reaction of acyclic and alicyclic 1,2-aminoalcohols, only a few papers dealing with acyclic and alicyclic 1,3-aminoalcohol derivatives were published. N→O acyl migration of cyclic 1,3-aminoalcohols has been investigated mainly on models containing the nitrogen in a piperidine ring. Representants of this type are the N-benzoyl-2-(2'-piperidyl)-2-phenylethanol diastereomers studied by WEISZ and DUDÁS [62]. The authors found no difference in reactivity between the *erythro* and *threo* isomers in the N→O acyl migration reaction.

A review of further publications can be found in our earlier paper [6]. The simplified mechanism of the N→O acyl migration reaction occuring with retention (R) mechanism is shown in Fig. 9, that of the reaction with inversion (I) mechanism in Fig. 10. The participation of water in this latter process has been recently proved by WELSH [52] using isotope technique.

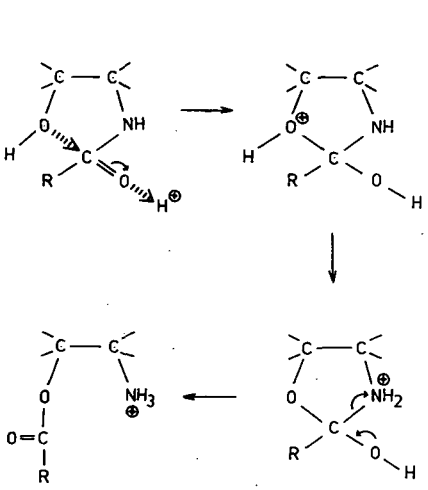


Fig. 9

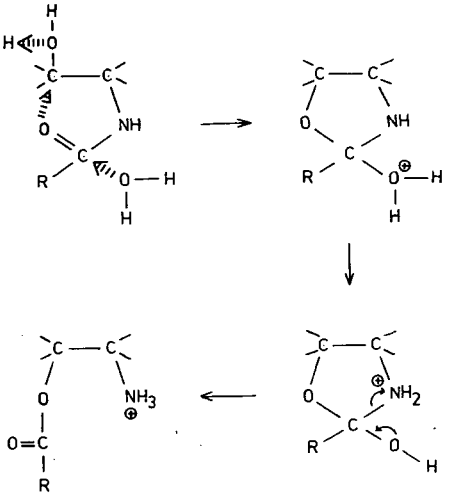


Fig. 10

We studied [1, 2, 6] the N→O acyl migration reaction of N-benzoyl and *p*-substituted N-benzoyl derivatives of *cis*- and *trans*-2-aminomethylcyclohexanol and of *cis*- and *trans*-2-hydroxymethylcyclohexylamine (LVII—LXVIII) (Fig. 11) in abs. dioxane solution in presence of a 0.5 mole excess of hydrochloric acid under nitrogen protecting blanket at 2—4 different temperatures in the temperature range 70—112.3°C for each compound. The rate constants determined at 100 ± 0.3°C, as well as the activation energies and activation entropies are listed in Table I. In these 1,3-aminoalcohols the N→O acyl migration proceeds faster in the *trans* isomers, whereas in the case of 1,2-aminoalcohols with cyclohexane skeleton, in the *cis*- and *trans*-2-benzamidocyclohexanol [53—55], the rate of the N→O acyl migration reaction of the *cis* isomer is significantly higher.

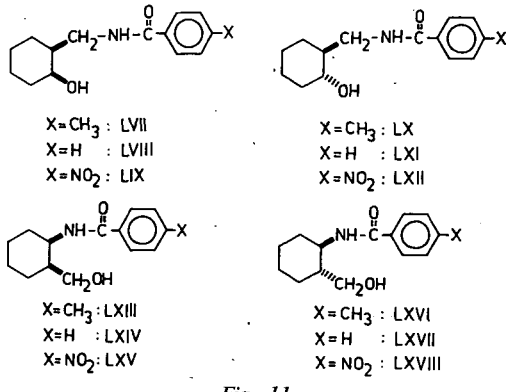


Fig. 11

The bicyclic transition state of the N→O acyl migration reaction of 2-benzamidocyclohexanols is of monoazamonooxahydrindane structure, while that of the 1,3-amino-

Table I

Rate constants and thermodynamic parameters for N→O *acyl migration of* N-*benzoyl and p-substituted* N-*benzoyl derivatives of cis- and trans-2-aminomethylcyclohexanol and cis- and trans-2-hydroxymethylcyclohexylamine*

Compound	Configuration	No.	°C	$k_2 \cdot 10^3 \cdot \cdot sec^{-1}$	ΔE^{+}_{+} (kcal/mole)	ΔS^{+}_{+} e. u.	$\frac{k_{trans}}{k_{cis}}$
N-*p*-methylbenzoyl-2-aminomethylcyclohexanol	*cis*	LVII	100.3	2.93	18.3	−23.6	1.64
	trans	LX	100.3	4.83	15.4	−30.3	
N-benzoyl-2-aminomethylcyclohexanol	*cis*	LVIII	100.0	2.02	15.8	−30.7	2.18
	trans	LXI	100.0	4.78	14.7	−32.2	
N-*p*-nitrobenzoyl-2-aminomethylcyclohexanol	*cis*	LIX	100.1	1.17	18.2	−25.7	2.04
	trans	LXII	100.3	2.14	14.8	−33.6	
N-*p*-methylbenzoyl-2-hydroxymethylcyclohexylamine	*cis*	LXIII	99.7	7.50	14.7	−31.2	3.20
	trans	LXVI	99.7	24.04	12.6	−32.4	
N-benzoyl-2-hydroxymethylcyclohexylamine	*cis*	LXIV	100.3	5.15	11.7	−40.0	3.93
	trans	LXVII	100.3	20.28	11.1	−38.7	
N-*p*-nitrobenzoyl-2-hydroxymethylcyclohexylamine	*cis*	LXV	100.3	5.13	14.7	−32.7	4.67
	trans	LXVIII	99.7	13.17	11.8	−25.9	

alcohols has a monoazamonoxadecalin arrangement. The interpretation of the relative reaction rates of the N→O acyl migration reaction merely on the basis of the energetics of the transition state involves, however, some problems. As known, the tendency of ring closure does not go parallel with the stability of the product [56] even if the product is isolable and stable, because other factors (*e.g.* probability factor, ring strain, etc.) influence the process.

The bicyclic transition states (LXIX—LXXII) of the N→O acyl migration reaction of N-benzoyl and *p*-substituted N-benzoyl derivatives of *cis*- and *trans*-2-aminomethylcyclohexanol and of *cis*- and *trans*-2-hydroxymethylcyclohexylamine are shown in Fig. 12. The *trans*-monoazamonooxadecalin-like transition states (LXXI, LXXII) of the N→O acyl migration reaction of the *trans* isomers (LX—LXII, LXVI—LXVIII) are evidently more easily formed than the *cis*-monoazamonooxadecalin-like transition states (LXIX, LXX) of the *cis* isomers (LVII—LIX, LXIII—LXV), because there are three *gauche*-butane interactions more in *cis*-decalin than in *trans*-decalin. This leads to an enthalpy difference of 2.4—3.1 kcal/mole [57].

In first approximation, the mechanism of these N→O acyl migration reactions may be regarded as analogous to that of the 1,2-aminoalcohols, proceeding with

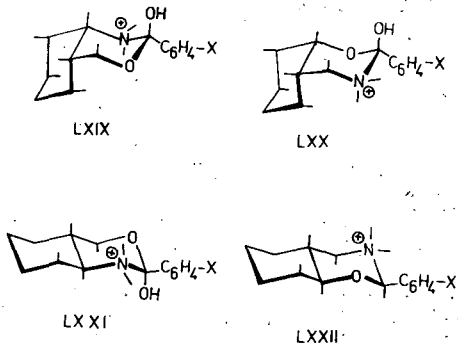


Fig. 12

retention (Fig. 9). The elementary steps and thermodynamic characteristics of this reaction are similar to those of the reactions of the acid catalysed A-2 type bimolecular hydrolysis of esters and acid amides [58]. BENDER [59] described the latter processes as involving six steps. However, most of the steps are very fast, as is general in the case of acid catalysed reactions [60], therefore the first two steps are rate determining [61].

In acid catalysed reactions the reaction proceeds through an activated complex formed by proton addition. If solvation of the activated complex takes place in the rate determining step, the rate equation will include the activity coefficient of the solvent. The degree of solvation is of importance from the point of view of proton transfer and for determining the compression of the transition state.

As indicated by NMR results [63, 64], the protonation of acid amides, which is important in the N→O acyl migration reaction, takes place on the carbonyl oxygen. The next step is an intramolecular nucleophilic attack of the alcoholic hydroxyl group on the carbon atom of the protonated carboxyl group, leading to the formation of the cyclic transition state. This proceeds, instead of a „back side" attack on the protonated carbonyl carbon atom of the acid amide, perpendicularly to the plane of the three substituents attached to it. This steric course is widely accepted in the reactions of the carboxylic acid derivatives. In the hydrolysis of esters, BENDER [59] pointed out, that the perpendicular attack is energetically favoured because it allows the maximum overlap of the nucleophil and of the carbonyl π-orbitals. The rearrangement of the transition complex into O-acyl product proceeds in several steps, by protonation, deprotonation and cleavage of the carbon-nitrogen bond.

The reaction rate of the cyclohexylamine derivatives (LXIII—LXVIII) is higher than that of the aminomethylcyclohexanol derivatives (LVII—LXII), the formation of the cyclic transition state beeing obviously easier with the less shielded hydroxymethyl group. The energy of activation is the lowest for the N→O acyl migration reaction of N-acyl-*trans*-2-hydroxymethylcyclohexylamine (LXVI—LXVIII) derivatives. The two substituents attached to the cyclohexane ring are in *equatorial* position and the formation of the *trans*-monoazamonooxadecalin-like transition state (LXIX) requires a relatively low activation energy (11.1—12.6 kcal/mole). This is less than the activation energy of the N→O acyl migration reaction of the *cis*-2-benzamidocyclopentanol (12.9 kcal/mole) and significantly lower then the activation energies for *cis*- and *trans*-2-benzamidocyclohexanol (15.2 and 17.2 kcal/mole, respectively [53]). The energy of activation for the acyl migration reaction in the corresponding N-benzoyl-*cis*-2-hydroxymethylcyclohexylamine (LXIV) is 11.7 kcal/mole, while that of the *trans* hydroxymethyl derivative (LXVII) is 11.1 kcal/mole.

Comparing the N→O acyl migration reaction of *cis*- and *trans*-2-benzamidocyclohexanol and of the analogous 1,3-aminoalcohols, lower energies of activation in the latter are to be found associated with larger negative entropies of activation. We found the entropies of activation for the N→O acyl migration of *cis*- and *trans*--N-benzoyl-2-aminomethylcyclohexanol (LVIII, LXI) and *cis*- and *trans*-N-benzoyl-2-hydroxymethylcyclohexylamine (LXIV, LXVII) to be —30.7, —32.2 and —40.0, 38.7 e.u., respectively. These are significantly more negative than the values —25.3 and —20.1 e.u., reported for *cis*- and *trans*-2-benzamidocyclohexanol [53]. The energies of activation of all 1,3-aminoalcohol derivatives investigated (LVII—LXVIII) are higher for the *cis* isomers (LVII—LIX, LXIII—LXV) than for the

trans isomers (LX—LXII, LXVI—LXVIII), whereas the entropies of activation are more negative in *trans*-2-aminomethylcyclohexanol (LX—LXII) and *cis*-2-hydroxymethylcyclohexylamine derivatives (LXIII, LXV).

LXIX was indicated as the most probable transition state of the N→O acyl migration of N-benzoyl-*cis*-2-hydroxymethylcyclohexylamine. Among the transition states of isomeric 1,3-aminoalcohols this is apparently the most crowded (Fig. 12). This explains the high negative entropies of activation of *cis*-2-hydroxymethylcyclohexylamine derivatives.

The four theoretically possible transition states in which the hydroxyl group corresponds to that of the *cis-trans*-2-decalol (LXXIII, LXXIV) and *cis-cis*-2-decalol (LXXV, LXXVI) are shown in Fig. 13. As can be seen, the internal strain due to *axial* 1,3-interactionsis the lowest for structure LXXIII. The phenyl group is *equatorial* also in LXXV, however in this conformation the *gauche*-butane interaction of the hydroxyl group and of the C_8—C_9 carbon-carbon bond is much stronger than the interaction of the hydrogen and the C—C bond in LXXIII. In the other two conformations the phenyl group is *axial*, therefore these conformations of the transition states are energetically not favoured. As a conclusion, it can be stated, that the large negative entropy of activation of the *cis*-2-hydroxymethylcyclohexylamine derivatives (LXIII—LXV) is to be explained by the crowded steric arrangement of the transition state of the N→O acyl migration reaction, the inability of the transition state to undergo conformational changes, and by the low probability factor of its formation.

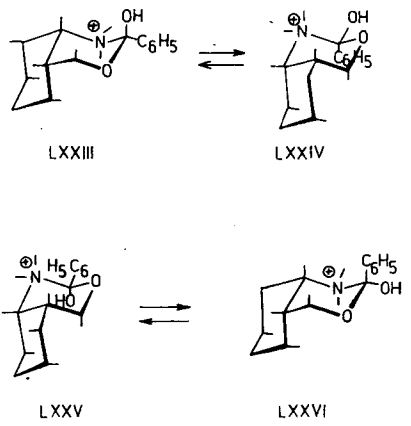


Fig. 13

The logarithms of the rate constants at 100°C are shown in Fig. 14, in the or-

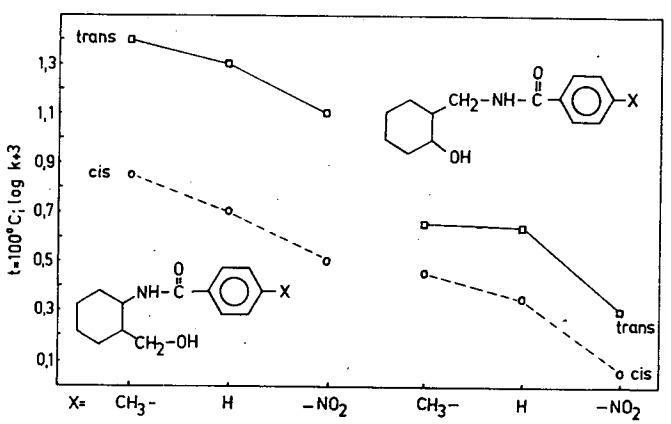


Fig. 14

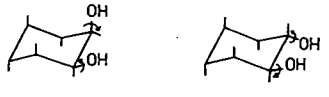
der of the *p*-substituent of the benzoyl group. Investigations on the effect of further *p*-substituents are in course. The N→O acyl migration reaction being a multistep process and the electrostatic effect of the *p*-substituents attached to the benzoyl group being different in the part-processes, a nonlinear Hammett relation [65] is to be expected. By determining the reaction rates for other *p*-substituents and evaluating the nonlinear Hammett relation, deeper insight into the part-processes of the reaction may be expected.

The above mechanism of the N→O acyl migration process leads to a deeper understanding of the N→O acyl migration reaction of the *cis*- and *trans*-2-benzamidocyclohexanol. Namely, the earlier explanation of the significant difference in the reactions rates of the N→O acyl migration reaction of *cis*- and *trans*-2-benzamidocyclohexanol and related cyclic 1,2-aminoalcohols included some difficulties. The lower reactivity of the *trans* isomers was explained by the *trans diaxial* conformation of substituents both in the 2-benzamidocyclohexanol [53] and in 2-amino--3-hydroxytetralin derivatives [20]. However, on the basis of the principles of conformational analysis, the *diequatorial* arrangement of the substituents in the *trans* isomers is most favoured.

ANGYAL and MCDONALD [66] pointed out that, though the dihedral angle between the *equatorial-axial* hydroxyl groups in *cis*-cyclohexane-1,2-diol (LXXVII) and *diequatorial trans*-2-cyclohexane-1,2-diol (LXXVIII) is equal to 60° and their distance is 2.86 Å in both cases, the *cis* diol readily gives acetonid, while the *trans* does not. The motion of hydroxyl groups of the *trans* isomer in the direction shown by the arrows (Fig. 15) results in increasing the 1,3 *axial-axial* hydrogen-hydrogen interactions, while in the *cis* isomers it corresponds to a chair-chair interconversion.

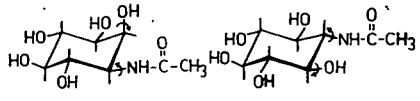
In addition to the 1,3-*axial* interactions, the conformational requirements involved in the formation of the bicyclic transition state by perpendicular attack of the alcoholic hydroxyl should also be taken into account. In the N→O acyl migration reaction of *cis*-2-benzamidocyclohexanol the substituents attached to the amide-carbon atom can occupy in-plane positions relative to the plane of the cyclohexane skeleton, the *axial* hydroxyl attacking from above, as part of a chair-chair conformational change. On the other hand, the above substituents of the *diequatorial trans* isomer should lie in a plane perpendicular to the cyclohexane ring, which is apparently less favourable. In the case of the *trans* isomer the bicyclic transition state forms by the attack of the *equatorial* hydroxyl from the side, this process being also less favourable.

Considering the great difference in the rate constants of the N→O acyl migration reaction of *cis*- and *trans*-inosamine derivatives (LXXIX, LXXX), (Fig. 16), it follows that besides the 1,3 *axial-axial* interactions also the approach of the *equatorial* substituents plays a role. The *equatorial* substituents being hydroxyls in this case the difference in the reaction rates is more pronounced, than in the case of the *cis*- and *trans*-2-benzamidocyclohexanol, where hydrogen-hydrogen interactions occur.



LXXVII LXXVIII

Fig. 15



LXXIX LXXX

Fig. 16

N→O *acyl migration reaction of* N-*benzoyl-cis- and trans*-2-*aminomethylcyclopentanol and* N-*benzoyl-cis- and trans*-2-*hydroxymethylcyclopentylamine*

N→O acyl migration reactions of the cyclopentane derivatives (LXXXI—XXXIV) (Fig. 17) were investigated [3, 12] under the same conditions as those of the analogous cyclohexane derivatives [2, 12]. The N→O acyl migration reaction of N-benzoyl-*cis*-2-aminomethylcyclopentanol (LXXXI) was studied in the temperature range 100.8 to 125°C, that of the N-benzoyl-*cis*-2-hydroxymethylcyclopentylamine (LXXXIII) between 84.0 and 110.0 °C. The reactivity of the corresponding *trans* isomers being essentially lower, the N→O acyl migration reaction of N-benzoyl-*trans*-2-aminomethylcyclopentanol (LXXXII) and N-benzoyl-*trans*-2-hydroxymethylcyclopentylamine (LXXXIV) could only be studied at 130.2°C. Because of the extremely low reactivity of the *trans* isomers (LXXXII, LXXXIV) at lower temperatures and side reactions occuring at higher temperatures, it was not possible to obtain well reproducible rate constants and to determine the activation energies and activation entropies of these reactions.

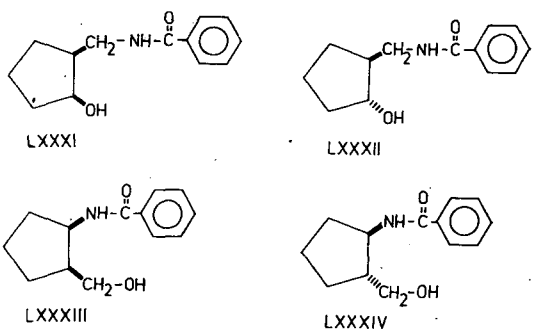


Fig. 17

Rate constants calculated from the second order equation, activation energies and activation entropies are listed in Table II. In contrast with the analogous cyclohexane derivatives, the reaction rate, as well as the activation energy and activation entropy of N-benzoyl-*cis*-2-aminomethylcyclopentanol (LXXXI) and N-benzoyl-*cis*-2-hydroxymethylcyclopentylamine (LXXXIII) are essentially higher than those of the corresponding *trans* isomers (LXXXII, LXXXIV).

A similar relation has been found in the N→O acyl migration reaction of *cis*- and *trans*-2-benzamidocyclopentanol and *cis*- and *trans*-2-*p*-nitrobenzamidocyclopentanol [67], where the reaction rate of the *cis* isomer also exceeds that of the *trans* isomers by orders of magnitude. The striking rate difference is due to the fact that the N→O acyl migration reaction of the *trans*-2-aminocyclopentanol derivatives occurs with inversion.

However, as we pointed out [6], the relative rates of the N→O acyl migration reaction of 1,2- and 1,3-aminoalcohols do not necessarily show parallelism. Namely, while the reaction rate of the N→O acyl migration reaction of *cis*-2-benzamidocyclohexanol significantly exceeds that of the *trans* isomer (303:76), in the case of *cis*- and *trans*-2-aminomethylcyclohexanol and *cis*- and *trans*-2-hydroxymethylcyclohexylamine derivatives (LVII—LXII and LXIII—LXVIII) it is the *trans* isomer which has the higher reaction rate (see Table I).

In the acyl migration reactions of N-benzoyl-*cis*-2-aminomethylcyclopentanol (LXXXI) and N-benzoyl-*cis*-2-hydroxymethylcyclopentylamine (LXXXIII) the reaction rate of the latter is higher — as found also with the analogous cyclohexane deriv-

Table II

Reaction rate constants, activation energies and activation entropies of the N→O *acyl migration reactions of cis- and trans-*N*-benzoyl-2-aminomethylcyclopentanol and cis- and trans-*N*-benzoyl--2-hydroxymethylcyclopentylamine*

N-benzoyl-*cis*-2-aminomethylcyclopentanol (LXXXI)		N-benzoyl-*cis*-2-hydroxymethylcyclopentylamine (LXXXIII)	
t = °C	$k_2 \cdot 10^3 \cdot sec^{-1}$	t = °C	$k_2 \cdot 10^3 \cdot sec^{-1}$
		84	3.87
100.8	2.89	100.4	7.80
110.0	3.37	110.4	10.31
125.0	5.33		
$\Delta E^{\ddagger} = 11.7$ kcal/mole		$\Delta E^{\ddagger} = -11.2$ kcal/mole	
$\Delta S^{\ddagger} = -41.8$ e.u.		$\Delta S^{\ddagger} = -36.9$ e.u.	
N-benzoyl-*trans*-2-aminomethylcyclopentanol (LXXXII)		N-benzoyl-*trans*-2-hydroxymethylcyclopentylamine (LXXXIV)	
t = °C	$k_2 \cdot 10^3 \cdot sec^{-1}$	t = °C	$k_2 \cdot 10^3 \cdot sec^{-1}$
130.2	0.74	130.2	0.87

atives (LVIII, LXIV) — the hydroxymethyl group being less shielded than the secondary hydroxyl group.

There are no marked differences between the activation energies of the N→O acyl migration reactions of N-benzoyl-*cis*-2-aminomethylcyclopentanol (LXXXI) and N-benzoyl-*cis*-2-hydroxymethylcyclopentylamine (LXXXIII) ($\Delta E^{\ddagger} = 11.70$ and 11.22 kcal/mole, respectively). The difference in the reaction rate of the above compounds can be explained by the fact that the activation entropy of the N-benzoyl--*cis*-2-hydroxymethylcyclopentylamine (LXXXIII) is less negative ($\Delta S^{\ddagger} = -36.9$ e.u.) than that of the N-benzoyl-*cis*-2-aminomethylcyclopentanol (LXXXI) ($\Delta S^{\ddagger} = -41.8$ e.u.). It is to be mentioned, that in the N→O acyl migration reaction of the cyclopentane derivatives (LXXXI, LXXXIII) the activation entropy of the compound LXXXI containing a secondary hydroxyl group is higher, whereas in the analogous cyclohexane derivatives (LVIII, LXIV) the compound LXIV containing a primary hydroxyl group has higher activation entropy.

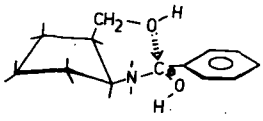


Fig. 18

The formation of the bicyclic transition state of the N-benzoyl-*cis*-2-hydroxymethylcyclopentylamine (LXXXIII) is shown in Fig. 18. According to the mechanism described for the cyclohexane derivatives, the three substituents involved in the formation of the transition state of the protonated acid amide in the half-chair conformation of the cyclopentane skeleton [4, 26, 68,

69] are in a plane perpendicular to that of the figure, the hydroxyl group attacking in the plane of the figure at right angle to the plane determined by the three substituents.

The formation of the bicyclic transition state from the N-benzoyl-*cis*-2-aminomethylcyclopentanol is, of course, less favoured; this explains the very high negative entropy of activation of the reaction, though in the present case, in contrast to the *trans* isomer, the hydrogen-hydrogen interactions in the formation of the transition state do not increase.

It is surprising that the rate constants of the N→O acyl migration reaction of the N-benzoyl-*trans*-2-aminomethylcyclopentanol (LXXXII) and of the N-benzoyl-*trans*-2-hydroxymethylcyclopentylamine (LXXXIV) are lower by about an order of magnitude even at 130.2°C than those of the *cis* isomers (LXXXI, LXXXIII) determined at 100.8 and 100.4°C, respectively (see Table II). Namely, the formation of the six-membered transition state from these 1,3-aminoalcohols could be expected to occur without difficulties even in the *trans* isomers, the energy difference between the analogous *cis*- and *trans* carbocyclic compounds (*cis*- and *trans*-hydrindane) being negligible.

However, examination of Dreiding models shows convincingly the great difference in the distances of the substituents in the *cis* and *trans* isomers. While the distance of the atoms taking part in the reaction is small in the *cis* isomers (LXXXI, LXXXIII) and so the attack of the alcoholic hydroxyl on the protonated carbonyl group of the acid amide can easily occur (Figs 19 and 20), in the *trans* isomers the

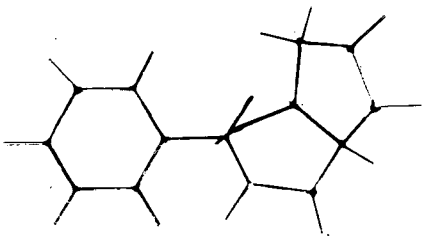


Fig. 19

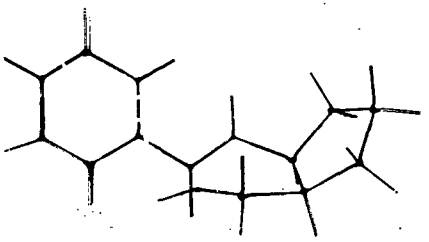


Fig. 20

functions are so far from each other owing to the rigidity of the cyclopentane skeleton that the attack of the hydroxyl group is markedly more difficult even in the hydroxymethyl derivative (LXXXIV) (Fig. 21).

Inspection of the Dreiding model shows that, because of the great distance of the substituents involved the N→O acyl migration reaction of the N-benzoyl-*trans*-2-aminomethylcyclopentanol can proceed more favourably with inversion, though the inversion mechanism is, in general, energetically much less favoured than the retention mechanism. In this case of LXXXII, however, the oxygen atom of the acid amide group may approach the cyclopentane ring, permitting the inversion mechanism, as could be proved by preparative and spectroscopical evidences [12], so the low reaction rate is not surprising. The moderate reaction rate of the N→O acyl migration reaction of the N-benzoyl-*trans*-2-hydroxymethylcyclopentylamine (LXXXIV), seeming less evident because of the primary hydroxyl group, may also be well interpreted on the basis of the Dreiding model (Fig. 21).

Comparison of the changes with temperature in the reaction rates of the N→O acyl migration reaction of analogous cyclopentane and cyclohexane derivatives shows the rigidity of the cyclopentane ring. Namely, the rate constant of the N→O acyl migration of the N-benzoyl-*cis*-2-aminomethylcyclohexanol (LVIII)

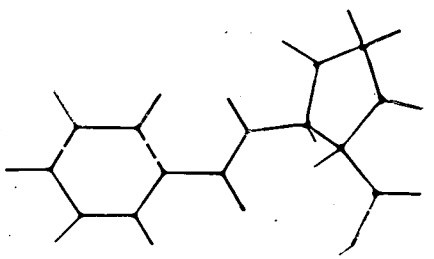


Fig. 21

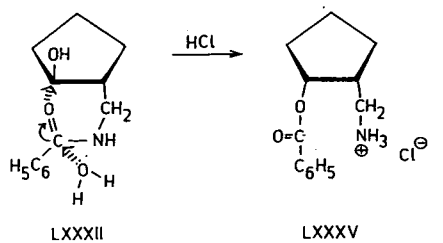


Fig. 22

increases to its threefold value by rising the temperature from 80 to 100°C and is approximately the same at 100°C as that of the analogous cyclopentane compound (LXXXI), while in case of N-benzoyl-*cis*-2-aminomethylcyclopentanol a rise of the temperature by 25°C increases the rate constant only by a factor of 1.5.

Investigations on the N→O acyl migration reaction of derivatives of analogous 1,3-aminoalcohols with cycloheptane skeleton (IX—XII) are in course.

Solvolysis and NMR spectroscopical data of cis- and trans-3-p-nitrophenyl-1-aza-3-oxadecalin and cis- and trans-3-p-nitrophenyl-2-aza-4-oxadecalin

Cis- and *trans*-3-*p*-nitrophenyl-2-aza-4-oxadecalin (LXXXVI, LXXXVII) and *cis*- and *trans*-2-*p*-nitrophenyl-1-aza-3-oxadecalin (LXXXVIII, LXXXIX) were prepared by reaction of the aminoalcohols V—VIII with *p*-nitrobenzaldehyde [10]. These monoazamonooxadecalin derivatives (Fig. 23) are closely related with the bicyclic transition states (Fig. 13) of the N→O acyl migration reaction of N-benzoyl derivatives of *cis*- and *trans*-2-aminomethylcyclohexanol (V, VI) and *cis*- and *trans*-2-hydroxymethylcyclohexylamine (VII, VIII) [2, 6].

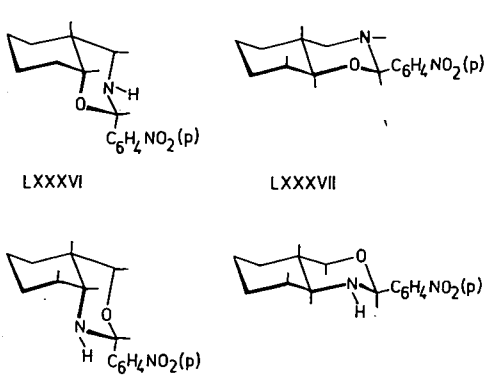


Fig. 23

LUKEŠ, BLÁHA and KOVÁŘ [70] determined the configuration of sedamine and *allo*-sedamine by showing that the tetrahydrooxazine derivative prepared from nor-*allo*-sedamine with *p*-nitrobenzaldehyde hydrolyzed much more easily than the tetrahydrooxazine formed from nor-sedamine. The importance of this method [18] is evident because, in comparison with 1,2-aminoalcohols, the stereospecific reactions of the 1,3-aminoalcohols received less

attention so far. Mechanical application of the rules found valid for 1,2-aminoalcohols in earlier studies [72] later proved to be incorrect [73]. LUKEŠ, BLÁHA and KOVÁŘ also investigated mainly reactions and condensation products of diastereomeric cyclic 1,2-aminoalcohols with *p*-nitrobenzaldehyde [18, 70, 71, 74] and found that the oxazolidine derivatives obtained from *trans* isomers were less stable both in the cyclohexane and tetralin series than *cis*-oxazolidine derivatives. The ratio k_{trans}/k_{cis} was found to be ranging from 63 to 1:420. The factors determining the reaction rate and mechanism of the reaction were discussed in detail by the Czechoslovakian authors [18, 74].

The above method has been applied recently for the determination of the configuration of 1,2-, 1,3- and 1,4-diols [75] and of some carbohydrates [76], by comparing the rate of hydrolysis of their cyclic acetals formed with benzaldehyde. SCHÖPF *et al.* in their paper published in 1970 [77] used the relative rate of hydrolysis of oxazine derivatives formed from stereoisomeric *meso*-1,3-di(2-piperidyl)-propan-2-ols with formaldehyde for determining the configuration of the parent compounds.

Recently also the NMR spectroscopy of tetrahydrooxazine derivatives has been studied [78, 79, 81]. Similar models were investigated by CRABB *et al.* [80]. The relationship between the above oxazidines and our model compounds is evident, though the starting aminoalcohols being piperidine derivatives in the former studies, the products obtained by ring closure of piperidines, differently from our model compounds (LXXXVI—LXXXIX), contain bridgehead nitrogen atoms. These tetrahydrooxazines, similarly to the analogous quinolizidine derivatives undergoing *cis*-*trans* inversion [82—84] are not configuratively stable. In contrary, our tetrahydrooxazine derivatives, like *cis*- and *trans*-decalin, are configuratively stable, their nitrogen atom being not in bridgehead position.

Table III contains the rate constants of the solvolysis reaction of the tetrahydrooxazines, determined in the presence of an excess of 2,4-dinitrophenylhydrazine at 50°C [70]. The stability of the tetrahydrooxazine derivatives studied desrease in the order LXXXIX > LXXXVII > LXXXVIII > LXXXVI. The stability of the *trans* isomers (LXXXIX, LXXXVII) exceeds that of the *cis* isomers (LXXXVI, LXXXVIII), in accordance with the general principles of conformational analysis. The relative

Table III

Rate of solvolysis and NMR data of tetrahydrooxazine derivatives

Compound	$k_1 \cdot 10^5 \cdot sec^{-1}$	C—2H	C—4H^a	C—4H^b	C—9H	$J_{4a,4b}$	$J_{1a,10}$	$J_{4b,10}$
LXXXVI	8.95	5.21	2.93	3.26	4.00≠	−13.5	1.8	3.2
LXXXVII	3.54	5.25	2.71	3.11	3.20*x*	−13.2	10.7	4.0
LXXXVIII	8.63	5.23	3.98	3.98	3.36≠	+	+	+
LXXXIX	1.42	5.26	3.52	4.10	2.63*x*	−11.2	10.2	4.1

Remarks:
Chemical shifts in δ ppm. Coupling constants in Hz units; solvent: $CDCl_3$
≠ Line width ~ 12 Hz; *x* Line width ~ 25 Hz;
+ Not meassured because of accidental coincidence of C—4H^a and C—4H^b chemical shifts.

rates found can be well interpreted with the reaction mechanism and energetical conditions of the transition state.

The conformations of the investigated compounds are shown in Fig. 23. In the favourable conformations the *p*-nitrophenyl group is evidently *equatorial*. According to recent investigations [85] the proton on the nitrogen can also be considered to be *equatorial*. In piperidines the „conformational rivalry between the non-bonding electron pair and the proton on nitrogen" (see: [86, 87]) has been extensively discussed [88] up to the present time. According to a quite recent paper [85] based on dipole moment measurements, the preferred *equatorial* position of the proton on the nitrogen and, consequently, the *axial* orientation of the lone pair seems to be unequivocally proved.

The enthalpy difference of *cis*- and *trans*-decalin in liquid phase is 2.69 ± 0.31 kcal/mole [89]. However, in interpreting the relative rate of decomposition it is not sufficient to consider the relative stability of decalins alone. *E.g.*, in the acid catalysed acetal hydrolysis of methyl-4,6-benzylidenehexosides the *trans* derivatives hydrolyse much faster [90]. The same was found [91] for the rate of solvolysis of 4,6-benzylidenehexosides, the *trans* derivative (XCI) solvolysing faster than the *cis* derivative (XC). In benzylidenehexosides the methylene groups are replaced by oxygen atoms, therefore the *axial* substituents on C-1, C-5 and C-6, destabilizing the *cis*-decalin, are absent. In the protonated *cis* isomer (XC) the hydrogen bonds formed with the aid of the oxygen atoms of the ring system also play a stabilizing role, which is absent in the *trans* isomer (XCI).

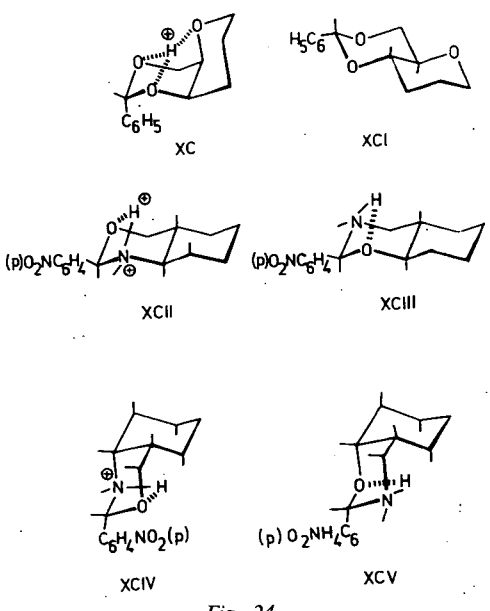


Fig. 24

Our model compounds are more nearly related to the decalin system than the above benzylidene derivatives. Under the conditions of reaction the nitrogen atom is protonated, and this plays an important stabilizing role. This stabilizing factor will appear in the *trans* isomers (XCII, XCIII). A hydrogen bond in *cis* isomers would result in a crowded system, which would compensate the stabilizing effect of the hydrogen bond by increased internal strain. In protonated *cis* isomers (XCIV, XCV) the internal strain is more pronounced in XCV, in accordance with the higher rate of solvolysis of *cis*-3-*p*-nitrophenyl-2-aza-4-oxadecalin. In the transition state XCVI produced by the attack of the 2,4-dinitrophenylhydrazine after protonation of LXXXIX, the increase of four 1,3 *axial-axial* interactions is to be taken into consideration, while in the other tetrahydrooxazine derivative LXXXVII only three 1,3 *axial-axial* interactions are increased (Fig. 25).

We compared the relative stability of the tetrahydrooxazine derivatives studied

earlier with that of our model compounds. The relative stability of our oxazine derivatives (LXXXVI—LXXXIX) compared with the rate of the N→O acyl migration reaction of the N-*p*-nitrobenzoyl derivatives (LIX, LXII, LXV, LXVII) of the parent 1,3-aminoalcohols (V—VIII) was also evaluated. The protonated forms of these oxazines show a very close similarity to the bicyclic transition state of the N→O acyl migration reaction (compare Fig. 13 and Fig. 23).

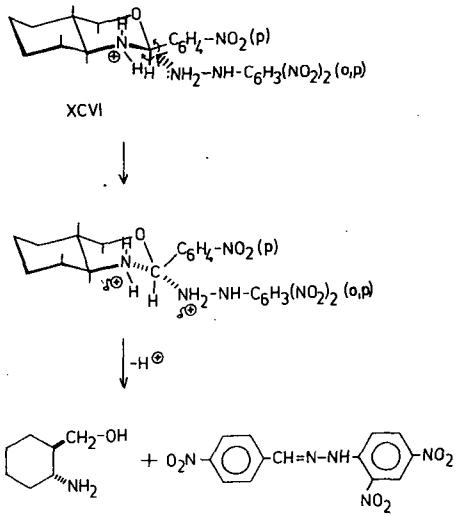


Fig. 25

The generation of the bicyclic transition state is the rate determining step in the N→O acyl migration reaction. The relative stability of the oxazine derivatives shows a reverse order compared with the rate of N→O acyl migration of the parent aminoalcohols. The rate of solvolysis of the tetrahydrooxazine derivatives (LXXXVI, LXXXVIII) prepared from aminoalcohols containing secundary hydroxyl (V, VII) exceeds that of the tetrahydrooxazine derivatives (LXXXVII, LXXXIX) prepared from hydroxymethylcyclohexylamines (VI, VIII). In accordance with the results obtained in the N→O acyl migration reaction, the oxazine derivatives prepared from the *trans* aminoalcohols (VI, VIII) show more marked differences in the reaction rates.

NMR spectroscopical studies on tetrahydrooxazine derivatives

Table III contains the NMR spectroscopical data important from stereochemical point of view of the oxazine derivatives (compare also: [79—81]). The ring numbering used in the spectroscopical part of our paper is shown in Fig. 26. The carbon atoms of the methylene group used for the evaluation of the spectra obtained the number 4 in both pair of diastereoisomers, the bridgehead atom adjacent to the hetero atom is designed by number 9.

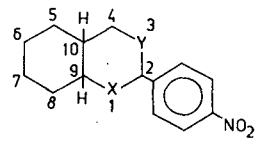


Fig. 26

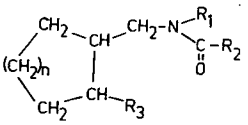
In the *trans* tetrahydrooxazine derivatives (LXXXVII, LXXXIX) the coupling contants of the C-4 methylene hydrogens with the adjacent angular proton have values of ~10 and ~4 Hz, respectively, showing that one of the hydrogens of the methylene group (C-4 H^a) and the C-10 are in the same *diaxial* position, therefore the angular proton on C-10 must be *axial*. The width of the resonance signal of C-9 H (~25 Hz) also shows that in the *trans* compounds this proton is in *trans* position to C-10 H, *i.e.* it is also *axial*; therefore the above are in accordance with the data resulting from the *trans* configuration.

The width of the resonance signal, of only about 12 Hz in the *cis* tetrahydrooxazine derivatives (LXXXVI, LXXXVIII), points to the fact, that in these compounds the proton is *equatorial* and in *cis* position to the angular C-10 H. In *cis* iso-

mers, the coupling constants of the methylene protons C-4 with the C-10 H could be determined only for the compound LXXXVI. The values found show that in the favourable conformation the proton C-10 is *equatorial* with respect to the hetero ring, in accordance with the *cis* ring system.

Further investigations

Without giving details, we shortly mention that we prepared a great number of N-acylaminomethylcyclopentane and cyclohexane derivatives (see Fig. 27) for pharmacological purposes. The N-cycloalkyl acid amides exert a very intensive



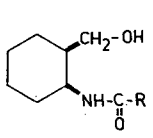
n = 1, 2

R_1 = H, C_6H_5-CH_2-, -CH_2-C_6H_4-OCH_3 (p)

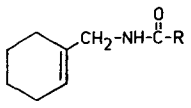
R_2 = C_6H_5-, -C_6H_4-Cl (o), -C_6H_5-Cl (p), -C_6H_4-Br (o), -C_6H_4-OCH_3 (m), -C_6H_4-OCH_3 (p), -C_6H_4-CH_3 (p), -C_6H_2-$(OCH_3)_3$ (m,m,p), -C_6H_4-NO_2 (p), -C_6H_3-$(NO_2)_2$ (m,m'), -C_6H_5-NH_2 (p)

R_3 = H, OH, Cl, Br

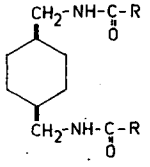
Fig. 27



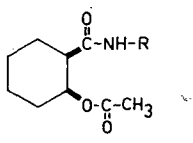
XCVII



XCVIII



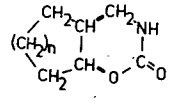
XCIX



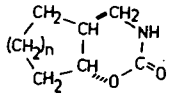
C

Fig. 28

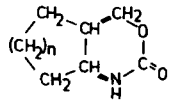
sedative effect on the central nervous system. In practice they can be used especially in the chemotherapy of epilepsy. It is advantageous that they are of low toxicity. The above compounds are subject of several patents [9, 13] (Fig. 27, 28).



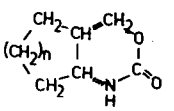
n=1 : CI
n=2 : CV
n=3 : CIX



n=1 : CII
n=2 : CVI
n=3 : CX



n=1 : CIII
n=2 : CVII
n=3 : CXI



n=1 : CIV
n=2 : CVIII
n=3 : CXII

Fig. 29

For similar purposes we also prepared some related N-acyl-*cis*-2-hydroxymethylcyclohexylamine derivatives (XCVII), N-acyl-1-aminomethylcyclohexene-1 derivatives (XCVIII), N,N'-diacyl-*cis*-1,4-diaminomethylcyclohexane derivatives (XCIX) and N-substituted-O-acetyl-*cis*-2-hydroxycyclohexane derivatives (XCIX) and N-substituted-O-acetyl-*cis*-2-hydroxycyclohexanecarboxamide derivatives (C) [8] (Fig. 28). In compounds XCVII—XCIX the acylating agents used were various substituted benzoic acids, whereas in the compounds of type C, R was *p*-methoxybenzyl, *i*-propyl, *i*-butyl and β-(3,4-dimethoxyphenyl)-ethyl.

Preparation of and investigations on

oxazinon derivatives with condensed skeleton, presented in Fig. 29, are in progress. As could be expected, in the cyclohexane series the *trans*-oxazinons (CVI—CVIII) prepared from aminoalcohols V—VIII were obtained with higher yield. NMR Spectroscopical investigation of these oxazinones, showing theoretically interesting features, is in progress.

* * *

This work was financially supported by Pharmaceutical Works G. RICHTER, Budapest, and by REANAL Factory of Laboratory Chemicals, Budapest. The authors express their thanks to Dr. P. SOHÁR (Pharmaceutical Research Institute, Budapest) for numerous NMR and IR spectra, to Mrs É. TOMORI (Pharmaceutical Research Institute, Budapest) for gas-chromatographical analyses, to Mrs. G. BARTÓK-BOZÓKI and Mrs. É. GÁCS-GERGELY for microanalyses. We are also indebted to Mr. L. GERA, Mrs. O. BITTÓ-CSAPÓ, Mrs. A. SÁNTHA-SZEGHY, Mrs. E. FELFÖLDI-CSÓKÁSI for taking part in some experiments, and to Miss A. VÍGH for valuable technical assistance.

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СТЕРЕОХИМИЧЕСКИЕ ИССЛЕДОВАНИЕ 1,3-ДИФУНКЦИОНАЛЬНЫХ ПРОИЗВОДНЫХ ЦИКЛОПЕНТАНА, ЦИКЛОГЕКСАНА И ЦИКЛОГЕПТАНА

Г. Бернат, К. Л. Ланг, Гь. Гендеш, П. Мараи и К. Ковач

Авторами даётая описание их синтетической и стереохимической работы с циклическими 1,3-аминоспиртами. Описывается стереоспецифический синтез *цис-* и *транс*-2-аминометилциклопентанола и *цис-* и *транс*-2-гидроксиметилциклопентиламина и их циклогексанных и циклогептанных аналогов. Тоже даётся кинетическое исследование и механизм N → O-миграции ацильных групп производных циклопентана и циклогексана.

Солволиз и ЯМР спектроскопический анализ тетрагидрооксазинов пригатовленных из *цис-* и *транс*-2-аминометилциклогексанола и *цис-* и *транс*-2-гидроксиметилциклогексиламина детально трактуруются. Авторам даётся описание пригатовления исследования нескольких других производных, в большинстве амидов вышеописанных аминоспиртов важных для фармакологии.