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N-O ACYL MIGRATION IN THE N-BENZOYL DERIVATIVES OF CIS- AND TRANS-2--AMINOMETHYLCYCLOPENTANOL AND CIS- AND TRANS-2-HYDROXYMETHYLCYCLOPENTYLAMINE

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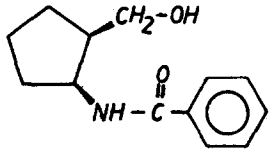
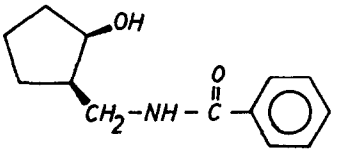
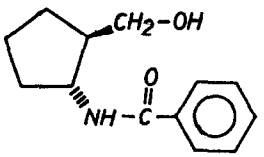
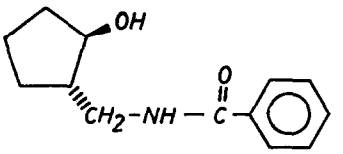
In a previous Letter /1/ the N-O acyl migration of cis- and trans-2--aminomethylcyclohexanol and cis- and trans-2-hydroxymethylcyclohexylamine derivatives was reported. The present communication deals with the stereospecific synthesis of the analogous cyclopentane derivatives, as well as the examination of the kinetics of their N-O acyl migration reaction.

The stereospecific synthesis of cis- and trans-2-aminomethylcyclopentanol and cis- and trans-2-hydroxymethylcyclopentylamine was achieved by $LiAlH_4$ reduction of cis- and trans-2-hydroxycyclopentanecarboxamide and cis- and trans-2-aminocyclopentanecarboxylic acid. The synthesis of these compounds published earlier /2,3/ cannot be considered stereospecific. Instead of the tedious fractional crystallization, used even today /4/, of cis- and trans-2--ethoxycarbonylcyclopentanol 3,5-dinitrobenzoates /5/, we separated the cyclopentanols by fractional distillation for the synthesis of cis- and trans-2--hydroxycyclopentanecarboxamide. The gas-chromatographically homogeneous (stationary phase: polyethyleneglycol adipate) cis- and trans-2-ethoxycarbonylcyclopentanols (b.p. 129-130° and 139-140°, respectively, both at 42 Hg mm.) afforded cis- and trans-2-hydroxycyclopentanecarboxamide (m.p. 86.5-87.5 and 102.5-103.5°, respectively) on treatment with methanolic ammonia for 8 days.

The kinetics of the N-O acyl migration reaction of the N-benzoyl derivatives of cis- and trans-2-aminomethylcyclopentanol and cis- and trans-2--hydroxymethylcyclopentylamine (I-IV) were examined in abs. dioxan in the presence of 0.5 mole excess hydrogen chloride, in the range between 84.0 and 130.2°. Apart from the acid concentration, the method was essentially the same as that applied by Fodor et al. /6/. The second-order rate constants, the energies of activation and the entropies of activation are summarized in Table I.

It is apparent that, in contrast to the corresponding cyclohexane derivatives /1/, the N-O acyl migration reaction of cyclopentane 1,3-aminoalcohols proceeds considerably faster in the cis (I, III) than in the trans (II, IV)

TABLE I

 (I)		 (III)	
t = °C	$k_2.10^3.sec^{-1}$	t = °C	$k_2.10^3.sec^{-1}$
84.0	3.87		
100.4	7.80 (5.15)	100.8	2.89 (2.20)
110.0	10.31	110.0	3.37
		125.0	5.33
$\Delta E^{\ddagger}$ = 11.22 (11.66) Kcal/mole		$\Delta E^{\ddagger}$ = 11.70 (15.84) Kcal/mole	
$\Delta S^{\ddagger}$ = -36.9 (-40.0) e. u.		$\Delta S^{\ddagger}$ = -41.8 (-30.7) e. u.	
 (II)		 (IV)	
t = °C	$k_2.10^3.sec^{-1}$	t = °C	$k_2.10^3.sec^{-1}$
100.0	---- (20.28)	100.0	---- (4.80)
130.2	0.87	130.2	0.74

Note: The corresponding constants of the analogous cyclohexane derivatives are given in parentheses. Rate constants at 100.0 ± 0.3°

derivatives. The former two compounds (I, III) react at 84-100° with a somewhat higher rate than the corresponding cyclohexane derivatives, while in case

of the trans derivatives (II, IV) the rate of the reaction becomes measurable only at 130.2°.

The energy of activation of the acyl migration reaction of cis-N--benzoyl-2-hydroxymethylcyclopentylamine (I) is close to that of cis-N-benzoyl--2-hydroxymethylcyclohexylamine, while the entropy of activation is somewhat more negative for the cyclohexane derivatives. On the contrary, the energy of activation of the acyl migration reaction of cis-N-benzoyl-2-aminomethylcyclopentanol (III) containing a secondary hydroxyl group is considerably lower than that of cis-N-benzoyl-2-aminomethylcyclohexanol, and the entropy of activation is again substantially more negative in the cyclopentane derivatives.

All these can be interpreted in terms of the interactions arising in the formation of the bicyclic transition state of the acyl migration reaction. Similarly to the mechanism of the hydrolysis of esters or amides according to Bender /7/, the formation of the transition state involves the perpendicular attack of the alcoholic hydroxyl on the carbonyl C-atom of the protonated amide group. In case of the cis isomers the greater interaction arises in the formation of the bicyclic transition state of the cis-2-aminomethylcyclopentanol derivative (III); though the valence angle made by the functional groups is favourable to ring closure, the quasi-carbonium amide C-atom carrying the protonated carbonyl oxygen and the shielded secondary hydroxyl approach each other, and this explains the greater negative entropy of activation.

The marked decrease in the reactivities of the trans derivatives (II, IV), as compared with the cis isomers (I, III), is analogous to that observed in the acyl migration reaction of 2-benzamidocyclopentanol isomers /8/. This may appear surprising in the case of our 1,3-aminoalcohols, as here the heterocycle of the transition state of the acyl migration reaction is six--membered. However, model examinations reveal a considerable difference in the interactions during the formation of the transition states of cis and trans isomers.

A description of the synthesis of the aminoalcohols and a detailed discussion of the acyl migration reaction will be published in Acta Chim. Acad. Sci. Hung.

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