MANNICH REACTION IN SIX-MEMBERED HETEROCYCLIC γ-KETONES

XIII. STEREOCHEMISTRY OF THE REDUCTION OF 2,2-DIMETHYL-5-AMINOMETHYL-4-OXOTETRAHYDROPYRANS

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The stereochemical principles of the reduction of 2,2-dimethyl-5-aminomethyl-4-oxotetrahydropyrans with lithium aluminum hydride, sodium borohydride, aluminum isopropoxide, and lithium in liquid ammonia were investigated by determination of the dependence of the quantitative ratio of the resulting epimeric amino alcohols in the mixtures on the character of the reducing agent and its concentration and the nature of the solvent. The individual geometrical isomers of the amino alcohols were isolated, and their structures were established by PMR and IR spectroscopy.

Compounds that have high anesthetizing activity have been observed among the esters of secondary γ-amino alcohols of the tetrahydropyran series [1]. The development of stereoselective methods for the synthesis of the spatial isomers of the γ-amino alcohols by reduction of the corresponding β-amino ketones is necessary for the elucidation of the dependence of the pharmacological properties of the preparations on their three-dimensional structures and for a purposeful search for new anesthetizing agents in this little studied series of compounds. It is well known that the stereochemical result of the reduction of cyclic ketones depends on the structure of the starting ketone (on the degree of steric hindrance of the carbonyl group) and the "effective" volume of the reducing agent. The latter is directly related to the degree of association and solvation of the reagent as a function of its concentration and the nature of the solvent. The dependence of the stereoselectivity of the reactions on these factors is extremely complex. In this connection, in addition to its practical value, the investigation of the stereochemistry of the indicated reactions is of independent theoretical interest.

In order to study the effect of the character of the reagent and its concentration and the nature of the solvent on the stereospecificity of the reactions we carried out the reduction of 2,2-dimethyl-5-aminomethyl-4-oxotetrahydropyrans (I-III) with lithium in liquid ammonia, lithium aluminum hydride in ether and tetrahydrofuran (THF), sodium borohydride in 1 N NaOH and methanol, and aluminum isopropoxide in isopropyl alcohol. In the case of reduction of amino ketones I-III with lithium in liquid ammonia the reaction proceeds stereospecifically and leads to only trans-2,2-dimethyl-5e-aminomethyl-4e-hydroxytetrahydropyrans (IV-VI) (98%) in 73-80% yields. In all other cases of reduction mixtures of trans-IV-VI and cis-2,2-dimethyl-5a-aminomethyl-4e-hydroxytetrahydropyrans (VII-IX) are formed. The compositions of the mixtures of stereoisomeric amino alcohols are presented in Tables 1 and 2, and their overall yields are presented in Table 3.

The amino ketone bases and their hydrochlorides were subjected to reduction, but, like the basicities of the amino ketones, this does not have a substantial effect on the yields and compositions of the mixtures of the resulting amino alcohols. The same reagent ratios were observed for the reactions, and direct order of addition was used, i.e., the amino ketone was added to a solution or suspension of the reducing agent. The quantitative ratios of the isomers in the mixtures were determined by PMR spectroscopy with respect to the heights of the peaks of the characteristic signals corresponding to the individual isomers of the amino alcohols [2]. The individual cis isomers of amino alcohols VII-IX were isolated by fractional crystallization of the mixtures of hydrochlorides, in which the percentages of

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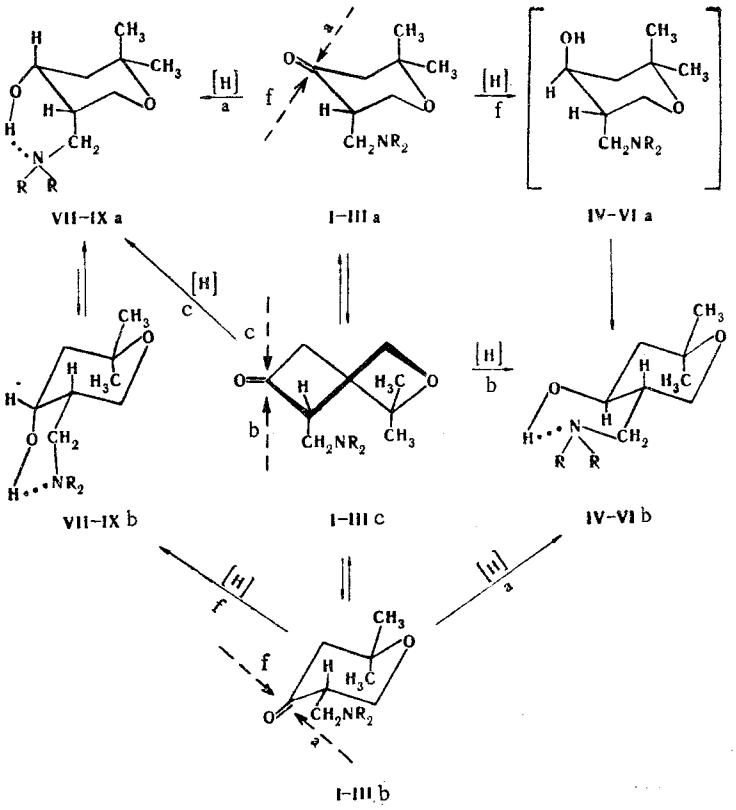

I, IV, VII $NR_2 = N(C_2H_5)_2$; II, V, VIII $NR_2 = N(CH_2)_6$; III, VI, IX $NR_2 = N(CH_2CH_2)_2O$

the cis isomers considerably exceed the percentages of the trans isomers (see Table 1). The properties of the individual trans- and cis-amino alcohols IV-IX are presented in Table 4. Amino alcohol bases VI and IX are crystalline substances with distinct melting points, whereas the remaining amino alcohols (IV, V, VII, and VIII) are colorless viscous liquids. The purity of the compounds was monitored by thin-layer chromatography (TLC).

The three-dimensional structures of the isomeric amino alcohols were established by means of their PMR and IR spectra [2, 3]. Intense absorption bands in the region of the stretching vibrations of the hydroxyl group linked by a hydrogen bond to the nitrogen atom of the amino group are observed in the IR spectra of dilute solutions of both the cis- and trans-amino alcohols. The $\nu_{OH\ assoc}$ bands for IV-VI are found at 3290, 3280, and 3312 cm^{-1}, as compared with 3230, 3250, and 3272 cm^{-1} for VII-IX.* The absorption bands of a free hydroxyl group are absent in all of the IR spectra. For the formation of an intramolecular hydrogen bond in the cyclic γ-amino alcohols the vicinal aminomethyl and hydroxyl groups should be either trans-diequatorially or cis-equatorially-axially oriented relative to one another.

First-order analysis of the PMR spectra of amino alcohols IV-VI, which are identical in the δ 1-1.2 and 3-4 ppm regions for all of the compounds, gave the following results. Multiplet signals of the 4-H proton are present at 3.57-3.70 ppm; the spin–spin coupling constants (SSCC) of this proton with the vicinal 3-H and 5-H protons correspond to two diaxial and one axial–equatorial interaction ($^3J_{4a3a}$ = 11 Hz, $^3J_{4a3e}$ = 5 Hz, and $^3J_{4a5a}$ = 11 Hz) [4]. This constitutes evidence for an axial orientation of the protons attached to the 4-C and 5-C atoms and, consequently, to an equatorial orientation of the adjacent hydroxyl and aminoethyl groups in amino alcohols IV-VI. In addition, it was found to be possible in the indicated spectra to identify two resonance signals of the axial and equatorial 6-H protons, analysis of which confirms the above-indicated conclusion regarding the axial orientation of the proton attached to the 5-C atom. Thus a triplet signal of the 6-H_a proton ($^3J_{6a5a}$ = 12 Hz, $^2J_{6a6e}$ = 12 Hz) is present at 2.97-3.04 ppm, and a quartet signal of the 6-H_e proton ($^3J_{6e5a}$ = 5 Hz, $^2J_{6e6a}$ = 12 Hz) is present at 3.30-3.42 ppm. According to the data from the PMR spectra of amino alcohols VII-IX, the SSCC [found from the multiplet signals of the 4-H proton (3.88-3.92 ppm)] with the vicinal 3-H and 5-H protons ($^3J_{4a3a}$ = 11 Hz, $^3J_{4a3e}$ = 5 Hz, and $^3J_{4a5e}$ = 5 Hz) correspond to one diaxial and two axial–equatorial interactions [4].

*The values given correspond to the respective order of numbering of the compounds.

TABLE 1. Dependence of the Quantitative Ratio (%) of the Stereoisomeric Amino Alcohols on the Nature of the Reducing Agent and the Solvent

Amino ketone		Amino alcohol		Li/liq. NH_3	$LiAlH_4$[a]		$NaBH_4$[a]		$Al(O-C_3H_7\text{-}i)_3$[b]
No.	pK_a	No.	configuration	C_2H_5OH	ether	THF	1 N NaOH	CH_3OH (CH_3ONa)	i-C_3H_7OH
I	7,55	IV	trans	98	55	32	33	44	31
		VII	cis	—	45	68	67	56	69
II	7,42	V	trans	98	47	29	36	45	30
		VIII	cis	—	53	71	64	55	70
III	5,07	VI	trans	98	48	28	24	30	29
		IX	cis	—	52	72	76	70	71

[a]Data for 0.1 mole/liter solutions of the complex hydrides are presented (see Table 2). [b]The reaction was carried out under equilibrium conditions (without removal of the acetone by distillation).

TABLE 2. Dependence of the Quantitative Ratio (%) of the Stereoisomeric Amino Alcohols on the Hydride Concentration

Amino alcohol		$LiAlH_4$ in ether			$NaBH_4$ in 1 N NaOH			$NaBH_4$, CH_3OH (CH_3ONa)		
No.	configuration	hydride concn., mole/liter								
		0,01	0,1	1	0,01	0,1	1	0,01	0,1	1
IV	trans	49	55	57	36	33	43	43	44	53
VII	cis	51	45	43	64	67	57	57	56	47
V	trans	44	47	51	35	36	47	44	45	47
VIII	cis	56	53	49	65	64	53	56	55	53
VI	trans	48	48	51	30	24	45	26	30	31
IX	cis	52	52	49	70	76	55	74	70	69

TABLE 3. Yields (%) of Mixtures of Stereoisomeric Amino Alcohols under Various Reduction Conditions

Mixture of amino alcohols	Li/liq. NH_3	$LiAlH_4$						$NaBH_4$						$Al(O-C_3H_7\text{-}i)_3$
		ether			THF			1 N NaOH			CH_3OH (CH_3ONa)			
	C_2H_5OH	hydride concn., mole/liter												i-C_3H_7OH
		0,01	0,1	1	0,01	0,1	1	0,01	0,1	1	0,01	0,1	1	
IV, VII	76	97	80	94	74	82	83	73	86	86	84	77	79	44
V, VIII	80	80	79	78	80	84	86	72	83	86	91	76	88	40
VI, IX	73	85	80	73	76	79	82	72	67	64	85	71	71	48

Consequently, amino alcohols VII-IX, like amino alcohols IV-VI, are equatorial alcohols, but the aminomethyl group has an axial orientation, since the 4-H proton is axially oriented, and the 5-H proton is equatorially oriented. The axial orientation of the aminomethyl group in VII-IX is also confirmed by the character of the splitting of the resonance signals and the SSCC of the **geminal protons** attached to the 6-C atom with the vicinal 5-H protons. The PMR spectra of amino alcohols VII-IX contain two **quartet** signals of 6-H_a (3.04-3.34 ppm) and 6-H_e (3.55-3.62 ppm) protons, the SSCC of which with the 5-H protons are 3 Hz (**with** $^2J_{6a6a}$ = 12 Hz) in both cases: **This** constitutes evidence for the equatorial orientation of the latter. Thus on the basis of the data obtained from the PMR and IR spectra one may conclude that amino alcohols IV-VI in solution have primarily a conformation with a trans-diequatorial orientation of the hydroxyl and aminomethyl groups, whereas amino alcohols VII-IX have a cis configuration relative to these groups and primarily a conformation with an equatorial

TABLE 4. 2,2-Dimethyl-5-aminomethyl-4-hydroxytetrahydropyrans

Compound	bp, °C (mm)	mp, °C (heptane)	n_D^{20}	Rf [acetone–benzene (1:4)]	Found, %			Empirical formula[a]	Calc., %			Hydrochloride, mp, °C[b]
					C	H	N		C	H	N	
IV	82—83 (2)	—	1,4548	0,54	—	—	5,6	$C_{12}H_{25}NO_2 \times HCl$	—	—	5,6	72—73
V	123—124 (1)	—	1,4825	0,68	69,7	11,2	5,8	$C_{13}H_{25}NO_2$	69,7	11,3	5,8	192—193
VI	—	71—72	—	0,42	63,0	10,3	6,0	$C_{12}H_{23}NO_3$	62,8	10,1	6,1	190—191 (dec.)
VII	78—79 (2)	—	1,4593	0,37	—	—	5,6	$C_{12}H_{25}NO_2 \times HCl$	—	—	5,6	114—115
VIII	133—135 (1)	—	1,4880	0,53	69,6	11,4	5,4	$C_{13}H_{25}NO_2$	69,7	11,3	5,8	207—208
IX	—	91—92	—	0,32	63,0	10,2	6,0	$C_{12}H_{23}NO_3$	62,8	10,1	6,1	206—207 (dec.)

[a]The results of the analysis for nitrogen in the hydrochlorides are presented for IV and VII. [b]The hydrochlorides of IV and VII were recrystallized from alcohol–acetone (1:3); V, VI, VIII, and IX were recrystallized from methanol–ethyl acetate (1:3). The compositions of the hydrochlorides were confirmed by analysis for chlorine.

hydroxyl group and an axial aminomethyl group.

The three dimensional structures and quantitative ratios of the stereoisomeric amino alcohols IV-IX in the mixtures formed in reduction by the various reducing agents show that the reaction evidently proceeds with the participation of all three conformation forms of amino ketones I-IIIa,b,c, which exist in an equilibrium state in solution. Proceeding from the two existing models of the mechanism of the reduction of cyclic amino ketones [5], it may be assumed that in the case of the reduction with lithium aluminum hydride the formation of trans-amino alcohols IV-VIb occurs as a result of intramolecular transfer of a hydride ion in the cyclic chelate complex from the axial region of conformers I-IIIb, whereas cis-amino alcohols VII-IX are obtained as a result of a bimolecular reaction between the hydride ion and the activated (by the metal cation) carbonyl group of the amino ketones I-III. In this case approach of the hydride from the equatorial region of conformers I-IIIb is more favorable than approach from the axial side of conformers I-IIIa. The resulting cis-amino alcohols, initially in the VII-IXb conformations, undergo inversion with a shift in the conformational equilibrium to favor the VII-IXa conformers. In the case of ionic borohydrides the reduction should be a bimolecular process, and trans-amino alcohols IV-VI are obtained as a result of equatorial attack on conformers I-IIIa. The resulting axial amino alcohols IV-VIa, being unstable, undergo inversion to conformers IV-VIb with a diequatorial orientation of the functional groups; this is also promoted by the development between them of an OH...N intramolecular hydrogen bond. The ratio between the cis- and trans-amino alcohols is determined by the difference in the enthalpies of activation of the equatorial attack of the amino ketones in the I-IIIa and I-IIIb conformations [6]. The effect of solvents, which leads to a certain change in the ratio of the amino alcohols (see Table 1), can be explained by their different ionizing capacities and abilities to coordinate with the reducing agent [7]. A study of the dependence of the stereoselectivity of the reduction on the concentrations of complex hydrides (see Table 2) showed that a decrease in the concentration is accompanied by a decrease in the percentages of the trans-amino alcohols as a consequence of an increase in the volume of the hydride particles as a result of solvation and a decrease in their coordinating capacities [5, 8]. The results obtained in the reduction with aluminum isopropoxide also confirm the advantage of equatorial attack on conformers I-IIIb, which leads to predominance of cis configurations VII-IX in the resulting mixtures of amino alcohols. trans-Amino alcohols IV-VI are formed in smaller amounts because equatorial attack on amino ketones in the I-IIIa conformations is less favorable because of shielding of the carbonyl group of the adjacent axial aminomethyl group. However, one cannot exclude the possibility of a flexible (twist) form of amino ketones I-IIIc in the reduction. Steric hindrance will be at a minimum in this case because of the fact that both methyl groups attached to the 2-C atom are symmetrically oriented with respect to the ring, and the probability of approaching the carbonyl group by the reducing agent on one or the other side will be determined only by the polar aminomethyl group attached to the 5-C atom. As a

result of this, mixtures of cis- and trans-amino alcohols will be obtained, and attack by the reagents in direction c, which leads to the formation of cis-amino alcohols VII-IX, will predominate. All of this is in good agreement with the data obtained relative to the compositions of the mixtures of amino alcohols. The stereospecificity of the reduction of amino ketones I-III with lithium in liquid ammonia, which leads to only trans-amino alcohols IV-VI, follows from the reaction mechanism, according to which [9] the most stable of the possible diastereoisomers of amino alcohols IV-VIb is formed.

EXPERIMENTAL

The PMR spectra of CCl_4 solutions of the compounds were recorded with a Varian HA-100 spectrometer (100 MHz) with tetramethylsilane as the internal standard. The IR spectra of $5 \cdot 10^{-3}$ mole/liter solutions of the compounds in CCl_4 were recorded with a UR-10 spectrometer. Thin-layer chromatography (TLC) was carried out on plates with a loose layer of activity II Al_2O_3 in an acetone–benzene system (1:4). The hydrochlorides of the amino alcohols were obtained by the addition of a saturated solution of dry hydrogen chloride in anhydrous ether to a solution of the base in ether.

Reduction of 2,2-Dimethyl-5-diethylaminomethyl-4-oxotetrahydropyran (I). A) With Lithium in Liquid Ammonia. A solution of 12.5 g (0.05 mole) of the hydrochloride of amino ketone I in 100 ml of ethanol was added with stirring and cooling (−70°C) to 300 ml of liquid ammonia, after which 2.8 g (0.4 mole) of fine lithium shavings was added in small portions. The cooling bath was then removed, and the temperature of the reaction mixture was gradually raised to room temperature. The ammonia was allowed to evaporate completely and the mixture was hydrolyzed with 150 ml of water. The aqueous mixture was saturated with potassium carbonate and extracted repeatedly with ether. The ether extract was dried with $MgSO_4$, the ether was removed by distillation, and the residue was vacuum distilled to give 8.2 g (76%) of trans-2,2-dimethyl-5e-diethylaminomethyl-4e-hydroxytetrahydropyran (IVb).

trans-Amino alcohols Vb and VIb were similarly obtained. Base VIb began to crystallize after the ether was removed from the ether extract by distillation.

B) With Lithium Aluminum Hydride. 1) A 1.56 g (0.006 mole) sample of the hydrochloride of amino ketone I was added in small portions with stirring and cooling (to 0°C) to a suspension of 0.48 g (0.012 mole) of lithium aluminum hydride in 125 ml of anhydrous ether, and the mixture was maintained at 0-4°C for 2 h. It was then hydrolyzed with 5 ml of 1 N NaOH, and the precipitate was removed by filtration and washed on the filter with ether. The ether solution was dried with $MgSO_4$, the ether was removed by distillation, and the residue was vacuum distilled to give 1.07 g (80%) of a mixture of amino alcohols IV and VII with R_f 0.54 and 0.37.

2) The method of reduction of amino ketone I with lithium aluminum hydride in THF was similar to the procedure described above. Workup gave 1.1 g (82%) of a mixture of amino alcohols IV and VII.

C) With Sodium Borohydride. 1) A 1.56 g (0.006 mole) sample of the hydrochloride of amino ketone I was added with stirring and cooling (to 0°C) to a solution of 0.24 g (0.006 mole) of sodium borohydride in 64 ml of 1 N NaOH, and the mixture was stirred at 0-4°C for 1 h. The product was then extracted with ether. The ether extract was dried, the ether was removed by distillation, and the residue was vacuum distilled to give 1.16 g (86%) of a mixture of amino alcohols IV and VII with R_f 0.54 and 0.37. Crystallization of the mixture of salts obtained from amino alcohols IV and VII gave the hydrochloride of the individual cis-amino alcohol VII. A similar procedure was used to obtain cis-amino alcohols VIII and IX. Crystalline amino alcohol IX was isolated in pure form also as a result of crystallization of the mixture of amino alcohols VI and IX from n-heptane.

2) A 1.56 g sample of the hydrochloride of amino ketone I was added to a cooled (to 0°C) solution of 0.24 g of sodium borohydride and 0.2 g of sodium methoxide in 64 ml of anhydrous methanol, and the mixture was stirred at 0-4°C for 1 h. The methanol was removed by vacuum distillation, and the residue was dissolved in 30 ml of water. The aqueous solution was saturated with potassium carbonate and extracted with ether. The ether extract was dried with $MgSO_4$, the ether was removed by distillation, and the residue was vacuum distilled to give 1.03 g (77%) of a mixture of amino alcohols IV and VII.

D) With Aluminum Isopropoxide. A solution of 3.6 g (0.017 mole) of amino ketone I in 20 ml of isopropyl alcohol was added dropwise to a solution of 8.2 g (0.04 mole) of aluminum isopropoxide in 100 ml of anhydrous isopropyl alcohol, and the mixture was refluxed for 2 h. It was then cooled to 0°C and hydrolyzed with 100 ml of 1 N NaOH. The organic layer was separated, acidified to pH ∿ 2 with hydrochloric acid, and vacuum evaporated to dryness. A solution of the residue in water was saturated with potassium carbonate, and the base was extracted with ether. The extract was dried with $MgSO_4$ and vacuum distilled to give 1.6 g (44%) of a mixture of amino alcohols IV and VII.

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SYNTHESIS OF 4-NITROISOXAZOLINE N-OXIDES*

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The reaction of some aliphatic diazo compounds with trans-1-phenyl-1,2-dinitroethylene gave the first representatives of 4-nitroisoxazoline N-oxides, which differ from the unknown 3-nitroisoxazoline N-oxides with respect to their individual physical and chemical properties.

The formation of 3-nitroisoxazoline N-oxides (I) by reaction of aliphatic diazo compounds (II) with gem-dinitroalkenes was described in [2]. The known reactions of II with vic-dinitroalkenes lead to pyrazoles that do not contain a nitro group or to 3,4-dinitro-Δ^1-pyrazolines [3]. It seemed of interest to study the possibility of the participation of the nitro group in vic-dinitroalkenes in cycloaddition reactions with diazoalkanes.

We found that the previously unknown 4-nitroisoxazoline N-oxides (IVa-d) are formed in rather high yields in the reaction of II containing various substituents in the benzene ring [for example, p-methoxyphenyl-(IIa) and p-bromophenylmethyl-(IIb)] such as p-nitrophenylmethyldiazomethane (IIc) and o-bromodiphenyldiazomethane (IId) with trans-1-phenyl-1,2-dinitroethylene (III) at 20-25°C. In the case of diazo compound IIc a decrease in the yield of IVc is observed because of the effect of the electron-acceptor nitro group in the aromatic ring, and the corresponding 3,4-dinitro-Δ^1-pyrazoline (V) is formed as a side product.

It is apparent that the trans configuration is retained in 4-nitroisoxazoline N-oxides IVa-d; this is characteristic for cycloaddition to trans-olefins under the given conditions [4]. Isomers of IV were not detected in the reaction mixtures.

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