INVESTIGATIONS IN THE FIELD OF 1-AZABICYCLANES

XI.* THE STEREOCHEMISTRY OF THE HYDROGENATION OF 5- AND 7-(β-HYDROXYETHYL)-1,2-DIHYDROPYRROLIZINES ON RHODIUM AND NICKEL. CONFIGURATIONAL ASSIGNMENT OF THE REACTION PRODUCTS

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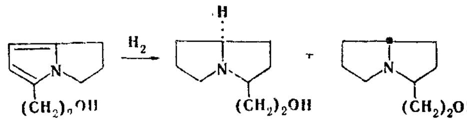
The stereochemistry of the catalytic hydrogenation of 5- and 7-(β-hydroxyethyl)-1,2-dihydropyrrolizines on 2.5% Rh/Al_2O_3 and Raney nickel under various conditions has been studied. On the basis of information on the configurational catalytic isomerization and the competing quaternization of the isomers, a consideration of the relative retention times, and an analysis of the geometries of the molecules of the 1- and 3-(β-hydroxyethyl)pyrrolizidines a configurational assignment of the stereoisomers has been made.

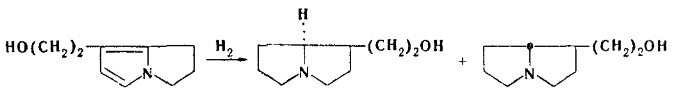
The stereochemistry of the catalytic hydrogenation of 5- and 7-(β-hydroxyethyl)-1,2-dihydropyrrolizines [2] and the stereochemistry of the saturated reaction products is of considerable interest.

In the hydrogenation of 5-(β-hydroxyethyl)-1,2-dihydropyrrolizine (I) the formation of two isomers is possible – cis- and trans-3H,7aH-3-(β-hydroxyethyl)pyrrolizidine (II and III, respectively):



I II III

Similarly, 7-(β-hydroxyethyl)-1,2-dihydropyrrolizine (IV) can be converted into cis- and trans-1H,7aH-1-(β-hydroxyethyl)pyrrolizidine (VI):



IV V VI

The hydrogenation of (I) was performed in the presence of 2.5% Rh/Al_2O_3 or Raney nickel [3], and in the latter case a larger amount of catalyst was also used to ensure the complete hydrogenation of the initial (I) and, possibly, more rapid isomerization at the selected reaction temperature (120°C) [4]. The conditions of hydrogenation and its stereochemical result are given in Table 1. The ratio of (II) and (III) in the catalyzate was determined by the GLC method. On the chromatograms of the hydrogenation products, the configurational assignment of the peaks was made on the basis of the following considerations. It follows from a consideration of molecular models that in the case of (III) a relatively strong intramolecular hydrogen bond may be formed. In the cis-linked conformation (IIA), such a bond, if it arises at all, must, from steric principles, be very weak. However, if an inversion of the nitrogen in this system similar to that described by Skvortsov and Elvidge [5] is assumed, which appears probable in view of the presence of

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*For communication X, see [1].

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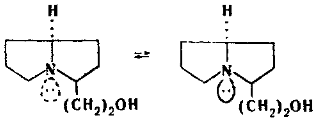
TABLE 1. Conditions and Stereochemical Result of the Hydrogenation of 5-(β-Hydroxyethyl)-1,2-dihydropyrrolizine in Methanol

Catalyst	Amt. of metal in % on the compound undergoing hydrog.	Temp., °C	Proportions of the epimers according to GLC, %	
			II	III
Ni	300	120	26	74
2,5% Rh/Al_2O_3	2,5	~25	86	14

steric interactions of the 3-CH_2 and trans-5-H group, then in the trans-linked form (IIB) the geometry necessary for the formation of an intramolecular hydrogen bond will be realized.



II A

II B

In (IIB), the intramolecular hydrogen bond must be weaker than in (III) because of the less favorable geometric parameters. Of these parameters, the most important is the angle α formed by the line of the OH bond and the axis of the unshared electron pair of the nitrogen, and the N···O distance [6]. It is obvious that the closer the angle α is to 180°, the stronger is the hydrogen bond [7]. On the other hand, beginning with the optimum N···O distance of ~2.8 Å [8], an increase in this distance leads to a weakening of the hydrogen bond [6].

For (III), the angle α = 140°, for (IIB) 125°, and for (IIA) 75°. The linear characteristics of the intramolecular hydrogen bond in (III) and (IIB) are similar – the distance between O and N amounts to 2.5 Å for (III) and 2.7 Å for (IIB).*

Although the position of the equilibrium (IIA) $\rightleftharpoons$ (IIB) is unknown, nevertheless the presence of the invertomer (IIA) leads, as it were to an additional reduction of the mean value of the angle α and, therefore, to a strengthening of the bond with the stationary phase. It is known that isomers forming less strong intramolecular hydrogen bonds or no such bonds at all are retained by a polar liquid phase more strongly than isomers with a stronger bond [9-11].

In the present work we used the same stationary phase as previously [9-11], and the compounds investigated have a similar chemical nature.

From what has been said, it follows that the epimer with the smaller retention time is (III) (Table 2). This assignment will be confirmed below in a consideration of experiments on configurational catalytic isomerization on nickel, and also by the results of the competing quaternization reaction [12].

As the figures given in Table 1 show, the hydrogenation of (I) on Rh/Al_2O_3 is stereoselective and leads mainly to the epimer (II). This result can probably be explained by the preferential cis addition of hydrogen in catalytic hydrogenation [13, 14]. The high proportion of the epimer (III) in the hydrogenation of (I) on Raney nickel is a consequence of a secondary isomerization process.

To study the possibilities of the preparative isolation of the individual isomers from the total mixture of (II, III, V, and VI), and also to investigate the stereochemistry of the hydrogenation of (IV), experiments were performed on the hydrogenation of a mixture of (I) and (IV) [2] (Table 3). The assignment of the peaks on the chromatogram of the hydrogenizate to the epimers (V) and (VI) was performed as in the preceding case on the basis of a comparison of the retention times and an analysis of the geometry of the molecules of both epimers (Table 2). A study of models shows that (V) cannot form an intramolecular hydrogen bond, while (VI) has a geometry for which the appearance of such a bond is probable.

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*The measurements were performed on models based on Framework Molecular Models (Prentice-Hall, Inc., Englewood Cliffs) in the open form of the bicyclic system [5]. A skew conformation was found in the CH_2-CH_2-O fragment, and the axis of the unshared pair of electrons of the nitrogen and the line of the O–H bond were in the same plane. In view of the difficulties in the choice of the optimum conformations in the hydroxyethyl group, the measurements made in this way contain some element of arbitrariness. Nevertheless, they reflect the order of magnitude of the angles α in (IIA, IIB, III, V, and VI) (Table 2).

TABLE 2. Geometric Parameters of the Intramolecular Hydrogen Bonds and of the Retention Times of the Isomers (II, III, V, and VI)

Compound	Angle α, deg	N···O distance, Å	Retention time, min
III	140	2,5	16
II (IIA	75	2,9	24
IIB)	125	2,7	
VI	110	3,4	32
V	0	4,0	42

TABLE 3. Conditions and Stereochemical Result of the Hydrogenation of a Mixture of (I) and (IV). The Ratios (II) : (III) and (V) : (VI) as a Function of the Conditions of Hydrogenation of a Mixture of (I) and (IV)

Catalyst	Amt. of metal in% on the compound undergoing hydrogen.	Solvent	Temp. °C	Content of isomers according to GLC, %				Ratio of epimers, %		Ratio of epimers, %	
				II	III	V	VI	II	III	V	VI
Ni	20	CH_3OH	120	29	31	28	12	48	52	70	30
Ni	300	CH_3OH	120	5	49	12	34	9	91	26	74
2,5% Rh/Al_2O_3	2,5	CH_3OH	~20	50	9	32	9	85	15	78	22
2,5% Rh/Al_2O_3	2,5	CH_3COOH	~25	34	22	31	13	61	39	70	30

The results given in Table 3 show that when small amounts of nickel are used as catalyst the amounts of (II) and (III) in the catalyzate do not differ fundamentally. However, with an increase in the amount of Raney nickel in the reaction mixture there is a marked rise in the proportion of (III), which can be explained by secondary isomerization transformations on this catalyst. A similar conclusion can be made concerning the participation of nickel in the hydrogenation of (IV) and the subsequent epimerization of (V) into (VI).

As a result of configurational isomerization, the main isomers obtained are the thermodynamically more stable ones, and in the pyrrolizidine series these are the trans isomers [11, 15, 16]. From the pairwise consideration of models of (II) [the strong unbound interactions in (IIA) and the considerable angular strain in (IIB)] and of (III) and (V) (unbound interactions of the 1-CH_2 and the trans-7-H) and (VI) it can be understood that compounds (III) and (VI)* have a smaller stock of free energy than their epimers. Consequently, on catalytic epimerization, they must become the predominating components of the mixture. An acceleration of the isomerization process was achieved by an increase in the amount of catalyst [4]. Consequently, the results of hydrogenation and subsequent isomerization on nickel form an important argument in favor of the configurational assignment made.

In the hydrogenation of (I) in the presence of 2.5% Rh/Al_2O_3, a passage from methanol to acetic acid as solvent causes a rise in the amount of (III). Nevertheless, in this case, too, the epimer (II) remains predominant. Similar characteristics are observed with respect to (V) and (VI) in dependence on the conditions of the hydrogenation of (IV).

In the present work, we also set ourselves the task of developing a method for the preparative separation of (III) from its mixture with (II), (V), and (VI), using the quaternization method [12]. As can be seen from molecular models, the unshared pair of nitrogen in (III) is shielded by the β-hydroxyethyl group to a greater degree than in (II), (V), and (VI) and, in addition to this, it is partially passivated by the presence of a strong intramolecular hydrogen bond.

To achieve separation, it was necessary to select an alkyl halide the steric interaction of the radical of which with the β-hydroxyethyl group present in various positions would be such that under the conditions adopted a rapid quaternization reaction would be possible in all cases with the exception of (III). Of the compounds tested, methyl iodide, ethyl iodide, isopropyl iodide, and n-propyl iodide proved to be the most suitable for these purposes. The reaction was performed at room temperature in ether with an ex-

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*We did not consider an additional stabilization of (III) and (VI) through an intramolecular hydrogen bond, since isomerization was performed in methanol.

cess of n-propyl iodide. The precipitate of quaternary salts obtained from (II), (V), and (VI), was filtered off, and (III) was isolated from the mother solution. The method of isolating (III) from the mixture serves as an additional independent proof of its structure.

The existence of a strong intramolecular hydrogen bond in (III) ($\Delta\nu_{OH} = 380$ cm^{-1}) was shown by the IR spectroscopic study of the concentration dependence of ε^a of the band of the stretching vibrations of the bound hydroxyl [17].

EXPERIMENTAL

The IR spectra were taken by I. Ya. Evtushenko, to whom the authors express their thanks, at room temperature on a UR-10 spectrometer (LiF prism). The solvent (CCl_4) was previously dried with phosphorus pentoxide and distilled. Solutions with concentrations of 0.005, 0.003, 0.002, 0.001, and 0.0005 M were studied at cell lengths of 20 mm for the first four concentrations and 50 mm for the last. The values of ε^a of the bound hydroxyl at these concentrations were, respectively, 41, 42, 44, 47, and 48. In 0.005 M solution, ν_{OH} is 3640 cm^{-1} and ν'_{OH} 3260 cm^{-1}.

Hydrogenation of (I) [18] and Analysis of the Catalyzate. A 160-ml autoclave was charged with 0.5 g of (I), 15 ml of methanol, and 1.5 g of Raney nickel. The reaction was performed at 120°C and an initial pressure of hydrogen of 115 atm for 5 h. The hydrogenizate was filtered from the catalyst and evaporated to a volume of 5 ml. This solution was analyzed on a UKh-2 chromatograph with thermal-conductivity detection. Polyethyleneglycol 20,000 deposited in an amount of 15% on INZ-600 carrier treated successively by published methods [19, 20] was used as the stationary phase. The length of the column was 4 m, the diameter 4 mm, the temperature 234°C, and the rate of flow of the carrier gas (helium) 200 ml/min.

The conditions of hydrogenation in the other experiments are given in Tables 1 and 3. When acetic acid was used as the solvent, the catalyst was filtered off, the acetic acid was distilled off under reduced pressure on the water bath, and the residue was dissolved in a sevenfold amount of benzene. The benzene solution was treated with concentrated caustic soda solution, and the benzene layer was separated off and dried with caustic potash.

Mixture of 3-(β-Hydroxyethyl)pyrrolizidines (II and III) and 1-(β-Hydroxyethyl)pyrrolizidines (V and (VI). A. A 160-ml autoclave was charged with 8.1 g of a mixture of (I) and (IV) [2], 80 ml of methanol, and 1.7 g of Raney nickel. Hydrogenation was performed at 120°C and an initial pressure of hydrogen of 115 atm. for 5 h. The hydrogenizate was filtered from the catalyst, the methanol was evaporated off, and the residue was treated with 80 ml of hydrochloric acid. The solution was washed three times with benzene and twice with ether (50-75 ml portions) and was dried with caustic potash. The oil isolated and benzene extracts from the alkaline solution were combined and dried with caustic potash. The benzene was distilled off and the residue was fractionated under reduced pressure, giving 4.7 g (56%) of a mixture of (II), (III), (V), and (VI). Bp 119-130°C (2 mm); d_4^{20} 1.0218; n_D^{20} 1.4997. Found, %: C 69.6; H 11.0; N 9.1. $C_9H_{17}NO$. Calculated, %: C 69.6; H 11.0; N 9.0.

B. The hydrogenation of 8 g of a mixture of (I) and (IV) on 24 g of Raney nickel under the same conditions and the isolation of the product by the method described above gave 4.2 g (51%) of a mixture of (II), (III), (V), and (VI). Bp 132-150°C (10 mm); n_D^{20} 1.4985.

C. A 160-ml rotating autoclave was charged with 7 g of a mixture of (I) and (IV), 50 ml of glacial acetic acid, and 7 g of 2.5% Rh/Al_2O_3. Hydrogenation was performed at room temperature and an initial pressure of hydrogen of 110 atm. The calculated amount of hydrogen was absorbed in 40 min. The catalyzate was treated by the method described above, giving 4.38 g (61%) of a mixture of isomeric hydroxyethylpyrrolizidines. Bp 124-135°C (5 mm), d_4^{20} 1.0314; n_D^{20} 1.4974.

In all cases, according to GLC, the yields of the hydrogenation products were considerably higher than those given in the preparative syntheses, which is explained by losses in the isolation and purification stages.

trans-3-(β-Hydroxyethyl)-3H,7aH-pyrrolizidine (III). A solution of 8.7 g (0.051 mole) of n-propyl iodide in 35 ml of ether was added to 4.4 g (0.028 mole) of a mixture of isomers containing 5% of (II), 49% of (III), 12% of (V), and 34% of (VI). After only one of the isomers remained in the solution (5 days, chromatographic check), the precipitate was filtered off, the filtrate was treated with 5% hydrochloric acid, the ethereal layer was separated off, and the aqueous layer was treated with caustic potash. The oil that separated out and benzene extracts from the aqueous layer (2 × 30 ml) were combined and were dried with solid KOH. The benzene was evaporated off and the residue was distilled under reduced pressure. Yield 1.77 g [40% on the total weight of the mixture of isomers and 82% on the (III) contained in the initial mixture] in the form of a colorless viscous liquid. The purity of the isomer was confirmed chromatographically. Bp 91-94°C (2 mm), d_4^{20} 1.0177; n_D^{20} 1.4955. Found, %: C 69.6; H 11.1; N 9.0; MR_D 44.52. $C_9H_{17}NO$. Calculated, %: C 69.6; H 11.0; N 9.0; MR_D 44.83.

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