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RESEARCH ON TWO-RING 1-AZA COMPOUNDS

XIII.* SYNTHESIS OF 3(5)-HYDROXYMETHYLPYRROLIZIDINES BY CATALYTIC HYDROGENATION OF 5-HYDROXYMETHYL-1,2-DIHYDROPYRROLIZINES. DETERMINATION OF THE CONFIGURATIONS OF THE REACTION PRODUCTS

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5-Hydroxymethyl-1,2-dihydropyrrolizines were catalytically hydrogenated to 3(5)-hydroxymethylpyrrolizidines, and the ratios of the isomers in the products of the reaction, which proceeds stereoselectively, were determined. The configuration of the diastereomers was established on the basis of the results of catalytic isomerization, a study of the chromatographic behavior of the isomers on a polar stationary phase, and a discussion of the isomeric composition of the hydrogenation products in the light of the general principles of the stereochemistry of catalytic hydrogenation. trans- and cis-3,8-H-3-Hydroxymethylpyrrolizidine and trans-3,8-H-3-methyl-trans-5,8-H-5-hydroxymethylpyrrolizidine were isolated from the mixtures of isomers. The existence of an intramolecular hydrogen bond in trans-3,8-H-3-hydroxymethyl- and trans-3,8-H-3-methyl-trans-5,8-H-5-hydroxymethylpyrrolizidine was shown by IR spectroscopy.

Up until now, very little study has been devoted to 3(5)-hydroxymethylpyrrolizidines. The simplest route to these compounds is catalytic hydrogenation of 5-hydroxymethyl-1,2-dihydropyrrolizidines [2, 3].

The hydrogenation of 5-hydroxymethyl-1,2-dihydropyrrolizine (I) and its 2- and 3-methyl-substituted derivatives (II, III) is examined in the present paper.

Hydroxymethylpyrrolizidines were obtained in 50-70% yields by hydrogenation of I-III on a 5% Rh/Al_2O_3 catalyst from Engelhard Industries, Baker Platinum Division, or one prepared by means of the method in [4, 5] at room temperature in methanol at 90-150°C (Raney nickel caused hydrogenolysis of the C−O bond, whereas a mixed Rh−Pt catalyst or 5% Rh/C from the above company were ineffective at 20-100°).

*See [1] for communication XII.

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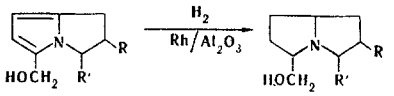

I-III IV-XIII

I, III-V, X-XIII R=H; II, VI-IX R=CH_3; I, II, IV-IX R'=H; III, X-XIII R'=CH_3

According to the results of gas–liquid chromatography (GLC), hydrogenation of alcohol I gives a mixture of two compounds. It follows from the results of elementary analysis, refractometric data, and the results of experiments of configurational catalytic isomerization that these compounds are trans- (IV) and cis-3,8-H-3-hydroxymethylpyrrolizidines (V). The configurational assignment of epimers IV and V was made as in [6] on the basis of data on their retention on polyethylene glycol 20,000 and configurational catalytic isomerization [7]. Isomer V (95%) is the predominant component in the mixture of amino alcohols IV and V in the hydrogenation products. This fact served as an independent confirmation of the stereochemical assignment above, inasmuch as it is in agreement with the known peculiarities of the catalytic hydrogenation of aromatic and heteroaromatic systems, particularly 1,2-dihydropyrrolizines with substituents in the pyrrole portion of the two-ring system [6-8]. These peculiarities are expressed in terms of preferred cis addition of hydrogen.

The configurational assignment of the epimeric 3-methylpyrrolizidines was previously made in [9] by means of the quaternization method. An idea regarding the possibility of the application of this method for the configurational assignment in diastereomeric pairs of any 3-substituted pyrrolizidines was simultaneously expressed. However, cis-trans conversion of the ring, which may occur in substituted cis-3,8-H-pyrrolizidines [10], was not taken into account in [9]. Although the correctness of the configurational assignment of 3-methylpyrrolizidines made by means of the quaternization method was confirmed by the PMR spectroscopic data [10], the subsequent application of the method for the solution of the problem of the configurations of 3- or 5-substituted pyrrolizidines requires verification in other compounds with known stereochemistry. We investigated the possibility of the application of this method for the establishment of the configuration of pyrrolizidines with hydroxymethyl groups in the 3 or 5 positions. In the reaction of a mixture of epimers of IV and V with alkyl halides, of the tested halides (methyl iodide, ethyl iodide, and N-propyl iodide, n-propyl iodide proved to be the most convenient in a preparative respect: In the reaction of the latter with a mixture of isomers IV (26%) and V (74%) the percentage of isomer V fell to practically 0%, and IV remained in solution. Consequently, isomer IV, which has a trans configuration reacts with propyl iodide more slowly than epimer V.

In order to preparatively isolate the isomer we used a mixture enriched in epimer IV by catalytic isomerization. After the peak of isomer V had disappeared on the chromatogram, further quaternization was stopped by the addition of hydrochloric acid solution. Pure isomer IV was obtained in 50% yield. Isomer V was isolated by fractional distillation from a mixture enriched in this compound.

The formation of four diastereomers – trans-2,8-H-2-methyl-trans-5,8-H- (VI), cis-2,8-H-2-methyl-trans-5,8-H- (VII), trans-2,8-H-2-methyl-cis-5,8-H- (VIII), and cis-2,8-H-2-methyl-cis-5,8-H-5-hydroxymethylpyrrolizidine (IX) – is possible in the hydrogenation of alcohol II. Two pairs of poorly separated peaks (the area ratio of the pairs is 6:94) are detected on the chromatogram of the catalyzate. The methyl group in starting II is more remote from the ring undergoing hydrogenation than in 3-methyl-1,2-dihydropyrrolizine (XIV), and its effect on the stereochemical results of the hydrogenation will therefore be manifested more weakly than in the case of XIV. In the hydrogenation of XIV, as a result of the steric effect of the methyl group during the substrate–catalyst interaction, the principal product is cis-3,8-H-3-methylpyrrolizidine, but its epimer is also formed [11]. One should especially expect the formation of two isomers with cis and trans relationships at C_2 and C_8 (for the same configurations of the other asymmetric centers) in the hydrogenation of 1,2-dihydropyrrolizine systems with a methyl group in the 2 position. In analogy with the hydrogenation of I, one may suppose that the principal components of the mixture will be isomers with a cis orientation of the hydrogen atoms attached to C_5 and C_8 (VIII and IX), and the isomers with a trans orientation of the hydrogen atoms attached to these same centers (VI and VII) should be formed in smaller amounts. The validity of this assumption was demonstrated in the following manner.

From models it is apparent that isomers VI and VII, as in the case of IV, may form a relatively strong intramolecular hydrogen bond. Like amino alcohol V, isomers VIII and IX will form a weaker intramolecular hydrogen bond. Consequently, in analogy with epimers IV and V and [6], one might assume that when the mixture is subjected to gas–liquid chromatography (GLC), isomers VI and VII* will emerge

*The order of emergence of the isomers within the VI, VII and VIII, IX pairs was not established.

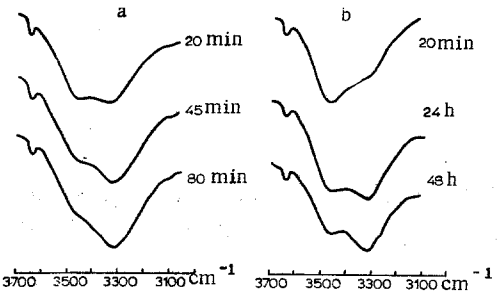

Fig. 1. IR spectra of CCl_4 solutions of amino alcohols IV (a) and X (b) at various time intervals reckoned from the instant of preparation of the solutions.

from the column first, followed by isomers VIII and IX. This sort of assignment with respect to C_5 was confirmed by catalytic configurational isomerization. On Raney nickel the total percentage of VI and VII in the mixture increased from 5% to 91%. In the reaction of isomers VI-IX with alkyl halides the effect of the differences in the configurations at C_2 will be smaller than in the case of C_5, inasmuch as C_2 is removed from the reaction center by nitrogen. The principles found for the quaternization of epimers IV and V should therefore be reproduced with respect to the configurational difference at C_5. An increase in the fraction of VI and VII to 34% and a corresponding decrease in the total amount of isomers VIII and IX were observed during the reaction of a mixture of isomers VI+VII (6%) and VIII+IX (94%) with propyl iodide. Thus the configurational assignment at C_5 receives yet another independent confirmation.

The hydrogenation of alcohol III leads to four possible isomers – trans-3,8-H-3-methyl-trans-5,8,H- (X), cis-3,8-H-3-methyl-trans-5,8-H- (XI), trans-3,8-H-3-methyl-cis-5,8-H- (XII), and cis-3,8-H-3-methyl-cis-5,8-H-5-hydroxymethylpyrrolizidine (XIII) – which are separated sharply by GLC on polyethylene glycol 20,000 (the order of emergence of the isomers was XIII, X, XI, and XII, and the ratio of the areas of the peaks was 56 : 14 : 8 : 22, respectively; the order of emergence of isomers XI and XII was established conjecturally).

The configurational assignment of isomers X-XIII was made by means of catalytic configurational isomerization, determination of the order of emergence of the isomers from a column with a polar stationary liquid phase, analysis of their geometry, and consideration of the quantitative composition of the catalyzate as being a consequence of stereoselective catalytic hydrogenation processes [7].

In order to isolate amino alcohol X, we carried out the preparative catalytic isomerization of a mixture of isomers X-XIII. We obtained a mixture containing ~80% isomer X, treatment of which with propyl iodide in ether made it possible to obtain a sample containing 96% of the desired compound.

An intramolecular hydrogen bond was detected in IV and X by IR spectroscopy by investigation of dilute solutions of the compounds in CCl_4. Despite the fact that CCl_4 reacts with amino alcohols IV and X, we were able to determine the ν_{OH} and ν'_{OH} bands by a study of the dependence of the absorption on the time (Fig. 1). Three peaks are isolated in the spectrum of IV at 3000-3700 cm^{-1}. The intensity of the band with a maximum at 3460 cm^{-1} decreases with time, whereas the intensity of the band at 3320 cm^{-1} increases.* This observation can be explained if one assumes that the third peak with a maximum at 3637 cm^{-1} is associated with the ν_{OH} band of IV and possibly also with superimposition on it of the absorption of a free hydroxyl group in the product of reaction of IV with CCl_4. The absorption at 3460 cm^{-1} is due to the stretching vibrations of the hydroxyl group involved in the formation of an intramolecular hydrogen bond in amino alcohol IV, whereas the band at 3320 cm^{-1} should be assigned to the manifestation of the vibration of the hydroxyl group in the product of the reaction of IV with CCl_4. This product is insoluble in CCl_4 and appears as an emulsion in the initial stages of the reaction. The absorption at 3320 cm^{-1} is therefore related to the stretching vibrations of a free hydroxyl group participating in the formation of intermolecular associates, as indicated also by the frequency. The $\Delta\nu_{OH}$ value for IV is 177 cm^{-1}. The following values were similarly found for X: ν_{OH} 3638, ν'_{OH} 3460, and $\Delta\nu_{OH}$ 178 cm^{-1}. The ν_{OH} value for the product of the reaction of X with CCl_4 is 3310 cm^{-1}. As one should have expected, amino alcohol X reacts with CCl_4 considerably more slowly than IV because of additional shielding of the methyl group by the unshared electron pair of nitrogen.

*The maxima were found by graphical separation of the overlapped bands.

EXPERIMENTAL METHOD

The chromatographic analysis was carried out with an LKhM-8M chromatograph with a thermal conductivity detector. Polyethylene glycol 20,000 applied to sferokhrom-1 treated by the method in [12] served as the stationary phase. Hydrogen was used as the carrier gas. The column was made of stainless steel and had an inner diameter of 3 mm. The mixtures of epimers IV and V were analyzed with a column filled with 15% of the stationary phase (length 2.9 m) at 165° and a hydrogen flow rate of 68 ml/min. Chromatography of mixtures of isomers VI-IX and X-XIII was realized with a 6-m-long column containing 8.3% of the stationary phase. The column temperatures were, respectively, 157 and 160°, and the hydrogen flow rates were 55 and 43 ml/min.

The IR spectra of IV and X were recorded with a UR-20 spectrometer at room temperature. The initial concentrations of IV and X in CCl_4 solution were $4 \cdot 10^{-3}$ and $5 \cdot 10^{-3}$ mole/liter, respectively. The solution was placed in a 20-mm-long cuvette with CaF_2 windows.

Five-Percent Rh/Al_2O_3 Catalyst. A 6-g sample of chromatographic γ-Al_2O_3, which had been previously calcined at 550-600° for 2 h, and a solution of 1 g of rhodium chloride crystal hydrates in 10 ml of distilled water acidified to pH 2 with hydrochloric acid, were mixed in a porcelain dish, after which the mixture was evaporated with stirring in a water bath to dryness. The aluminum oxide with the applied rhodium chloride was transferred to a beaker, treated with 2.5 ml of 36% formalin, and allowed to remain under these conditions for 30 min. The resulting slurry was cooled to 5° and treated with 6 ml of 50% KOH solution. The mixture was allowed to stand in an ice bath for 30 min, after which it was stirred and heated for 30 min on a boiling-water bath. The catalyst was washed with distilled water (four 200-ml portions) to neutrality, after which it was washed twice with water, acidified with acetic acid, removed by filtration with a Buchner funnel, and dried at 105° for 4 h.

3-Hydroxymethylpyrrolizidines IV and V. A 160-ml rotating autoclave was charged with 6 g (44 mmole) of freshly distilled I, 80 ml of methanol, and 1.5 g of the 5% Rh/Al_2O_3 catalyst. The initial hydrogen pressure was 128 atm, and the hydrogenation temperature was 18-20°. After 50% of the calculated amount of hydrogen had been absorbed (after 20-30 min), the rate of hydrogenation decreased. Another 1.5 g of catalyst was added to the autoclave, and hydrogenation was continued under the same conditions for another 5-6 h. The hydrogenation product was removed by filtration, the solvent was removed from the filtrate by distillation at reduced pressure, and the residue was acidified to pH 4-5 with 8% hydrochloric acid. The solution was then extracted with ether (three 10-ml portions) and benzene (two 10-ml portions). The extracts were discarded, and the aqueous solution was cooled and saturated with solid KOH. The oily layer was separated, and the solution was extracted with benzene. The combined extracts were combined with the organic layer and dried with solid KOH. The solvent was removed by distillation, and the residue was distilled at reduced pressure to give 3.8 g (61%) of a mixture of epimers IV and V as a colorless viscous liquid with bp 83-85° (2 mm), d_4^{20} 1.0500, and n_D^{20} 1.5030. Found: C 67.8; H 10.7; N 10.2%; MR_D 39.76. $C_8H_{15}NO$. Calculated: C 68.0; H 10.7; N 9.9%; MR_D 40.21.

2-Methyl-5-hydroxymethylpyrrolizidines (VI-IX) and 3-Methyl-5-hydroxymethylpyrrolizidines (X-XIII). These compounds were obtained by hydrogenation of, respectively, II and III and were isolated by the method described above. A mixture of VI-IX was obtained in 52% yield and had bp 107-110° (3.5 mm), d_4^{20} 1.0208, and n_D^{20} 1.4952. Found: C 69.8; H 11.1; N 9.1%; MR_D 44.37. $C_9H_{17}NO$. Calculated: C 69.6; H 11.0; N 9.0%. MR_D 44.83. A mixture of X-XIII was obtained in 69% yield and had bp 89-92° (5 mm), d_4^{20} 1.0010, and n_D^{20} 1.4935. Found: C 69.7; H 11.5; N 9.1%; MR_D 45.11. $C_9H_{17}NO$. Calculated: C 69.6; H 11.0; N 9.0%; MR_D 44.83.

Catalytic Configurational Isomerization. Analytical and preparative variants of this isomerization were examined. For analytical purposes, the isomerization was carried out in a 20-ml rotating autoclave with 0.5 g of mixtures of the pyrrolizidine alcohols in 1.5 ml of methanol at 100°. Raney nickel (3 g) was used as the catalyst [13]. The trend of the reaction was monitored by chromatography.

Competetive Quaternization Reactions. A mixture of 0.21 g (1.5 mmole) of isomers IV (26%) and V (74%) in 2 ml of ether at room temperature was treated with 0.425 g (2.5 mmole) of n-C_3H_7I. Quaternization of a mixture of amino alcohols VI-IX was carried out similarly.

In view of the relatively high reaction rates and the time required for chromatographic analysis, a new portion of the reaction mixture was prepared for each determination of the isomer ratio, and samples were selected at the appropriate time from the start of the reaction. The samples were taken into the syringe through a filter.

trans-3,8-H-3-Hydroxymethylpyrrolizidine (IV). A 160-ml autoclave was charged with 7.6 g (54 mmole) of a mixture containing 6% of epimer IV and 94% of epimer V, 14.5 g of Raney nickel [13], and 25 ml of methanol. The autoclave was flushed with hydrogen, a hydrogen pressure of 15 atm was established, and the hydrogenation was carried out by rotating the autoclave at 100° for 2 h. The catalyst was then removed by filtration, the solvent was removed by distillation, and the residue was distilled at reduced pressure to give 6 g (79%) of a mixture of IV (92%) and V (8%). Ether (35 ml) and 6.7 g (47 mmole) of a mixture of IV (88%) and V (12%), prepared by catalytic isomerization as described above, were placed in a 50-ml flask, and 8.4 g (50 mmole) of propyl iodide was added to the resulting solution. The solution became turbid, and a light yellow precipitate appeared. The trend of the reaction was monitored by GLC. After 4 h, at which time the peak of V had practically vanished on the chromatogram, the solid material was removed by filtration and washed with ether. The filtrate was acidified to pH 1-2 with 5% hydrochloric acid, and the aqueous layer was extracted with ether. The ether extracts were discarded. The aqueous solution was cooled, saturated with solid KOH, and worked up as in the preparation of a mixture of epimers IV and V to give 2.95 g (50%) of isomer IV with bp 70-71° (2.5 mm), d_4^{20} 1.0369, and n_D^{20} 1.4961. Found: C 68.1; H 11.1; N 9.9%; MR_D 39.79. $C_8H_{15}NO$. Calculated: C 68.0; H 10.7; N 9.9%; MR_D 40.21.

cis-3,8-H-3-Hydroxymethylpyrrolizidine (V). This compound was isolated from a mixture of amino alcohols IV and V, obtained as a result of hydrogenation of I, by fractional distillation at reduced pressure. The product, with bp 102° (3 mm), d_4^{20} 1.0575, and n_D^{20} 1.5052, was obtained in 20% yield. Found: C 67.8; H 11.0; N 10.1%; MR_D 39.62. $C_8H_{15}NO$. Calculated: C 68.0; H 10.7; N 9.9%; MR_D 40.21.

trans-3,8-H-3-Methyl-trans-5,8-H-5-hydroxymethylpyrrolizidine (X). A mixture of X (19%), XI (10%), XII (35%), and XIII (46%) was subjected to catalytic isomerization by a method similar to that described above for a mixture of epimers IV and V. Workup of the mixture gave a mixture of the isomers (in 76% yield) containing 80% X. A solution of 5.2 g (34 mmole) of the mixture in 25 ml of ether was treated with 6.2 g (37 mmole) of propyl iodide. The reaction was carried out for 32 h, and amino alcohol X was isolated in the same way as IV. The yield was 3.6 g (86%). According to GLC data, the isomeric purity of the isolated sample was 96%. The product had bp 88-88.5° (5 mm), d_4^{20} 1.0079, and n_D^{20} 1.4884. Found: C 69.5; H 11.1; N 9.3%; MR_D 44.40. $C_9H_{17}NO$. Calculated: C 69.6; H 11.0; N 9.0%; MR_D 44.83.

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