RESEARCH ON 1-AZABICYCLIC SYSTEMS

XIII.* CHEMICAL METHODS FOR THE SEPARATION OF A MIXTURE OF EPIMERIC 3-METHYLPYRROLIZIDINES. RELATIVELY HIGH BASICITIES OF THE ISOMERS

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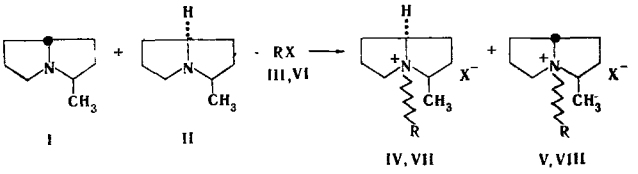
Epimeric 3-methylpyrrolizidines were separated preparatively. Competitive quaternization of the mixture of isomers with n-propyl iodide and catalytic isomerization were used to obtain trans-3, 8-H-3-methylpyrrolizidine. cis-3,8-H-3-Methylpyrrolizidine was isolated from the mixture by quaternization with benzyl chloride and subsequent hydrogenolysis of the resulting quaternary salt. The pK_a values of trans- and cis-3,8-H-3-methylpyrrolizidines, pyrrolizidine, and indolizidine were measured. It is shown that in a series of saturated amines with a tertiary nitrogen atom pyrrolizidine and 3-methylpyrrolizidines are among the strongest bases.

Various methods for the synthesis of mixtures of isomeric 3-methylpyrrolizidines were presented in a previous communication [2]. In the present paper we propose methods for the preparative isolation of trans- (I) and cis-3,8-H-3-methylpyrrolizidine (II) from their mixtures; the methods are based on our previously described [3] method of competitive quaternization.

To isolate base I we selected an alkyl halide whose rate of reaction with this compound is considerably lower than the rate of reaction with isomer II for steric reasons. In ether solutions methyl iodide and ethyl iodide react very vigorously with both epimers. Good selectivity is achieved by the use of isopropyl iodide, but the reaction rate in this case is low. In a preparative respect it was found to be more convenient to use n-propyl iodide (III) as the quaternizing agent; base I can be isolated in up to 50% yields after treatment of a mixture enriched in isomer I with III and separation of quaternary salts IV and V.



III-V $R = n\text{-}C_3H_7$, X = I; VI-VIII $R = C_6H_5CH_2$, X = Cl

Pyrrolizidine I can also be obtained by catalytic isomerization of epimer II. We used Raney nickel and 15% Pd/C as the catalysts; better results are obtained when the latter catalysts are used.

To obtain II we used the ability of benzylhalides of tertiary amines to undergo specific hydrogenolysis [4]. Isomer II was prepared in this way on Raney nickel from cis-3, 8-H-3-methyl-4-benzylpyrrolizidinium chloride (VII), which was isolated in the first crystal fractions from the reaction of a mixture of bases I and II with benzyl chloride (VI).

According to data obtained by gas-liquid chromatography (GLC), the isomeric purity of the isolated I and II was no less than 99%.

*See [1] for communication XII.

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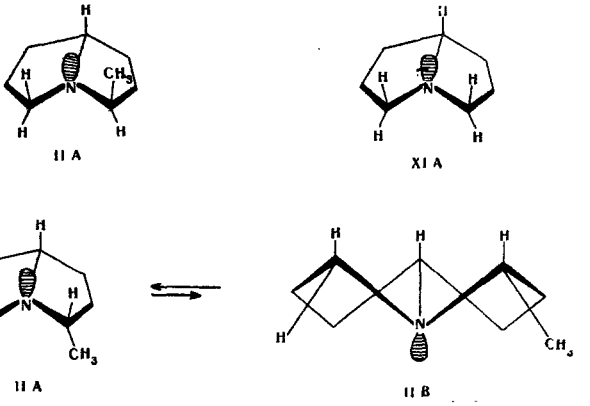
A distinct difference in the absorption at 480-560 cm^{-1}, which depends on the configuration at the 3-C atom, is observed in the IR spectra of the products. A band of medium intensity at 525-537 cm^{-1} is characteristic for the trans isomer of I and its derivatives – quaternary salt VIII and hydrochloride IX; cis isomers II and VII and hydrochloride X have two absorption bands of medium intensity at 485-500 and 542-550 cm^{-1}. This difference in the spectra can be used to monitor the purity of the chloride VII fractions in the quaternization reactions. The absorption band peculiar to salt VIII at 525 cm^{-1} shows up clearly when 5% VIII is present in the mixture, as shown by the IR spectrum of an artificially prepared mixture of isomers VII and VIII.

In examining the results of the determinations of the pK_a values of the investigated bases, one must take into account the fact that I, like unsubstituted pyrrolizidine XI, exists in cis-fused conformations IA and XIA.* According to the PMR spectral data, isomer II exists in nonpolar solvents as a mixture of cis- (IIA) and trans-fused (IIB) forms, and the equilibrium is shifted substantially to favor the former [5].

According to the available data [6], polar solvents stabilize conformations with higher dipole moments. The equilibrium is therefore shifted to an even greater extent to favor the cis-fused conformation of IIA on passing from a nonpolar solution to an aqueous solution of II, since cis-fused conformation IIA, as follows from an examination of models, has a higher dipole moment than trans-fused form IIB. Isomer II in aqueous solution exists primarily, if not practically entirely, in cis-fused form IIA, just like I and XI. The methyl group in epimer I is cis-oriented with respect to the unshared electron pair of nitrogen (exo orientation with respect to the bicyclic system) and creates greater steric hindrance to hydration than in epimer II, in which the methyl group (endo orientation) and unshared electron pair are mutually trans-oriented. This explains the lower basicity of I (pK_a 11.62 ± 0.09) as compared with the basicity of epimer II (pK_a 11.94 ± 0.07). The basicity of II also exceeds the basicity of unsubstituted pyrrolizidine (XI), for which the pK_a value is 11.68 ± 0.06. It is known [7] that in a series of saturated amines the change in basicity when an alkyl group is introduced in the α position relative to nitrogen is the result of the effect of two opposing factors – an increase in the basicity due to a positive inductive effect of the alkyl substituent and a weakening because of steric hindrance to solvation. In the case of isomer I the effects of these factors are partially compensated. The change in the exo orientation of the methyl group in epimer I to the endo orientation in epimer II leads to a decrease in the steric hindrance and, consequently, to an increase in the basicity of the latter compound as compared with the basicity of isomer I.



The pK_a values of pyrrolizidines I, II, and XI are higher than the corresponding constants of saturated tertiary amines (7, 8), particularly related bicyclic systems with a nodal nitrogen atom such as indolizidine (pK_a 10.15 ± 0.05) and quinolizidine (pK_a 10.19 ± 0.07 [9]. The increased basicities of the pyrrolizidines under consideration here may be due to the peculiarities of the geometries of their cis-fused forms. Their first specific peculiarity consists in the fact that, in contrast to quinolizidine and indolizidine, the cis-fused conformations of pyrrolizidines do not have anticoplanar fragments involving the unshared electron pair of nitrogen and the α-C–H bond. Hence the degree of partial delocalization of the unshared pair of nitrogen via the well-known scheme in [10] is reduced (if not excluded entirely) in pyrrolizidines I, II, and XI as compared with the above-named 1-azabicyclic systems. The second peculiarity that is characteristic of pyrrolizidines with cis-fused rings [11] is due to the high steric accessibility of the sp^3 orbital of the nitrogen atoms of II and XI. Features of this sort are also peculiar to the quinuclidine molecule, the basicity of which (pK_a 10.95, 10.65) [7] is explained by the exposed configuration of the unshared electron pair of its nitrogen atom [12]. However,

*The general and essential properties of the various cis-fused conformations [5] – the cis relationship of the hydrogen atom attached to 8-C and the unshared electron pair of nitrogen – are reflected in the scheme.

quinuclidine is a weaker base than pyrrolizidine XI. This difference is probably determined by the fact that the unshared electron pair of the nitrogen atom in the former is shielded by six syn-hydrogen atoms as compared with only three in the latter.

EXPERIMENTAL

The IR spectra of thin layers of bases I and II and mineral oil and hexachlorobutadiene suspensions of crystalline derivatives VII-X were recorded with a UR-20 spectrometer. Chromatographic analysis was carried out with an LKhM-8M chromatograph with a thermal-conductivity detector. Triethanolamine applied in 15% amounts to silanized N-AW-HMDS Chromaton (Chemapol, Czechoslovakia) with a grain size of 0.20-0.25 mm was used as the stationary phase. The column was 2.9-m-long and had an inner diameter of 3 mm, the temperature was 120°, and the carrier-gas (hydrogen) flow rate was 50 ml/min.

The pK_a values were determined by potentiometric titration [13] with an LPU-01 pH-meter with glass and silver chloride electrodes. The apparatus was adjusted by means of groups of standard buffer solutions with pH 9.5, 11.0, and 12.0; and 10.0, 11.0, and 12.5. Titration was carried out in a thermostated (at 25°) vessel that excluded contact between the solution and air. A stream of argon was bubbled through the solution continuously. The aqueous solution of the test base (0.01 M at the half-neutralization point) was titrated with 0.1 M HCl solution. The pK_a values were calculated from a set of determinations (35-44) in parallel experiments. The reliability was assumed to be 95% in the calculation of the confidence interval [14]. Since the investigated compounds have pK_a values higher than 11, control determination of the pK_a value of purified piperidine, for which constants measured at 25° with both glass (pK_a 11.22) [15] and hydrogen (pK_a 11.12) [8] electrodes are known, were made prior to each experiment. We found a pK_a value of 11.29 for piperidine.

Pyrrolizidines I, II, and XI were obtained by methods previously described in [2, 16]. Indolizidine was prepared by intramolecular dehydration of 2-(γ-hydroxypropyl) piperidine [17] by the method in [2]. The product was obtained in 56% yield and had bp 66-67° (34 mm) and n_D^{20} 1.4703 [bp 71-72° (32 mm) and n_D^{21} 1.4702 [2]].

trans-3,8-H-3-Methylpyrrolizidine (I). A) A 17-g (0.1 mole) sample of propyl iodide was added to a solution of 12.3 g (0.1 mole) of a mixture containing 77% isomer I and 23% isomer II in 30 ml of ether, and the solution was allowed to stand at room temperature until isomer II vanished completely (monitoring by GLC), which took ~17 h. The precipitate was removed by filtration and washed with ether. The filtrate was acidified to pH 3-4 with 15% aqueous HCl solution, and the aqueous layer was separated and extracted with ether. The ether extracts were discarded, and the aqueous solution was saturated with solid KOH. The liberated I was extracted with ether, and the ether solution was dried with KOH. The solvent was removed by distillation, and the residue was fractionated at reduced pressure to give 4.8 g (50%) of a product with bp 77-78° (72 mm), d_4^{20} 0.8919, and n_D^{20} 1.4608 [bp 64-65° (35 mm), d_4^{20} 0.8942, and n_D^{20} 1.4606]. The hydrochloride (IX) of pyrrolizidine I, with mp 185-186° (from ethyl acetate), was obtained in 48% yield by mixing ether solutions of base I and dry HCl. Found: C 59.6; H 9.9; N 8.6%. $C_8H_{15}N \cdot HCl$. Calculated: C 59.4; H 10.0; N 8.6%.

B) A 30-ml rotating autoclave was charged with 2 g (16 mmole) of a mixture consisting of 16% epimer I and 84% epimer II, 0.5 g of 15% Pd/C, and 5 ml of ethanol. The air was displaced from the autoclave with hydrogen, and the isomerization was carried out at 100°. After 9 h, isomer II was converted practically completely to isomer I. The catalyst was removed by filtration, the alcohol was removed by distillation at reduced pressure, and the residue was vacuum distilled to give 1.1 g (55%) of product.

trans-3,8-H-3-Methyl-4-benzylpyrrolizidinium Chloride (VIII). A 2.02-g (16 mmole) sample of benzyl chloride was added to a solution of 2 g (16 mmole) of base I in 20 ml of ether, and the mixture was refluxed for 60 h. The resulting salt was removed by filtration and washed with ether to give 2.76 g (68%) of a product with mp 235-236° (from cyclopentanone). Found: C 71.5; H 8.4; N 5.9%. $C_{15}H_{22}ClN$. Calculated: C 71.5; H 8.8; N 5.6%.

cis-3,8-H-3-Methyl-4-benzylpyrrolizidinium Chloride (VII). A 7.0-g (55 mmole) sample of benzyl chloride was added to a solution of 7.6 g (61 mmole) of a mixture of epimers (12% I and 88% II) in 30 ml of ether, and the resulting precipitate was separated in portions as it formed. The quaternary salt fractions were analyzed, beginning with the last, by subjecting them to hydrogenolysis by the method presented below and chromatography of the resulting base. The fraction that yielded pure isomer II was established, and all of the preceding crystal fractions were united. The yield of salt VII, with mp 226-227.5° (from dichloroethane), was 5.5 g (41%). Found: C 71.6; H 8.5; N 5.6%. $C_{15}H_{22}ClN$. Calculated: C 71.5; H 8.8; N 5.6%.

cis-3,8-H-3-Methylpyrrolizidine (II). A 250-ml rotating autoclave was charged with 5.5 g (22 mmole) of salt VII, 27 ml of ethanol, and 1.5 g of highly active alkaline nickel (Urusibar nickel). The initial hydrogen

pressure was 50 atm. Hydrogenolysis was carried out at 50-60° for 2.5 h. The catalyst was removed by filtration, the solution was acidified to pH 3-4 with 15% HCl solution, and the alcohol was removed by distillation. Isomer II was then isolated as in the case of isomer I to give 1.6 g (59%) of a product with bp 85-86° (72 mm), d_4^{20} 0.9092, and n_D^{20} 1.4689. Found: C 76.9; H 12.2; N 11.2%; MR_D 38.34. $C_8H_{15}N$. Calculated: C 76.7; H 12.1; N 11.2%; MR_D 38.68. The hydrochloride (X) of isomer II, with mp 197-198° (from benzene), was obtained by the method used to prepare salt IX. Found: C 59.4; H 10.1; N 8.9%. $C_8H_{15}N \cdot HCl$. Calculated: C 59.4; H 10.0; N 8.6%.

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