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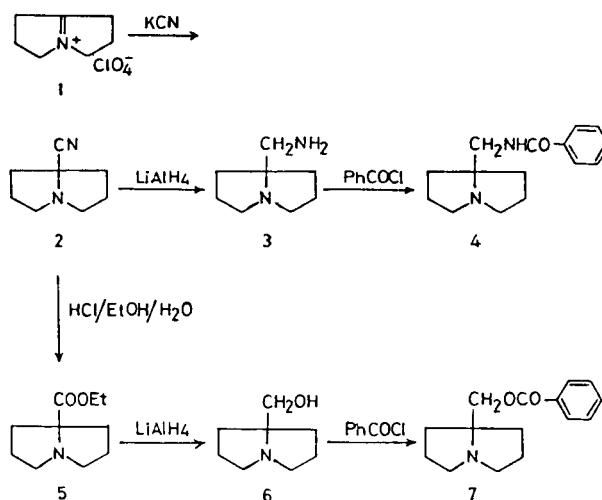
Chemical transformations of 7a-cyano-1H-pyrrolizine (**2**) into 7a-substituted hexahydro-1H-pyrrolizines are described. In the reaction of **2** with lithium aluminum hydride, the orientation of the lone pair of the bridgehead nitrogen against C-CN bond can be regarded as significant.

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We have already communicated that the reaction of an iminium perchlorate, 1,2,3,5,6,7-hexahydropyrrolizinium perchlorate (**1**), with an equivalent amount of potassium cyanide in water gave 7a-cyano-1H-pyrrolizine (**2**) [2] in excellent yield. In this paper we wish to demonstrate that the α -aminonitrile **2** is a useful key starting material for the synthesis of 7a-substituted hexahydro-1H-pyrrolizines [3], as well as a consideration of mechanistic rationalizations for the reductions of α -aminonitriles with LAH. Thus, the reduction of the nitrile **2** with lithium aluminum hydride (LAH) in ether at room temperature afforded the corresponding diamine, 7a-aminomethylhexahydro-1H-pyrrolizine (**3**), as a colorless oil, boiling at 103-104°/30 mm Hg, in 76% yield. Furthermore, the nitrile **2**, when refluxed in 20% hydrogen chloride in ethanol containing 1 equivalent of water for 13 hours could be easily transformed into 7a-ethoxycarbonylhexahydro-1H-pyrrolizine (**5**) in good yield. Though the treatment of the nitrile **2** with a strong acid such as 70% perchloric acid affords the starting iminium salt (**1**) in spite of a meticulous workup of above reaction. The compound **5** could further be derived to a β -aminoalcohol, 7a-hydroxymethylhexahydro-1H-pyrrolizine (**6**) in 75% yield by treatment with LAH in anhydrous ether at room temperature. The structures of the products were established by elemental and spectroscopic analyses (see EXPERIMENTAL), and confirmed by further transformations to the corresponding amide **4** and ester **7**. The synthetic pathway summarized in Scheme I is applicable to the synthesis of a wide variety of 7a-substituted hexahydro-1H-pyrrolizines which are of considerable interest for the purpose of pharmacological evaluation [4].

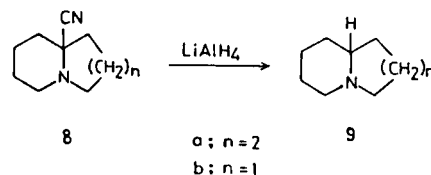
In the above reactions, it is also noteworthy that the reduction of the α -aminonitrile **2** with LAH gave the diamine **3** in contrast to the fact that the reduction of higher congeners such as 9a-cyano-1H-pyrrolizine (**8**) [5] and 8a-cyano-1H-pyrrolizine (**8b**) [6] with LAH only resulted in the formation of octahydro-2H-quinolizine (**9a**) and octahydroindolizine (δ -coniceine, **9b**) (see EXPERIMENTAL), respectively, with splitting of the cyano group (Scheme II).

Scheme I



quinolizine (**8a**) [5] and 8a-cyano-1H-pyrrolizine (**8b**) [6] with LAH only resulted in the formation of octahydro-2H-quinolizine (**9a**) and octahydroindolizine (δ -coniceine, **9b**) (see EXPERIMENTAL), respectively, with splitting of the cyano group (Scheme II).

Scheme II



Regarding the factor controlling the reaction process to bring about the transformation of the nitrile group into the corresponding aminomethyl functionality or the formal displacement of the nitrile group with a hydride, no rationalization has appeared, so far [5,7]. The results with

1-azabicycloalkane systems described above seem to permit the following considerations regarding to the mechanistic rationalization. The possibility is the participation of a "stereoelectronic control" in these reactions [8]. Thus, according to the theory of stereoelectronic control, the elimination of a leaving group [CN group possibly associated with LAH in above reductions (see Figure I)]; *i.e.*, cleavage of C-CN bond leading to the iminium ion **C** as a probable intermediate [9], is favored for conformations in which lone pair electrons lie antiperiplanar to the bond to the leaving group [see **A** in Figure I]. In fact, compounds **8a** and **8b** giving decyanated compounds **9a** [5] and **9b** require an antiperiplanar conformation regarding the cyano group and bridgehead nitrogen lone pair as the most energetically stable one, which was dictated by molecular mechanics calculations [10], though there is not so great an energy difference between the *cis/trans* ring junctions (see EXPERIMENTAL). On the other hand, 8-cyano-octahydro-1*H*-pyrrolizine (**2**) requiring *syn* orientation of the lone pair to C-CN bond should be predicted to be stereoelectronically unfavorable for the bond cleavage (see the dotted arrow in **B**). The result **2** → **3** is in accord with this interpretation [11].

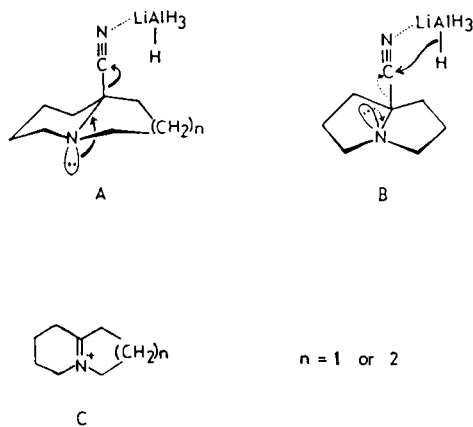


Figure I

In the above rationalization, it should be emphasized that the orientations of the nitrogen lone pair to the C-CN bond play an important part in the processes of these reductions [12]. Since it has been accepted that the additions of various nucleophiles to the iminium functionalities are under stereoelectronic control [14], the decyanation process discussed above would be regarded as an example for the retro-process of such additions.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded with a Hitachi-295 instrument. The ¹H-Nmr spectra were measured with

Hitachi-R-22 (90 MHz) and JEOL JNM-PMX60SI (60 MHz) spectrometers using tetramethylsilane as an internal standard. High resolution mass spectra were obtained with a JEOL JMS-DX300 instrument with a direct inlet system operating at 70 eV. Gas chromatographic (gc) analysis for the products in the reaction of 8a-cyano-octahydroindolizine with LAH was performed on a Yanako-G180 instrument, using a 1.5 m x 3 mm column (10% Themon-1000 + 3% KOH Chromosorb W80/100 AW DMCS) at 1.2 kg/cm² nitrogen flow pressure, and at 150° column temperature.

7a-Cyano-hexahydro-1*H*-pyrrolizine (**2**).

This compound, bp 93-94°/5 mm Hg, was prepared from the iminium perchlorate **1** by the method described previously [2a].

Reaction of 7a-Cyano-hexahydro-1*H*-pyrrolizine (**2**) with LAH. Preparation of 7a-aminomethylhexahydro-1*H*-pyrrolizine (**3**).

To a stirred suspension of LAH (6.37 g, 0.168 mole) in anhydrous ether (300 ml) was added dropwise 7a-cyano-hexahydro-1*H*-pyrrolizine (3.80 g, 0.028 mole) under ice cooling. After stirring for 14 hours at room temperature, aqueous sodium hydroxide (20%, 100 ml) was added portionwise to the reaction mixture. After separation of the ether layer, the aqueous layer was extracted twice with ether (100 ml). The combined ether layer was washed with saturated sodium chloride (100 ml), and then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave an oily material. Redistillation of this material gave a colorless oil **3** in 76% yield, 103-104°/30 mm Hg; ms: m/z 140 (M⁺); ir (liquid film): 3290, 3370 cm⁻¹ (NH₂); nmr (deuteriochloroform): 1.27 (2H, bs, NH₂, disappeared by the treatment with deuterium oxide), 2.52 (2H, bs, -CH₂-), 1.20-3.34 (12H, m, hexahydro-1*H*-pyrrolizine ring H). Dipicrate of this base had mp 216-218 dec (from methanol).

Anal. Calcd. for C₂₀H₂₂N₂O₄: C, 40.14; H, 3.76; N, 18.72. Found: C, 39.97; H, 3.66; N, 18.42.

Reduction of 8a-Cyano-octahydroindolizine (**8b**) [6] with LAH.

In the same manner described above, octahydroindolizine (**9b**) was the sole product, which was confirmed by gc analysis, from the reaction of **8b** (0.016 mole) with LAH (0.048 mole) in anhydrous ether. The product **9b** [15] was easily characterized as its picrate, mp 226-229° (lit [15a] mp 225-228°). The isolated yield was 88%. The reaction of 9a-cyano-octahydro-2*H*-quinolizine (**8a**) with LAH in anhydrous ether has already been reported by Leonard [5b].

8-(*N*-Benzoyl)aminomethylhexahydro-1*H*-pyrrolizine (**4**).

A mixture of 1 equivalent of 7a-aminomethylhexahydro-1*H*-pyrrolizine (**3**) and 1 equivalent of benzoyl chloride in benzene was stirred for 20 hours at room temperature. After evaporation of the solvent, the residue was recrystallized from 2-propanol-ether to afford compound **4** (88%) as its hydrochloride, mp 137.5-139°; ir (potassium bromide): 3245 (NH) and 1645 cm⁻¹ (C=O); nmr (deuteriochloroform): (as the free base) 3.92 (2H, d, J = 6.4 Hz, CH₂-NH-), 7.27-8.30 (5H, m, ArH), 8.88-9.38 (1H, t, J = 6.4 Hz, -NH-), 1.20-3.34 (12H, m, hexahydro-1*H*-pyrrolizine ring H).

Anal. Calcd. for C₁₅H₂₁ClN₂O: C, 64.16; H, 7.54; N, 9.98. Found: C, 64.18; H, 7.60; N, 9.82.

7a-Ethoxycarbonylhexahydro-1*H*-pyrrolizine (**5**).

According to the procedure mentioned previously, this compound **5** was obtained as a colorless oil, bp 80-81°/4 mm Hg, the spectroscopic data of which has already been noted [4].

Reaction of 7a-Ethoxycarbonylhexahydro-1*H*-pyrrolizine (**5**) with LAH. Preparation of 7a-Hydroxymethylhexahydro-1*H*-pyrrolizine (**6**).

To a suspension of LAH (3.15 g, 0.083 mole) in anhydrous ether (100 ml) was added 7a-ethoxycarbonylhexahydro-1*H*-pyrrolizine (**5**) (3.66 g, 0.02 mole) with stirring under ice cooling. After stirring for 14 hours at room temperature, 100 ml of aqueous sodium hydroxide (20%) was added carefully to the resulting mixture and then the ether layer was

separated. The aqueous layer was extracted with ether (100 ml x 2). The combined ether layer was washed with saturated aqueous sodium chloride (100 ml) and dried over anhydrous magnesium sulfate. After evaporation of the solvent, redistillation of the oily residue afforded a colorless oil **6** (75%), bp 76-77°/3 mm Hg; ms: *m/z* 141 (*M*⁺); ir (liquid film): 3150 cm⁻¹ (OH); nmr (deuteriochloroform): 3.30 (2H, s, -CH₂-), 3.66 (1H, bs, OH, disappeared by treatment with deuterium oxide), 1.20-3.34 (12H, m, hexahydro-1H-pyrrolizine ring H). The picrate of this base showed mp 249-253° dec (from ethanol).

Anal. Calcd. for C₁₄H₁₈N₂O₆: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.23; H, 4.94; N, 14.90.

7a-Benzoyloxyhexahydro-1H-pyrrolizine (7).

To a stirred solution of benzoyl chloride in benzene was added dropwise slowly an equivalent amount of 7a-hydroxymethylhexahydro-1H-pyrrolizine (**6**) at room temperature, and stirring was continued for 6-10 hours. After evaporation of the solvent, the residue was recrystallized from ethanol-ether to give the hydrochloride of the product **7** (90%), mp 148-153.5°; ir (potassium bromide): 1719 cm⁻¹ (C=O); nmr (deuteriochloroform): (as the free base) 4.65 (2H, s, -CH₂-OCO-) 7.13-8.28 (5H, m, ArH) and 1.20-3.34 (12H, m, hexahydro-1H-pyrrolizine ring H).

Anal. Calcd. for C₁₅H₂₀ClNO₂·H₂O: C, 61.95; H, 7.27; N, 4.82. Found: C, 62.01; H, 7.43; N, 5.36.

MM2 Energy Calculation [10].

MM2 energy calculations were carried out with the Suntory Computer Aided Drug-design System (ACADS) [16]. Preferred conformations for the compounds, **8a**, **8b** and **2** were found to have *trans*, *trans*, and *cis* ring junctions, respectively [for reference, see **A** or **D** represented in the Figure for the *trans* junction, and **B** or **E** for the *cis* junction]. Calculated antiperiplanar conformations (*trans* junction) for **8a** and **8b** were >2.66 kcal/mol⁻¹ more stable the corresponding conformations having *cis* ring junction and had strain energy of 19.06 and 14.91 kcal/mol⁻¹, respectively. Whereas, the antiperiplanar conformation for 7a-cyano-hydro-1H-pyrrolizine (**2**) was 3.36 kcal/mol⁻¹ less stable than the *syn* conformation having a *cis* ring junction which showed strain energy of 24.47 kcal/mol⁻¹.

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[11] As an additional speculation, it is feasible that the transition states, **D** and **E** as shown below, coordinating LAH could lead to the formation of **9** and **3** respectively.

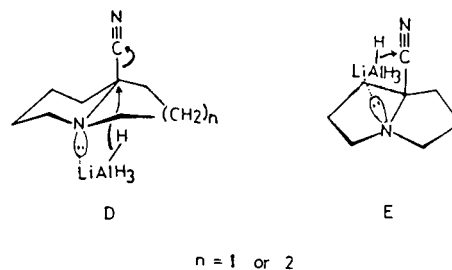
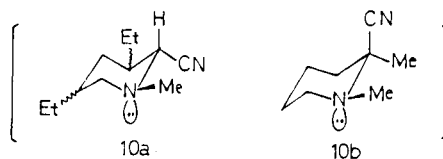
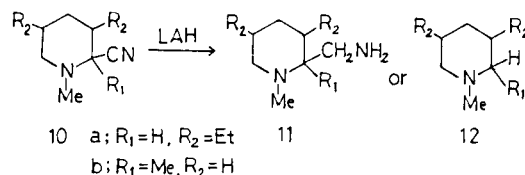


Figure II

[12] Since the result that the reduction of the CN group of the compound **2** is faster than its elimination also can be predictable on the basis of the extra strain in the iminium system **1** compared with larger rings **C**, one might propose that the stereoselective explanation would be redundant. The previous results of α -aminonitriles, **10a** - **11** and **10b** - **12**, by Leonard *et al.* [7], however, seem not to be explained with the ring strain. With our rationalization, the preferred conformations **10a** and **10b** predictable from lone pair stereochemistry of 1,2-disubstituted piperidines [13] would allow one to anticipate the products **11** and **12** respectively (Scheme III).

Scheme III



[13] See the following review: A. F. Casy, "PMR Spectroscopy in Medicinal and Biological Chemistry", Academic Press, London and New York, 1971, p 135.

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