# Application of 1,2,3,5,6,7-Hexahydropyrrolizinium Perchlorate in the Synthesis of 7a-Substituted Hexahydro-1*H*-pyrrolizines [1]



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The method for preparing 7a-substituted hexahydro-1*H*-pyrrolizines **2** from 1,2,3,5,6,7-hexahydropyrrolizinium perchlorate (**3**) was investigated, by which introduction of a wide variety of functionalities on C(7a) could be achieved easily.

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Although synthetic and biological attentions have recently been paid for a wide variety of heterocycles containing hexahydro-1*H*-pyrrolizine (so-called pyrrolizidine [2]) skeleton (**1**), few pharmacological studies have been reported for 7a-substituted hexahydro-1*H*-pyrrolizines [3] (8-substituted pyrrolizidines) **2** probably due to the difficulties involved in the synthesis for such compounds [3,4]. Aiming to establish the synthetic pathway of **2**, the derivatives of which are our target compounds for pharmacological evaluation [5], we carried out the chemical transformations of 1,2,3,5,6,7-hexahydropyrrolizinium perchlorate (**3**) [6] to introduce various functionalities into the C(7a) on the hexahydro-1*H*-pyrrolizine nucleus.

In this paper, we describe the reactions of the iminium perchlorate **3** with nucleophiles such as Grignard reagents and active methylene compounds [7], which provides the key to pharmacological evaluation of 7a-substituted hexahydro-1*H*-pyrrolizines.

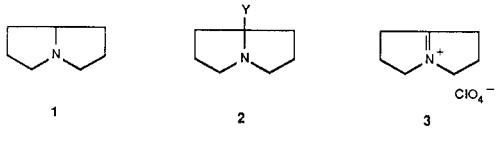
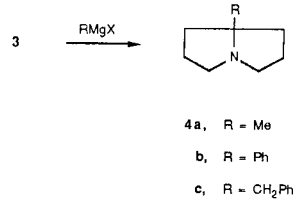



Figure 1

## Reactions With Grignard Reagents.

The reaction of the iminium perchlorate **3** with benzyl magnesium bromide as a nucleophile gave 7a-benzylhexahydro-1*H*-pyrrolizine (**4c**) in 83% yield. The reaction has been extended successfully to various Grignard reagents, which affords a simple method for the preparation of various 7a-alkyl or aryl substituted hexahydro-1*H*-pyrrolizines in moderate to good yields (Scheme 1). Three typical examples are listed in the Table. This procedure could be used as a convenient route to the otherwise unavailable 7a-substituted hexahydro-1*H*-pyrrolizines, for instance, 7a-phenylhexahydro-1*H*-pyrrolizine (**4b**). The structure of the products **4a-c** were easily confirmed by spectroscopic and elemental analysis (see EXPERIMENTAL and the Table).

Scheme 1




In the above results, of particular interest is that the reactivity of the perchlorate **3** toward phenylmagnesium bromide is different from that of the higher congener, 1,2,3,4,6,7,8,9-octahydroquinolizinium perchlorate (**5**). Thus, the failure of phenylmagnesium bromide to yield a 10-substituted product with **5** has been reported previously [8]. By molecular model examination, it is obvious that the nearly planar iminium ion **A**, apparently having a less steric hindrance rather than that of the 1,2,3,4,6,7,8,9-octahydroquinolizinium ion **B**, does not prevent access of the reagent to the reactive site (Figure 2).

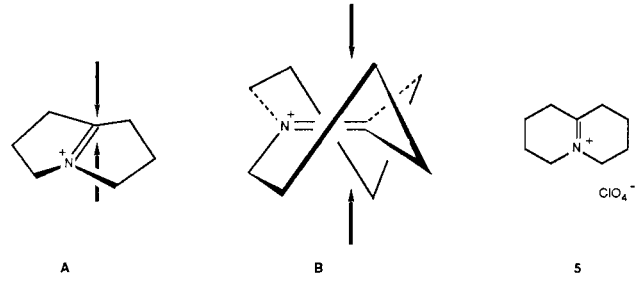



Figure 2

Furthermore, taking account of the ring cleavage of 1-azabicycloalkanes, the products also would be applicable as starting materials for the preparation of eight-

Table

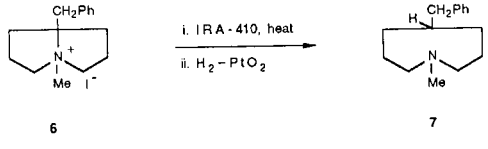
Synthesis of 7a-substituted (R)-Hexahydro-1*H*-pyrrolizines

| Compound | R | Yield, % (Starting Compound) | δ ppm (R) [a,b] |
|---|---|---|---|
| **4a** | Me | 48 (**3**) | 1.15 (3H, s, Me) |
| **4b** | Ph | 18 (**3**) | 7.05-7.55 (5H, m, ArH) |
| **4c** | $CH_2Ph$ | 83 (**3**) | 2.69 (2H, s, Ar-$CH_2$-), 7.15-7.22 (5H, m, ArH) |
| **10** [d] | $CH_2COOEt$ | 77 (**3**) | 1.24 (3H, t, 7.0 Hz, -$CH_3$), 2.43 (2H, s, -$CH_2$-CO-), 4.13 (2H, q, J = 7.0 Hz, -$OCH_2$-) |
| **12** | $CH_2CN$ | 65 (**11**) | 2.40 (2H, s, -$CH_2$-CN) |
| **13** [d] | $CH_2COOH$ | 66 (**11**) | 2.50 (2H, s, -$CH_2$CO-), 13.73 (1H, s, -COOH) [c] |
| **14** | $CH_2COOMe$ | 80 (**12**) | 2.44 (2H, s, -$CH_2$-CO-), 3.60 (3H, s, -COOMe) |
| **15** | $CH_2CH_2OH$ | 88 (**14**) | 1.70 (2H, t, J = 5.0 Hz, -$CH_2$), 3.79 (2H, t, J = 5.0 Hz, -$CH_2O$-), 7.15 (1H, br, -OH) [c] |
| **16** | $CH_2CH_2NH_2$ | 84 (**12**) | 1.58 (2H, t, J = 7.0 Hz, -$CH_2$-), 2.38 (2H, bs, -$NH_2$) [c], 2.70 (2H, t, J = 7.0 Hz, -$CH_2N$=) |

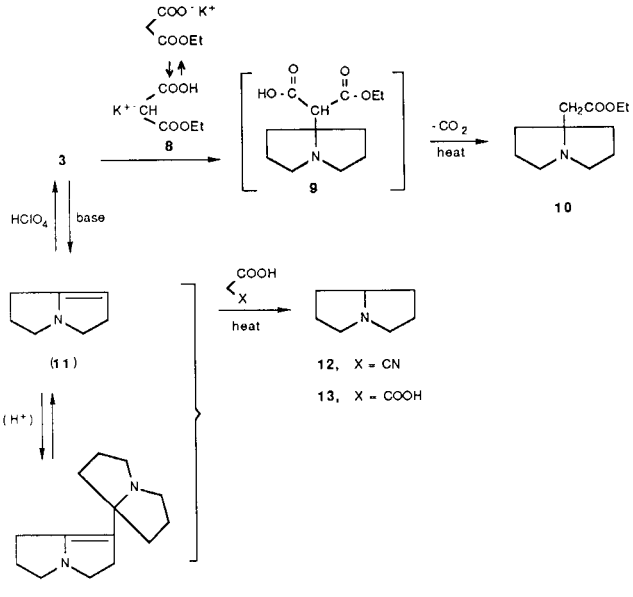
[a] Compounds were measured in deuteriochloroform. [b] Other aliphatic protons (12H) of the hexahydro-1*H*-pyrrolizine nucleus were observed δ 1.20-3.90 ppm as complicated multiplets. [c] Disappeared by treatment with deuterium oxide. [d] Taken from reference 5.

membered ring amines. For example, compound **4c** could be converted to the corresponding perhydroazocines **7** by C(7a)-N(4) bond cleavage of the corresponding quaternary ammonium salts such as **6** followed by catalytic hydrogenation [9] (Scheme 2).

Scheme 2




Scheme 3

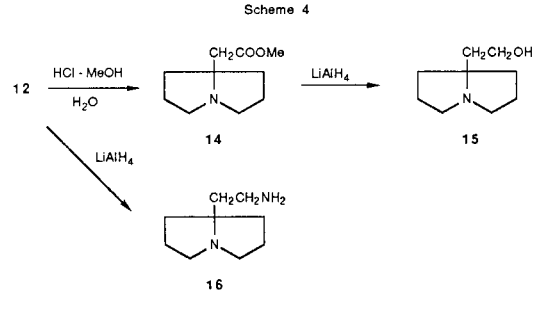



Reactions With Active Methylene Compounds.

The reaction of the iminium salt **3** with an equivalent molar amount of potassium ethyl malonate in dioxane under reflux gave 7a-ethoxycarbonylmethylhexahydro-1*H*-pyrrolizine (**10**) in 77% yield. A mechanistic rationalization of this reaction would involve a nucleophilic attack of a carbanion **8**, an equilibrium tautomeric anion of the ethyl malonate anion, to the electron deficient carbon of the iminium group giving rise to a labile intermediate **9**, which induces decarboxylation under the reaction conditions to give rise to the product **10** as shown in Scheme 3.

In view of the preparation of 7a-substituted hexahydro-1*H*-pyrrolizines **2**, the following reactions of the free enamine **11** [6] with active methylene compounds also gave satisfactory and reproducible results. Thus, the reactions of the free enamine **11** with cyanoacetic acid or malonic acid in THF or 1,4-dioxane under reflux gave 7a-cyanomethyl- (**12**) or 7a-carboxymethylhexahydro-1*H*-pyrrolizine (**13**) in good yields, respectively (Scheme 3). Similar reactivities of the 1,2,3,4,6,7,8,9-octahydroquinolizinium salt toward active methylene compounds are reported previously [10]. In terms of a synthetic methodology for 7a-substituted hexahydro-1*H*-pyrrolizines, it should

Scheme 4



be emphasized that the products **10**, **12** and **13** can be best made for use as synthetic intermediates. For example, the cyanomethyl group of compound **12** could be convertible to the other functionalities, *i.e.*, the methoxycarbonylmethyl **14** , the hydroxyethyl **15**, and the aminoethyl groups **16**, as shown in Scheme 4.

It is apparent that the reactions described in this paper, together with the results reported recently [11], provided a new strategy starting with the iminium salt **3** or the corresponding enamine, for the synthesis of various 7a-substituted hexahydro-1*H*-pyrrolizines, represented by the general formula **2**. Further chemical transformations of the 7a-substituents reported here are feasible, so that various 7a-substituted hexahydro-1*H*-pyrrolizines are in hand. The pharmacological evaluations will be discussed elsewhere in detail [5].

## EXPERIMENTAL

Melting points are uncorrected and determined on a Yanako micro melting point apparatus. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer. The ir spectra were recorded on a Hitachi 260-10 or a Hitachi EPI-G-3 instrument, and the $^1$H-nmr spectra were obtained with a Hitachi R-22, JEOL JNM-PMX60SI, or JEOL FX100 spectrometer using TMS as an internal standard. High-resolution mass spectra were obtained with a JEOL JMS-DX300 instrument.

1,2,3,5,6,7-Hexahydropyrrolizinium Perchlorate (**3**).

This compound was prepared by the procedure described previously [6a] in 76% yield as colourless flakes, mp 243° dec (from ethanol). Though the product recrystallized from ethanol showed slightly higher mp than that from acetone [mp 233° dec] [6a], both spectroscopic data were identical.

*Anal.* Calcd. for $C_7H_{12}ClNO_4$: C, 40.10; H, 5.77; N, 6.68. Found: C, 39.83; H, 5.80; N, 6.58.

Reaction of 1,2,3,5,6,7-Hexahydropyrrolizinium Perchlorate (**3**) with Grignard Reagents.

After the addition of the iminium perchlorate **3** (0.024-0.035 mole) to a solution of a Grignard reagent (0.090-0.165 mole) in ether or tetrahydrofuran (THF), the resulting mixture was stirred and heated under reflux for 15-20 hours. After addition of aqueous sodium hydroxide (20%, 50-100 ml) and ether (*ca.* 200 ml), the organic layer was separated by centrifugation. The organic layer was washed with saturated aqueous sodium chloride (30 ml), and then dried over anhydrous magnesium sulfate. After evaporation of the solvent, distillation of the residual oil gave a pure product. The yield and $^1$H-nmr data of the products are summarized in the Table. Other physical results and elemental analyses (as the picrate) are shown below.

7a-Methylhexahydro-1*H*-pyrrolizine (**4a**).

The reaction of **3** with methylmagnesium bromide in THF afforded a colourless oil **4a**, bp 89°/105 mm Hg; ms: m/z 125 ($M^+$). The picrate of this base melted at 285° dec (from ethanol) lit [3b] mp 281° dec.

*Anal.* Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.77. Found: C, 47.44; H, 5.20; N, 15.77.

7a-Phenylhexahydro-1*H*-pyrrolizine (**4b**).

The reaction of **3** with phenylmagnesium bromide in THF afforded a colourless oil **4b**, bp 142-144°/20 mm Hg; ms: m/z 187 ($M^+$). The picrate of this base had mp 168-169° (from ethanol).

*Anal.* Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.86; N, 13.46. Found: C, 54.66; H, 4.86; N, 13.19.

7a-Benzylhexahydro-1*H*-pyrrolizine (**4c**).

The reaction of **3** with benzylmagnesium bromide in ether gave a colourless oil, bp 171°/43 mm Hg; ms: m/z 201 ($M^+$). The picrate of this base had mp 171-172° (from ethanol).

*Anal.* Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.51; N, 13.02. Found: C, 55.95; H, 5.25; N, 12.90.

Reaction of the Perchlorate **3** with Potassium Ethyl Malonate.

This reaction has already been mentioned in our previous report [5]. The product **10** obtained by distillation was a colourless oil, bp 122°/17 mm Hg. The $^1$H-nmr spectrum is recorded in the Table. The picrate of this base melted at 96-97° (from ethanol).

*Anal.* Calcd. for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.14. Found: C, 47.78; H, 5.32; N, 13.08.

Preparation of 7a-Cyanomethylhexahydro-1*H*-pyrrolizine (**12**).

To a solution of 2,3,5,6-tetrahydro-1*H*-pyrrolizine (**11**) including its dimer [12] (boiling fraction between 110-180°), which was prepared by the cyclization procedure, (4.25 g, 0.039 mole) in THF (50 ml) was added cyanoacetic acid (5.53 g, 0.065 mole) at room temperature. The resulting solution was refluxed for 7 hours. After evaporation of the solvent, the residue was subjected to a distillation to give 7a-cyanomethylhexahydro-1*H*-pyrrolizine (**12**) as a colourless oil, bp 143-144°/32 mm Hg; ir (liquid film): 2242 $cm^{-1}$ (CN); ms: m/z 150.1157 ($M^+$, $C_9H_{14}N_2$). The yield and the $^1$H-nmr spectrum are listed in the Table. The picrate of this base had mp 227-231° (from ethanol).

*Anal.* Calcd. for $C_{15}H_{17}N_5O_7$: C, 47.49; H, 4.52; N, 18.46. Found: C, 47.43; H, 4.56; N, 18.56.

Preparation of 7a-Carboxymethylhexahydro-1*H*-pyrrolizine (**13**).

The procedure for this compound has been mentioned in our previous report [5]. The product **13** was obtained as needles, the picrate of which melted at 159° (from ethanol).

*Anal.* Calcd. for $C_{21}H_{24}N_8O_4$: C, 41.18; H, 3.95; N, 18.30. Found: C, 41.01; H, 3.95; N, 18.13.

Preparation of 7a-Methoxycarbonylmethylhexahydro-1*H*-pyrrolizine (**14**).

To a mixture of 52 ml of saturated hydrogen chloride in methanol and water (0.60 g, 0.033 mole) was added the compound **12** (4.96 g, 0.033 mole) under ice cooling. The resulting solution was kept at room temperature with stirring for 1 hour and then refluxed for 7 hours. After cooling, the precipitated materials were removed by filtration. After concentration of the filtrate, 20% of aqueous sodium hydroxide (18 ml) was added to the residual oil with stirring. The resulting mixture was extracted with chloroform (30 ml X 3) and then the chloroform layer was washed with saturated sodium chloride (50 ml). After being dried over anhydrous magnesium sulfate, evaporation of the solvent gave an oil. Distillation of this material afforded the product (**14**) as a colourless oil, bp 92-93°/7 mm Hg; ir (liquid film): 1750 $cm^{-1}$ (ester C=O); ms: m/z 183.12553 ($M^+$, $C_{10}H_{17}NO_2$). The yield and $^1$H-nmr data are listed in the Table. The picrate of **14** had mp 139-139.5° (from methanol).

*Anal.* Calcd. for $C_{16}H_{20}N_4O_9$: C, 46.60; H, 4.89; N, 13.59. Found: C, 46.56; H, 5.08; N, 13.34.

Preparation of 7a-(2-Hydroxyethyl)hexahydro-1*H*-pyrrolizine (**15**).

To a suspension of LAH (1.97 g, 0.052 mole) in anhydrous ether (100 ml) was added the compound **14** (2.38 g, 0.013 mole) under ice cooling. After being stirred for 14 hours, to the reaction mixture was added 20% aqueous sodium hydroxide (100 ml) portionwise, and the ether layer was separated. The aqueous layer was further extracted twice with ether (100 ml). The combined ether layer was washed with saturated sodium chloride (50 ml) and dried over anhydrous magnesium sulfate. After evaporation of the solvent, distillation of the oily residue gave the product **15** as a colourless oil, bp 93.5-94.5°/5 mm Hg; ms: m/z 155.12904 ($M^+$, $C_9H_{17}NO$). The yield and $^1$H-nmr data are listed in the Table. The picrate of **15** had mp 246-251° (from ethanol).

*Anal.* Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.52; N, 14.58. Found: C, 46.67; H, 5.39; N, 14.52.

Preparation of 7a-(2-Aminoethyl)hexahydro-1*H*-pyrrolizine (**16**).

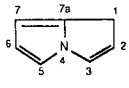
By using a procedure similar to that for **15** as described above, compound **16** was obtained as a colourless oil from the cyanomethyl derivative **12** (6.60 g, 0.044 mole) and LAH (5.05 g, 0.133 mole). The product **16** had bp 87-88°C/6 mm Hg; ir (liquid film) 3290, 3350 $cm^{-1}$ ($NH_2$); ms: m/z 154.14743 ($M^+$, $C_9H_{18}N_2$). The yield and $^1$H-nmr data are listed in the Table. The dipicrate of the base (**16**) had mp 216-217° (from methanol).

*Anal.* Calcd. for $C_{21}H_{24}N_8O_{14}$: C, 41.18; H, 3.95; N, 18.30. Found: C, 41.01; H, 3.95; N, 18.13.

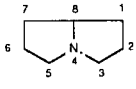
## REFERENCES AND NOTES

[1] Part **12** in the series of studies on pyrrolizidines and related compounds. For part **11**, S. Miyano, K. Shima, M. Hayashimastu, F. Satoh and K. Sumoto, *J. Pharm. Sci.*, (1986), submitted.

[2] The name of **1** according to Chemical Abstracts practice is hexahydro-1*H*-pyrrolizine derived from 1*H*-pyrrolizine as shown below. The use of the trivial name; pyrrolizidine, however, is commonly preferred for relatively simple derivatives of **1**.



1 H-pyrrolizine



pyrrolizidine

[3a] N. J. Leonard and G. L. Shoemaker, *J. Am. Chem. Soc.*, **71**, 1762 (1949); [b] N. J. Leonard and K. M. Beck, *J. Am. Chem. Soc.*, **70**, 2504 (1948); [c] F. Šorm and J. Beránek, *Chem. Listy*, **47**, 1359 (1953), and related references cited therein.

[4] For example, see the following reviews: [a] N. J. Leonard, *Alkaloids*, **5**, 35 (1960); [b] N. K. Kochetkov and A. M. Likhosherstov, *Adv. Heterocyclic Chem.*, **5**, 315 (1965); [c] D. J. Robins, *Adv. Heterocyclic Chem.*, **24**, 247 (1979).

[5] For example, S. Miyano, K. Sumoto, F. Satoh, K. Shima, M. Hayashimastu, M. Morita, K. Aisaka and T. Noguchi, *J. Med. Chem.*, **28**, 714 (1985).

[6a] S. Miyano, T. Somehara, M. Nakao and K. Sumoto, *Synthesis*, 701 (1978); [b] K. Sumoto, S. Fujii, O. Yamashita, T. Somehara and S. Miyano, *J. Heterocyclic Chem.*, **19**, 413 (1981), and related references cited therein.

[7] Preliminary communication, S. Miyano, O. Yamashita, S. Fujii, T. Somehara, K. Sumoto, F. Satoh and T. Masuda, *Heterocycles*, **16**, 755 (1981).

[8] N. J. Leonard and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).

[9] S. Miyano, N. Mibu, S. Fujii, N. Abe and K. Sumoto, *J. Chem. Soc., Perkin Trans. 1*, 2611 (1985).

[10] N. Kumagaya, K. Suzuki and M. Sekiya, *Chem. Pharm. Bull.*, **21**, 1601 (1973).

[11] S. Miyano, O. Yamashita, K. Sumoto, K. Shima, M. Hayashimatsu and F. Satoh, *J. Heterocyclic Chem.*, 1986, in press.

[12] The crude material can be used for this purpose with no particular problem. Since the dimer of the enamine also gave the same product **12**, approximately in an equal yield, it is obvious that the dimer reverts to the monomeric form under the acidic reaction condition (see reference [6]).