Studies on Pyrrolizidines and Related Compounds. Part 8.[1] A New Route to Perhydroazocines and Related Compounds using 1,2,3,5,6,7-Hexahydropyrrolizinylium Perchlorate

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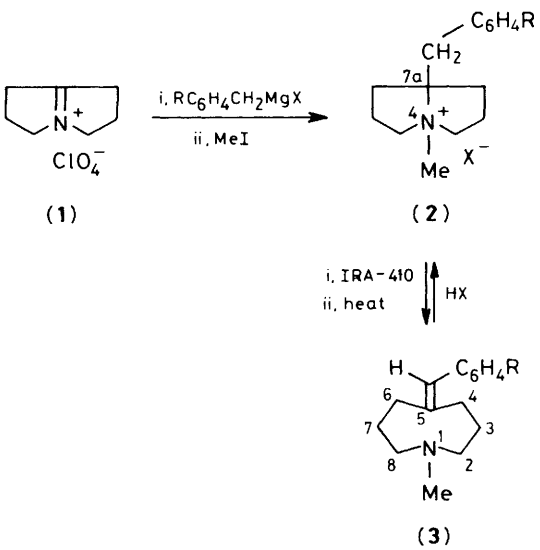
A new method for the synthesis of 5-substituted perhydroazocines and related compounds is described. The method consists of the C(7a)–N(4) bond cleavage of quaternary ammonium salts of 7a-substituted hexahydropyrrolizines which are easily prepared from 1,2,3,5,6,7-hexahydropyrrolizinylium perchlorate.

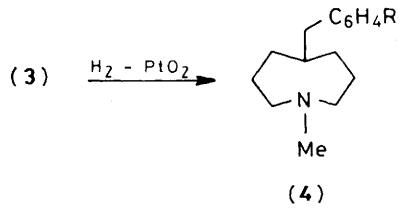
1,2,3,5,6,7-Hexahydropyrrolizinylium perchlorate (**1**),[2] an iminium salt with good shelf stability and ready availability, is a useful intermediate for the preparation of 7a-substituted pyrrolizidines and related compounds.[3] Here we report a new alternative to perhydroazocine derivatives starting from the iminium perchlorate (**1**). The products synthesized by this procedure are unavailable by known routes.[4]

The quaternary ammonium salts (**2**), which are the key intermediates in the procedure, were readily synthesized by the reaction of the iminium perchlorate (**1**) with substituted benzylmagnesium halides followed by treatment with methyl iodide in methanol (Table and general procedure). The compounds (**2**) obtained above were transformed into perhydroazocine derivatives (**3**) by simply heating a methanolic solution of (**2**) prepared by passage through a column of ion exchange resin ($^-$OH form). The structures of (**3**) could be easily confirmed by their spectroscopic data. In the n.m.r. spectra, a characteristic sharp singlet appeared at δ_H 6.14—6.47 which was assignable to a vinyl proton in the structure (**3**). The yields and spectroscopic



Scheme 1.

results of the products (**3**) are summarized in the Table. That these structures had an expected transannular interaction between their amino and alkene functionalities was established by treatment of (**3**) with an acid such as HCl to give the corresponding starting quaternary ammonium salt (**2**)[5] (see Experimental section). The products (**3**) listed in the Table are also convertible into the corresponding perhydroazocine derivatives (**4**). Thus, for instance, catalytic hydrogenation of (**3a**) using platinum oxide in glacial acetic acid at atmospheric pressure gave 5-benzyl-1-methylperhydroazocine (**4a**). The catalytic hydrogenation of compound (**3d**) also gave compound (**4d**).



Scheme 2.

In contrast to the difficulties involved in the conventional synthesis of perhydroazocine analogues,[4] our procedure using 1,2,3,5,6,7-hexahydropyrrolizinylium perchlorate (**1**) provides a new method for the preparation of 5-substituted perhydroazocines and its analogues.

Experimental

Melting points are uncorrected. I.r. spectra were recorded with a Hitachi-295 instrument. N.m.r. spectra were measured with Hitachi R-22 and JEOL JNM-PMX60SI 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.

1,2,3,5,6,7-*Hexahydropyrrolizinylium Perchlorate* (**1**).—This compound was prepared by the method described previously[2] in 65% yield as colourless flakes, m.p. 243 °C (decomp.) (from ethanol).

*General Procedure for 7a-Benzyl-4-Methylhexahydro-*1H*-pyrrolizinium Iodides* (**2**).—*Method A.* After the addition of 1,2,3,5,6,7-hexahydropyrrolizinylium perchlorate (**1**) (4.19 g, 0.02 mol) to an ethereal solution of a substituted benzylmagnesium halide,[6] (1M; 80—100 ml), the resulting mixture was stirred and kept at room temperature for 2—4 h. After addition of aqueous NaOH (20%; 50—70 ml), the ether layer was separated by centrifugation. The ether layer was washed with saturated aqueous NaCl (30 ml), and then extracted with aqueous HCl (10%; 70 ml). The extracted acidic aqueous layer

Table. Synthesis of 4-methyl-7a-(substituted benzyl)hexahydro-1*H*-pyrrolizinium iodides (**2**) and 1-methyl-5-(substituted benzylidene)perhydroazocines (**3**)

Compd.	R	Method (Yield%)	δ_H [a,b]
(**2a**)	H	A(59)	3.10 (2 H, s, PhCH_2), 3.16 (3 H, s, N ± Me), and 7.34 (5 H, br s, ArH)
(**2b**)	*o*-Cl	A(46)	3.44 (2 H, s, ArCH_2), 3.45 (3 H, s, N ± Me), and 7.3—7.7 (4 H, m, ArH)
(**2c**)	*m*-Cl	A(82)	3.14 (2 H, s, ArCH_2), 3.17 (3 H, s, N ± Me), and 7.3—7.5 (4 H, m, ArH)
(**2d**)	*p*-Cl	A(73)	3.35 (2 H, s, ArCH_2), 3.42 (3 H, s, N ± Me), and 7.3—7.6 (4 H, m, ArH)
(**2e**)	*p*-Me	A(81)	2.27 (3 H, s, Me), 3.03 (2 H, s, ArCH_2), 3.15 (3 H, s, N ± Me), and 7.16 (4 H, br s, ArH)
(**3a**)	H	B(84)	2.28 (3 H, s, Me), 6.20 (1 H, s, =C=CH), and 7.16 (5 H, br s, ArH)
(**3b**)	*o*-Cl	B(69)	2.33 (3 H, s, Me), 6.47 (1 H, s, =C=CH), and 6.9—7.4 (4 H, m, ArH)
(**3c**)	*m*-Cl	B(94)	2.32 (3 H, s, Me), 6.14 (1 H, s, =C=CH), and 7.0—7.3 (4 H, m, ArH)
(**3d**)	*p*-Cl	B(86)	2.33 (3 H, s, Me), 6.17 (1 H, s, =C=CH), and 7.0—7.4 (4 H, m, ArH)
(**3e**)	*p*-Me	B(80)	2.33 (6 H, s, 2 × Me), 6.23 (1 H, s, =C=CH), and 7.10 (4 H, br s, ArH)

[a] Compounds (**2a**), (**2c**), and (**2d**) were measured in $(CD_3)_2SO$; (**2b**) and (**2d**) in $(CD_3)_2NCDO$, and (**3a**—**e**) in $CDCl_3$. [b] Other aliphatic protons (12H) of (**2a**—**e**) and of (**3a**—**e**) were observed at δ_H 1.5—4.3 and 1.5—2.8 as complicated multiplets, respectively.

was basified by the addition of aqueous NaOH (20%; 40—50 ml) with ice-cooling, and the resulting solution was extracted with ether (90 ml). The ether layer was washed with saturated aqueous NaCl (2 × 20 ml) and dried ($MgSO_4$). After evaporation of the solvent, the residual oil was dissolved in hexane (20 ml) and insoluble precipitates were filtered off. Evaporation of the solvent gave a pale yellow oil.* To a solution of this material in methanol (10—20 ml) was added dropwise a two- to three-fold excess of MeI. The precipitated crystals were filtered off with cooling. Recrystallization from methanol or ethanol gave 8-benzyl-4-methylhexahydro-1*H*-pyrrolizinium iodides (**2**). The yields and n.m.r. data of the products are summarized in the Table. M.p.s. and elemental analysis are shown below.

7a-*Benzyl*-4-*methylhexahydro*-1H-*pyrrolizinium iodide* (**2a**). This had m.p. > 300 °C (from methanol) (Found: C, 52.2; H, 6.75; N, 3.8. $C_{15}H_{22}IN$ requires C, 52.48; H, 6.46; N, 4.08%).

7a-(o-*Chlorobenzyl*)-4-*methylhexahydro*-1H-*pyrrolizinium iodide* (**2b**). This had m.p. 299—300 °C (from methanol) (Found: C, 47.8; H, 5.55; N, 3.75. $C_{15}H_{21}ClIN$ requires C, 47.70; H, 5.60; N, 3.71%).

7a-(m-*Chlorobenzyl*)-4-*methylhexahydro*-1H-*pyrrolizinium iodide* (**2c**). This had m.p. 257—261 °C (from ethanol) (Found: C, 47.5; H, 5.85; N, 3.6. $C_{15}H_{21}ClIN$ requires C, 47.70; H, 5.60; N, 3.71%).

7a-(p-*Chlorobenzyl*)-4-*methylhexahydro*-1H-*pyrrolizinium iodide* (**2d**). This had m.p. 258—262 °C (from ethanol) (Found: C, 47.8; H, 5.5; N, 3.8. $C_{15}H_{21}ClIN$ requires C, 47.70; H, 5.60; N, 3.71%).

4-*Methyl*-7a-(p-*tolyl*)*hexahydro*-1H-*pyrrolizinium iodide* (**2e**). This had m.p. 226—227 °C (from ethanol) (Found: C, 53.85; H, 6.85; N, 3.95. $C_{16}H_{24}IN$ requires C, 53.78; H, 6.77; N, 3.92%).

General Procedure for 5-*Benzylidene*-1-*methylperhydroazocines* (**3**).—*Method B.* Compound (**2**) was dissolved in methanol (*ca.* 200—800 ml) and passed through a column of ion-exchange resin [Amberlite IRA-410 ($^-$OH form)]. After evaporation of methanol under reduced pressure, ethanol (20—50 ml) was added to the residue and the resulting solution was refluxed for 2—5 h. After evaporation of the solvent, ether (20—40 ml) was added to the residue, and the insoluble materials which separated were filtered off. Evaporation of the ether gave compound (**3**). The yields and n.m.r. data of (**3**) are summarized in the Table. Other spectroscopic results are shown below.

5-*Benzylidene*-1-*methylperhydroazocine* (**3a**). This had $\nu_{max.}$ (Nujol) 1 630 cm^{-1} (C=C) (Found: M^+, 215.1682. $C_{15}H_{21}N$ requires M, 215.1 674)

5-(o-*Chlorobenzylidene*)-1-*methylperhydroazocine* (**3b**). This had $\nu_{max.}$ (Nujol) 1 640 cm^{-1} (C=C) Found: M^+, 249.1290. $C_{15}H_{20}ClN$ requires M, 249,1284).

5-(m-*Chlorobenzylidene*)-1-*methylperhydroazocine* (**3c**). This had $\nu_{max.}$ (Nujol) 1 630 cm^{-1} (C=C) (Found: M^+, 249.1275. $C_{15}H_{20}ClN$ requires M, 249.1284).

5-(p-*Chlorobenzylidene*)-1-*methylperhydroazocine* (**3d**). This had $\nu_{max.}$ (Nujol) 1 630 cm^{-1} (C=C) (Found: M^+, 249.1275. $C_{15}H_{20}ClN$ requires M, 249.1284).

1-*Methyl*-5-(p-*methylbenzylidene*)*perhydroazocine* (**3e**). This had $\nu_{max.}$ (Nujol) 1 635 cm^{-1} (C=C) (Found: M^+, 229.1817. $C_{16}H_{23}N$ requires M, 229.1830).

Catalytic Hydrogenation;[7] *Preparation of* 1-*Methyl*-5-(*substituted benzyl*)*perhydroazocines* (**4**).—5-*Benzyl*-1-*methylperhydroazocine* (**4a**). A mixture of (**3a**) (1.45 g, 6.74 mmol), glacial acetic acid (50 ml), and platinic oxide (0.5 g) was shaken for 40 min at atmospheric pressure under hydrogen. After separation of the catalyst by decantation, the acid solution was basified with 40% aqueous NaOH and extracted with ether (150 ml). The combined extract was dried ($MgSO_4$) and then evaporated under reduced pressure to give 5-benzyl-1-methylperhydroazocine (**4a**) (0.71 g, 48.5%) as a colourless oil, *m/z* 217.1832 (M^+, $C_{15}H_{23}N$); δ_H($CDCl_3$) 1.0—2.3 (11 H, m, aliphatic H), 2.28 (3 H, s, =NMe), 2.2—2.6 (4 H, m, CH_2NCH_2), and 7.10 (5 H, br s, ArH). An analysis was carried out on the corresponding picrate; m.p. 117—118 °C (from methanol) (Found: C, 56.4; H, 6.0; N, 12.6. $C_{21}H_{26}N_4O_7$ requires C, 56.50; H, 5.87; N, 12.55).

1-*Methyl*-5-(p-*tolyl*)*perhydroazocine* (**4e**). In a similar fashion to that described above, (**4e**) (89%) was obtained, *m/z* 231.1993 (M^+, $C_{16}H_{25}N$); δ_H ($CDCl_3$) 1.1—1.9 (9 H, m, aliphatic H), 2.28 (6 H, br s,=NMe and ArMe), 2.3—2.6 (6 H, m, CH_2NCH_2 and ArCH_2) and 6.97 (4 H, br s, ArH). The m.p. of this picrate was 84—88 °C (from methanol–Et_2O) (Found: C, 57.4; H, 6.1; N, 12.35. $C_{22}H_{28}N_4O_7$ requires C, 57.38; H, 6.13; N, 12.17).

5-(p-*Chlorobenzyl*)-1-*methylperhydroazocine* (**4d**). A mixture of (**3d**) (2.05 g, 8.23 mmol) in ethanol (15 ml) was shaken for 8 h under hydrogen at a pressure of 78 kg cm^{-2} in the presence of platinum oxide (0.21 g). After filtration, the filtrate was concentrated to dryness to afford (**4d**) (1.96 g, 95%), *m/z* 251.1425 (M^+, $C_{15}H_{22}ClN$); δ_H ($CDCl_3$) 1.1—2.2 (9 H, m), 2.28 (3 H, s, =NMe), 2.3—2.7 (6 H, m, CH_2NCH_2 and ArCH_2), and 6.9—7.3 (4 H, m, ArH). The picrate of this base melted at 113.5—

* Free base of 7a-substituted hexahydro-1H-pyrrolizines the structures of which are easily confirmed by spectroscopic methods (i.r., mass, and n.m.r.) were submitted to subsequent preparative runs without further purification.

114.5 °C (from ethanol) (Found: C 52.5; H, 5.25; N, 11.75. $C_{21}H_{25}ClN_4O_7$ requires C, 52.45; H, 5.24; N, 11.65).

Reaction of (**3c**) *with Hydrochloric Acid.*—A large excess of hydrogen chloride was added to a solution of (**3c**) (1.64 g, 6.57 mmol) in methanol (30 ml) and the resulting mixture was evaporated under reduced pressure to give an oily material. Dry benzene (10—15 ml) was added to this oil and the resulting solution was subjected to an azeotropic distillation to remove water. The solid residue (1.52 g) was recrystallized from acetone–methanol to give the hygroscopic quaternary ammonium salt (**2**; R = *m*-Cl, X = Cl)(36%), m.p. 231—233 °C; δ_H [$(CD_3)_2NCOD + D_2O$] 1.75—2.65 (8 H, m, aliphatic H), 3.30 (2 H, s, $ArCH_2$), 3.38 (3 H, s, ≡N ± Me), 3.6—4.2 (4 H, m, CH_2NCH_2), and 7.35—7.55 (4 H, m, ArH) (Found: C, 58.9; H, 7.85; N, 4.35. $C_{15}H_{12}ClN{\cdot}H_2O$ requires C, 59.21; H, 7.62; N, 4.60).

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Received 22*nd March* 1985; *Paper* 5/473