SYNTHESIS AND NMR STUDY OF MANNICH BASES OF 8-ACETOXY-INDOLIZINES

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Abstract - Crystallized hydrochlorides of some unstable Mannich bases derived from 8-acetoxyindolizine (1) and 3-acetyl-8-acetoxyindolizine (3) have been prepared by condensation of iminium salts on these substrates. The nmr study of the free bases and their hydrochlorides shows the selectivity of the reaction which introduces the aminomethyl side chain at positions 3 in 1 and 1 in 3. The disappearance of the strong deshielding observed for H-5, in the 3-acetyl series, when one passes from the free base to the corresponding hydrochloride is discussed in terms of restricted rotation and dipolar interactions.

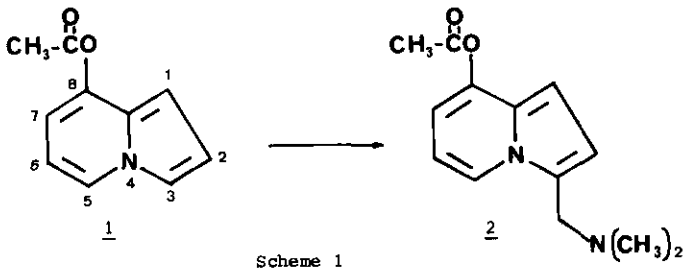
In preceeding papers[1,2,3], we have developped the synthesis and reactivity of 8-acetoxyindolizine (1) which can be considered as the precursor of 8-hydroxyindolizine, an unstable new phenol. Alkylation of this compound was not yet described. This report concerns the preparation and the nmr study of Mannich bases of this heterocyclic compound.

Since direct alkylation of indolizine leads to a mixture of 1- and 3-alkylindolizines[4] the synthesis of alkylindolizines has been generally achieved by cyclization reactions performed on suitably substituted pyridines derivatives[5]. For instance, the most convenient preparation of substituted indolizines is that of Tschitschibabin which consists in base treatment of the adduct of 2-picoline and an α-halogeno-ketone.[6]

By contrast, introduction of an amino-methyl side-chain by the Mannich reaction has been currently used in indolizine chemistry especially by Harrel and Doerge[7] who prepared potential CNS depressants from 2-phenylindolizines and miscellaneous secondary amines. Further transformation of indolizine Mannich bases has also been used in the preparation of functionnalized indolizine derivatives as is exemplified by synthesis of substituted indolizinylalanine[8] or acetic acid[9].

In order to get the Mannich base of 8-acetoxyindolizine, we first used the procedure described by Mannich.[10] By action of aqueous formaldehyde and dimethylamine on 8-acetoxyindolizine in dioxan

solution at room temperature (Scheme 1) we obtained 3-dimethylaminomethyl-8-acetoxyindolizine (2) as a crude oil, which was difficult to purify, owing to its instability.



Scheme 1

This crude product has been characterized by its nmr spectrum which is identical to that described in Table 2 for this free base prepared according to a different way (vide infra). By comparison with the spectrum of 8-acetoxyindolizine[1] we observe the disappearance of H-3 signal at 7.14-7.31 ppm and a slight deshielding of H-5 at 8 ppm (instead of 7.76 ppm in 1).

This result shows that substitution on indolizine nucleus took place exclusively at 3-position, which is known to be the most reactive towards electrophiles in accordance with electronic density calculations.[11]

In order to obtain product easier to handle we applied a method which has been employed in the synthesis of unstable Mannich bases using the Eschenmoser salt.[12] This reaction leads to the hydrochloride of the Mannich bases, which are generally more stable than the free bases.

The methylene iminium salt chemistry was developped by Böhme some years ago[13e] and has succesfully been applied to aminoalkylation of carbanions (Mannich reaction), electron-rich π-systems (enol ethers, enamines, ynamines) and reactive arenes and hetarenes (e.g. phenols or furans).[13]

8-Acetoxyindolizine (1) and 8-acetoxy-3-acetylindolizine (3) were allowed to react with the three following iminium hydrochlorides (Scheme 2, Table 1).

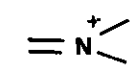
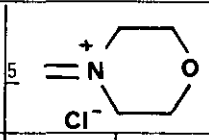
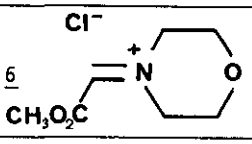
Generally the reaction was carried out in aprotic medium by addition of an equimolecular amount of the iminium salt to a solution of the indolizines 1 or 3 in acetonitrile at room temperature followed in some cases by a gentle heating. After a variable time, the hydrochloride of the Mannich base precipitated on standing at room temperature or by freezing the resulting mixture at 0°C.

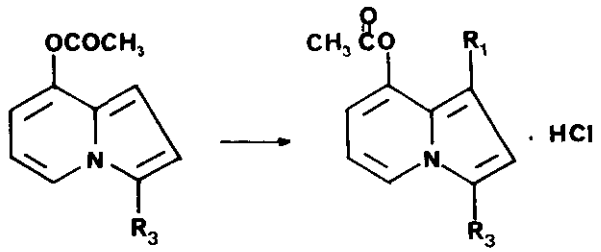
Table 1 indicates the modifications to the general procedure that have been introduced dependent on the different reactivity of iminium salts towards the two indolizines studied.

The hydrochlorides of the resulting Mannich bases have been obtained in good yields as crystallized products. Attempts to isolate the corresponding free bases have been successful only in two cases, the free base 13 isolated as a solid was stable ; but the free base 2 isolated as an oil appeared to be itself very unstable, owing to its tendency to polymerize. This polymerization proceeded very rapidly in the case of all other free bases and occurred during evaporation of the solvent.

Table 1

Reaction of iminium salts with 8-acetoxyindolizine and 8-acetoxy-3-acetylindolizine

Iminium salts	4 		5 		6 
Indolizine	8-acetoxy	3-acetyl 8-acetoxy	8-acetoxy	3-acetyl 8-acetoxy	3-acetyl 8-acetoxy
Time and temperature	6 hr 20°C	1 hr 80°C	10 min 20°C	10min,60°C 12hr, 20°C	10 min 20°C
Isolated hydrochloride and yield %	7 100	8 82	9 69	10 100	11 100
Free base: obtainment in solution	2 neutralization of hydrochloride dispersed in CH_2Cl_2 by solid $NaHCO_3$	12 addition of $NaHCO_3$ to aqueous solution followed by chloroformic extraction	13 same procedure as for 2	14 same procedure as for 12	15 direct chloroformic extraction from aqueous solution
Isolation of the free base	unstable oil	no stable	m.p.:109°C Yield 94%	no isolable	no isolable



1 R_3 = H

3 R_3 = $COCH_3$

R_1 = H

R_3 = $COCH_3$

7 R_3 = $-CH_2N(CH_3)_2$

9 R_3 = $-CH_2N\ C_4H_8O$

8 R_1 = $-CH_2N(CH_3)_2$

10 R_1 = $-CH_2N\ C_4H_8O$

11 R_1 = $-CHN\ C_4H_8O$ (with CO_2CH_3)

Scheme 2

Nevertheless, in each case we were able to study the free base in solution especially by nmr.

NMR STUDY

The results which are summarized in the table 2 show the selectivity of the reaction.

The Mannich bases derived from 8-acetoxyindolizine result from a substitution which takes place at the 3 position of the heterocycle. Actually the nmr spectra of the free bases show the disappearance of the H-3 signal at 7.3 ppm, and the existence of a zig-zag coupling between H-5 and H-1 indicating that this latter has not been substituted. In the Mannich bases derived from 3-acetyl-8-acetoxyindolizine the substituent has been introduced at position 1, as it is confirmed by the disappearance of the H-1 signal and its coupling with H-2 which gives rise to a singlet. Comparison of the spectra of the Mannich bases with those of their hydrochlorides shows a deshieding ($\Delta\delta$ = 0.5 to 1 ppm) for the groups linked to the nitrogen of the side chain in the salts, from which it can be concluded that protonation takes place at the amino group introduced by substitution.

A particularity concerning the signal of H-5 appears in the nmr spectra. In the Mannich compounds which are not acetylated at position 3, this signal has approximatively the same shift in the free base and in the corresponding hydrochloride. But in the 3-acetylated products a strong shielding ($\Delta\delta$ = 0.5 to 1 ppm) is observed when one passes from the base to its salt. In fact, a deshielding effect is shown by all the 3-acetylated indolizines. Since in the liberated bases, the signal of H-5 appears in the same region that in 3-acetyl-8-acetoxyindolizine (δ = 9.65 ppm), that means that the deshielding effect associated with a keto group is suppressed in the case of the hydrochlorides. An explanation for this observation can be put forwards, invoking a change from restricted to free rotation of the 3-acetyl group, depending on the protonation of the amino function. The deshielding effect on H-5 observed in 3-acylindolizines can be interpreted by a stable conformation which would place the carbonyl group in the plane of the indolizine nucleus (allowing conjugation) and in syn position towards H-5. In this conformation the H-5 proton is more particularly deshielded, owing to the diamagnetic anisotropy of the carbonyl group. Such a geometry has been described to explain the same observed deshielding effect on H-5 in 3-formyl and 3-thioformylindolizines, and, in the same manner, on H-8 in 1-formyl and 1-thioformyl indolizines.[14] From a variable temperature nmr study it has been concluded that this syn conformation may be frozen out as a consequence of favourable electrostatic interactions in the dipolar form of these compounds ; in the 3-substituted series, where a closer proximity of opposites charges is realized in the dipolar form, the rotation is still restricted at 120°C.[14]

A similar phenomenon would be responsible for the deshielding observed in the free bases which adopt a syn conformation for their 3-acetyl substituent (scheme 3a). Since the chemical shift of H-5 is about the same in our compounds as in 1,2-dimethyl-3-formylindolizine (δ = 9.66 ppm), this

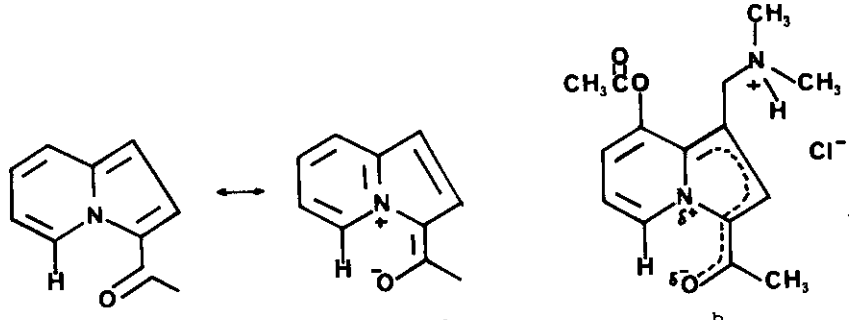
Table 2

NMR data for the Mannich bases (2,12,13,14 and 15) and their hydrochlorides (7,8,9,10 and 11).

	2	7	12	8	13	9	14	10	15	11
$OCOCH_3$	2.42, s	2.42, s	2.73, s	2.60, s	2.36, s	2.36, s	2.41, s	2,40, s	2.45, s	2.55, s
$COCH_3$	-	-	2.9, s	2.74, s	-	-	2.58, s	2.53, s	2.55, s	2.65, s
CH_3N, CH_2N or $CH_3\overset{+}{N}$, $CH_2\overset{+}{N}$	2.30, s	2.82, s	2.43, s	2.90, s	2.40-2.55 m	3.16-3.46 m	2.30-2.6 m	3.1-3.53 m	2.30-2.70 m	3.30-3.6 m
CH_2O	-	-	-	-	3.65-3.85 m	3.7-4.03 m	3.66, m	3.80-4.17 m	3.90-4.2 m	3.6-3.8 m
CO_2Me	-	-	-	-	-	-	-	-	4, s	3.70, s
$\overset{\oplus}{N}H$**	-	4.6, s	-	4.68, s	-	4.6, s	-	4.66, s	-	4.8, s
-CH-N, $CH-\overset{\oplus}{N}$	3.70, s	4.68, s	3.96, s	4.40, s	3.75, s	4.63, s	3.75, s	4.4., s	4.75, s	5.73, s
H-1	6.40-6.70 m	6.5, d*	-	-	6.35, dd	6.4-7.3 m	-	-	-	-
H-6		6.83, m	7.16, m	6.75, dd	6.38-6.82 m		6.83, m	6.6, dd	6.80-7.10 m	6.85, dd
H-7			7.16, m	7.30, dd			6.83, m	6.73, d		7.30, t*
H-2	6.75, d	7, d	7.73, s	7.8, s	6.63, d		7.3, s	7.53, s	7.75, s	7.98, s
H-5	8, m	8.1, m	10.1, dd	9.05, dd	8.16, m	8.16, m	9.66, dd	8.76, d*	9.84, dd	9.38, d*
Observed coupling values	-	-	J_{5-6}: 5Hz J_{6-7}: 5Hz J_{5-7}: 2Hz	J_{5-6}: 7Hz J_{6-7}: 8Hz J_{5-7}: 1Hz	J_{1-5}: 1Hz J_{1-2}: 4Hz	-	-	-	J_{5-6}: 6Hz J_{5-7}: 2Hz J_{6-7}: 6Hz	-

* broad signals ** Exchange with D_2O

syn conformation can be considered as frozen out in the free bases. In the hydrochlorides the equilibrium between syn and anti conformations would be restored as a consequence of a destabilizing effect of the positive charge of the protonated amino group on the dipolar form of the 3-acetylindolizine moiety. Indeed, the entire charge borne by the side chain nitrogen would prevent important development of a partial positive charge localized at the nitrogen atom of the indolizine nucleus (Scheme 3b).



a Scheme 3 b

In this hypothesis one can expect a direct relationship between the observed shielding and the basicity of the amino function of the Mannich bases. This appears to be the case in the series 15 → 11, 14 → 10, and 12 → 8 for which an increasing basicity can be predicted.

The ir study confirms the above assumptions since the stretching frequency of the carbonyl group occurs at higher wavelengths for the free bases (1620 cm^{-1}) than for the corresponding salts (1635 - 1650 cm^{-1}). This result shows that conjugation of the carbonyl group with indolizine nucleus is less pronounced in the salts than in the bases, in relation with a decreased dipolar character.

EXPERIMENTAL SECTION

Elemental analysis were obtained from Central Service of CNRS; all melting and boiling points are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer 337 spectrometer. ^1H nmr spectra were obtained from a A-60-A Varian or a WP 60 Bruker spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane used as internal standard in deuteriochloroforme solution and as external standard when D_2O was the solvent. Mass spectra were taken on a R-10-10 Riber spectrometer under 70 ev.

Bismorpholinomethane was prepared according to the procedure described by Schaeffer: [13b] yield 66%; b.p.$_{0.2}$ 71°C; $n_D^{22,4}$ 1.4804; ir (film) νcm^{-1} 3000-2800 (C-H); nmr ($CDCl_3$) δppm 2.3-2.6 (m, 4H, $N(CH_2)_2$), 2.90 (s, 2H, $N-CH_2-N$), 3.6-3.8 (m, 4H, $(CH_2)_2O$).

Bismethylaminomethane was purchased from Fluka.

N,N-Dimethylmethyleneiminium hydrochloride (4). To 20 g of bismethylaminomethane (0.196 mol) in

200 ml of anhydrous ethyl ether stirred under inert atmosphere (N_2) was added slowly acetyl chloride (13.9 ml, 0.196 mol). After two hours of reaction, the voluminous white precipitate was collected by filtration under inert atmosphere and rinsed largely with anhydrous ethyl ether. After desiccation, the iminium salt weighted 19 g (100% yield).

Morpholinomethyleneiminium hydrochloride (5) was quantitatively obtained by the same procedure.

Methyl 1-morpholino-1-methoxyacetate was obtained according to the procedure of Gross and Freiberg[13d] : b.p.$_{0.1}$ 75-76°C; $n_D^{21.2}$ 1.4584 [Litt.[13d]: b.p.$_{0.01}$ 68-70°C; n_D^{23} 1.4562; yield 60%]; ir (film) νcm^{-1} 2850 (CH_3O), 1750 (CO_2CH_3), nmr ($CDCl_3$) δppm 2.5-2.9 (m, 4H, CH_2-N), 3.45 (s, 3H, CH_3O), 3.65-3.90 (m, 4H, CH_2-O), 3.85 (s, 3H, CH_3O), 4.30 (s, 1H, CH).

Morpholinomethoxycarbonylmethyleneiminium hydrochloride (6). To a solution of 3.8 g of methyl 1-morpholino-1-methoxyacetate in 60 ml of anhydrous ethyl ether, was added slowly under nitrogen thionyl chloride (1.8 ml). Work up identical to that described for 4 yielded quantitatively the compound 6.

3-N,N-Dimethylaminomethyl-8-acetoxyindolizine hydrochloride (7). To a solution of 1.75 g of 8-acetoxyindolizine 1 (10 mmol) in 20 ml of freshly distilled acetonitrile 0.9 equivalent (0.84 g) of iminium salt 4 was added protionwise under inert atmosphere. The mixture was stirred during 6 hours at 20°C. Similar work up yielded quantitatively the compound 7 (2.4 g), m.p. 185°C; ir (KBr) νcm^{-1} 1765-1770 (OAc), 2500-2680 (⊕NH); nmr (D_2O) see Table 2; ms 232 (19.1%) $M^{+\cdot}$ -HCl; Anal. Calcd. for $C_{13}H_{17}N_2O_2Cl$: C, 58.10; H, 6.38; N, 10.42; Cl, 13.19. Found: C, 58.3; H, 6.5; N, 10.1; Cl, 13.2.

3-N,N-Dimethylaminomethyl-8-acetoxyindolizine (2). To a stirred suspension of 2.94 g of $NaHCO_3$ (35 mmol) in 200 ml of anhydrous methylene chloride, was added under nitrogen 1.61 g of the hydrochloride 7 (5.99 mmol). After two hours of stirring, the resultant mixture was filtered and the mother liquor was evaporated under reduced pressure (0.1 mmHg). 1.3 g (yield 93.5 %) of the Mannich base 2 was obtained in the form of a very unstable oily material: n_D^{22} 1.5651; ir (film) νcm^{-1} 1760-1770 (OAc); nmr ($CDCl_3$) see Table 2. This material was also obtained by the classical method of Mannich (action of aqueous dimethylamine and formol in dioxan towards 8-acetoxyindolizine) and presented the same spectrometric data.

1-N,N-Dimethylaminomethyl-3-acetyl-8-acetoxyindolizine hydrochloride (8). The procedure previously described for compound 7 was modified in the following manner : 1 equivalent of iminium salt 4 was used, the mixture was heated at 80°C for one hour and the precipitation was achieved at -5°C. The overall yield was 82%: m.p. 183-190°C (dec.); ir (KBr) νcm^{-1} 1770 (OAc), 1635 (3-$COCH_3$), 2450-2630

(⊕NH); nmr (D_2O) see Table 2; ms 274 (9.7%) $M^{+\cdot}$ - HCl -$^{\cdot}N(CH_3)_2$-CH_2CO, 187 (66 %) $M^{+\cdot}$ - HCl - $^{\cdot}N(CH_3)_2$ -CH_2CO - H. Anal. Calcd. for $C_{15}H_{19}N_2O_3Cl$: C, 57,97; H, 6.16; N, 9.01; Cl, 11.41. Found: C, 58.1; H, 6.2; N, 9.1; Cl, 11.6.

3-Morpholinomethyl-8-acetoxyindolizine hydrochloride (9) was obtained in 69% yield by the procedure described for compound 7, m.p. 150-160°C; ir (KBr) νcm^{-1} 1770 (OAc), 1635 (3-$COCH_3$), 2450-2630 (⊕NH); nmr (D_2O) see Table 2; ms 274 (10.6%) $M^{+\cdot}$ -HCl. Anal. Calcd. for $C_{15}H_{19}N_2O_3Cl$: C, 57.97; H, 6.16; N, 9.01; Cl, 11.41. Found: C, 58.1; H, 5.9; N, 9.1; H, 11.95.

3-Morpholinomethyl-8-acetoxyindolizine (13) was obtained by the procedure described for compound 2, in a 94% yield after addition of petroleum ether to the oil, precipitation and filtration under nitrogen, m.p. 109°C; ir (KBr) νcm^{-1} 1760-1770 (OAc); nmr ($CDCl_3$) see Table 2; ms similar in all points to the spectrum of the corresponding hydrochloride. Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. FOund: C, 65.5; H, 6.7; N, 10.0.

1-Morpholinomethyl-3-acetyl-8-acetoxyindolizine hydrochloride (10) was quantitatively obtained by the procedure described for the compound 7 with the following modifications : the temperature (60°C) was maintained for 10 min, after that the solution was kept for 24 hours at 20°C. M.p. 230°C; ir (KBr) νcm^{-1} 1770 (OAc), 1635 (3-$COCH_3$), 2450-2630 (⊕NH); nmr (D_2O) see Table 2; ms 316 (6.5%) $M^{+\cdot}$-HCl, 188 (100%) $M^{+\cdot}$ -HCl-$^{\cdot}NC_4H_8O$-CH_2CO, 187 (47%) $M^{+\cdot}$ -HCl-$^{\cdot}NC_4H_8O$-CH_2CO-H. Anal. Calcd. for $C_{17}H_{21}N_2O_4Cl$: C, 57.87; H, 6.00; N, 7.94; Cl, 10.05. Found C, 58.0; H, 5.9; N, 8.0; Cl, 9.9.

1-Morpholinomethoxycarbonylmethyl-3-acetyl-8-acetoxyindolizine hydrochloride (11) was obtained in a quantitative yield, following the procedure described for the preparation of 9. M.p. 176°C; ir (KBr) νcm^{-1} 1770 (OAc), 1770 (CO_2CH_3), 1650 (3-$COCH_3$), 2450-2800 (⊕NH); nmr (D_2O) see Table 2; ms 374 (5.8%) $M^{+\cdot}$ -HCl; Anal. Calcd. for $C_{19}H_{23}N_2O_6Cl$: C, 55.55; H, 5.64; N, 6.82; Cl, 8.63. Found C, 55.4; H, 5.7; N, 6.8; Cl, 8.6.

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