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PROTONATION AND HYDROLYSIS OF α-PIPERIDINOCROTONALDEHYDE

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The question of the regioselectivity of protonation of enamines has not been fully resolved and continues to attract attention [1-5]. The ambident nature of enamines is due to the possibility of protonating either the nitrogen or the β-carbon atom to form the corresponding enammonium or immonium salt. It has been shown that the first stage of the reaction is rapid formation of the N-protonated enamine followed by transfer of the proton to the carbon atom giving rise to the more stable C-protonated form]1].

We have studied the protonation of α,β-unsaturated α-aminoaldehydes through the reaction of α-piperidinocrotonaldehyde (I) with various carbocyclic and inorganic acids. Treatment of ether or pentane solutions of I with dry HCl led to precipitation of the enammonium salt, IIa. Its structure was unambiguously determined by NMR and IR spectroscopic methods and confirmed by elemental analytical data. PMR spectral parameters are given in Table 1.

$$\underset{\text{(I)}}{CH_3CH{=}C(NC_5H_{10})CHO} + HX \rightarrow \underset{\text{(II)}}{CH_3CH{=}C(\overset{+}{N}HC_5H_{10})CHO\ X^-}$$

X=Cl (a), CF_3COO (b), CH_3COO (c).

The existence of IIa in the N-protonated form was indicated by the presence in the spectrum of aldehyde proton singlets and of two alkene proton quartets, and by the marked low field shifts for these and for the α-protons of the piperidine ring (when compared with the starting base, I). Enammonium salt formation was accompanied by geometrical isomerization of the enaminoaldehyde (cf. [6]).

^{13}C NMR spectral parameters for the starting aminoaldehyde and its hydrochloride are given in Table 2.

A group of bands in the IR spectrum of IIa at 2350-2600 cm^{-1} also supports the enammonium structure ($\overset{+}{N}H$) [7]. The double bond band in the IR at 1660 cm^{-1} is shifted 40 cm^{-1} to high frequency of the analogous C=C band for aminoaldehydes (I) [cf. 7, 8] and is partly obscured by the carbonyl group absorption at 1673 cm^{-1}.

Formation of the hydrochloride of I is a rare example amongst the very labile enammonium salts which are readily converted to the immonium [7, 8]. Even over 1 h at 55°C the salt IIa in $CDCl_3$ did not undergo this conversion (cf. [7, 8]). This stability is apparently due to a shift of electron density in the acrylic system towards the carbonyl group on account of the removal of the N atom electron pair from conjugation with the multiple bond. The change in the nature of the conjugation in the chain C=C–C=O was confirmed spectroscopically. In the ^{13}C NMR spectrum the aldehyde carbon signal was shifted to high field in the hydrochloride (IIa) when compared with I and in the IR spectrum the carbonyl group absorption for IIa (1673 cm^{-1}) was shifted to low frequency of its position in aldehyde I (1680 cm^{-1}).

According to NMR data, CF_3COOH forms a trifluoroacetate with I and also has the enammonium structure (IIb). The low field shifts for the vinyl protons were somewhat less than for the hydrochloride IIa. Retention of the alkene quartet and methyl doublet signals in the PMR spectrum (see Table 1) and the ^{13}C NMR data (Table 2) also establish the structure IIb.

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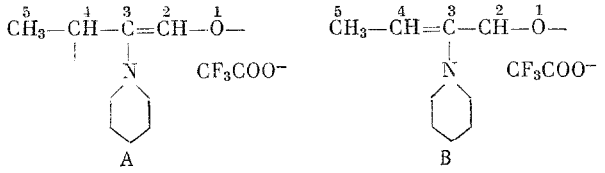
TABLE 1. PMR Spectra of α-Piperidinocrotonaldehyde and Its Salts

Compound	δ, ppm				
	CHO	CH=	CH_3	$N(CH_2)_2$	$(CH_2)_3$
(I)	9.24 s 9.87 s	6.07 q 5.74 q	1.98 d 2.00 d	2.98 m 2.72 m	1.53 m
(IIa)	9.96 s 9.42 s	8.46 q 7.20 q	2.30 d 2.70 d	3.66 m 3.39 m	1.90 m
(IIb)	9.57 s 9.93 s	7.11 q 6.74 q	2.00 d	3.15 m 3.34 m	1.68 m

In contrast to hydrochloride IIa, the trifluoroacetate IIb is much less stable and undergoes 1,2 or 1,4 type polymerization after several hours in concentrated $CDCl_3$ solution or after several days in dilute solution at 20°C.

The PMR spectrum of the mixture of the final reaction products showed the piperidine ring proton multiplet together with poorly resolved signals for methyl (δ 1.1 and 1.9), methine (δ 3.0 and 3.9) and alkene protons (δ 7.7 and 4.5 ppm) for structures A and B respectively

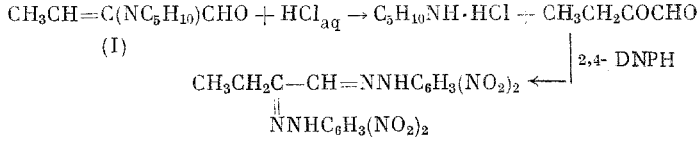


A B

Signals for A and B were also seen in the ^{13}C NMR spectrum of this mixture (δ, ppm), A: C^2 161.83, C^3 134.07, C^4 62.33, C^5 12.40; B: C^2 73.26, C^3 133.1, C^4 140.63, C^5 12.85.

When glacial AcOH was used as protonating agent in $CDCl_3$ the NMR signals corresponding to the N-protonated form IIc were not identified. A solution stored for 3 days at ~20°C showed only signals for piperidine acetate and polymer degradation products from the starting aminoaldehyde. Formation of the proposed immonium salt was not supported (^{13}C NMR). Signals in the region 185-195 ppm (for a $C=\overset{+}{N}\diagdown$ group [9]) were absent in the ^{13}C spectrum. The PMR spectrum revealed the α protons of the piperidine ring at 3.2 ppm (characteristic of piperidine acetate and not at 4.2 ppm as for immonium salts [5]) and the disappearance of the aldehyde proton signal. This behavior of AcOH is apparently due to the low degree of dissociation.

Despite the fact that isomerization of the enammonium to the immonium salt was not observed upon protonation, it was found that α-piperidinocrotonaldehyde (I) was rapidly hydrolyzed in acid media even with only traces of moisture. Thus passage of moist HCl through an ethereal solution of I led to a 74% yield of piperidine hydrochloride. Also formed in this reaction was ethylglyoxal which was identified as its 2,4-dinitrophenylhydrazone (80% yield)



Thus the hydrolysis reaction of I involves a first stage process of conjugative hydration with a shift of electron density in the C=C bond towards the β-carbon atom, as in the case of vinylamines, such that the hydrolysis proceeds according to the Markownikoff rule.

EXPERIMENTAL

NMR spectra were obtained on a Jeol FX-90Q spectrometer with working frequencies of 89.95 MHz (^1H) and 22.49 MHz (^{13}C) using $CDCl_3$ solvent with HMDS as standard for PMR. IR spectra were recorded on a Specord instrument for KBr tablets.

α-Piperidinocrotonaldehyde Hydrochloride (IIa). a) A solution of aldehyde I (2.0 g, 0.013 mole) in anhydrous pentane (35 ml) was protected from moisture in the air and scavenged by argon. Dry HCl was passed through at ~ 20°C until the formation of precipitate ceased.

TABLE 2. ^{13}C NMR Spectra of α-Piperidinocrotonaldehyde and Its Salts (δ, ppm)

Compound	CHO	CH=	C—N	CH_3	Piperidine ring		
					α-CH_2	β-CH_2	γ-CH_2
(I)	192.83 189.31	140.01 151.55	122.26	13.73	50.78	26.51	24.08
(IIa)	182.53 186.27	145.20 150.46	138.87 133.66	12.32	56.47 55.00	23.69	20.55 20.77
(IIb)	183.19 186.76	147.65 152.63	138.44	12.27	52.90	22.13	20.61 21.69

The crystalline product was washed on the filter with pentane and immediately dried in vacuo over P_2O_5. Hydroscopic IIa (1.9 g, 76%) was obtained with mp 70-88°C. Found: C 57.03; H 8.48; Cl 18.45; N 7.68%. Calculated: C 56.90; H 8.44; Cl 18.73; N 7.39%. IR spectrum (ν, cm^{-1}): 1660 (C=C), 1673 (C=O). b) By using an ethereal solution, I (1.5 g, 0.01 mole) gave IIa (1.6 g, 84%) when treated as above.

Reactions of I were also studied in an NMR tube using a four fold excess of acetic or trifluoroacetic acids.

Hydrolysis of α-Piperidinocrotonaldehyde. a) I (0.15 g, 0.001 mole) was treated with a solution of 2,4-dinitrophenylhydrazine (0.4 g) in HCl (0.5 N, 75 ml) and held at 60°C for 10 min. After cooling, the filtered precipitate was dried to give ethylglyoxal 2,4-dinitrophenylhydrazone (0.37 g, 84%). After recrystallization from nitrobenzene it has mp 247.5-248.0°C. Found: C 54.66; H 3.19; N 25.04%. Calculated: C 43.05; H 3.14; N 25.11%.

After removal of the above derivative the filtrate was evaporated to dryness, the residue washed with acetone and dried to give piperidine hydrochloride (0.09 g, 75%) which after recrystallization from methanol:dioxan (1:2) had mp 244°C (cf. [10]). b) Moist HCl was passed through an ether solution of I (1.2 g), the obtained mass decanted and the solid triturated with ether and then dioxan. The piperidine hydrochloride produced (0.7 g, 74%) had mp 245°C.

CONCLUSIONS

1. Treatment of α-piperidinocrotonaldehyde with hydrogen chloride or trifluoroacetic acid gave the corresponding enammonium salt. Reaction of the aldehyde with acetic acid caused dissociation and polymerization.

2. Hydration of the double bond of α-piperidinocrotonaldehyde in acid medium proceeded according to the Markownikoff rule to yield the piperidine salt and ethylglyoxal.

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