Synthesis and Nuclear Magnetic Resonance Spectra of Some N-Substituted 2-Iminopyrrolidines

RUSSELL KWOK AND PAUL PRANC

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

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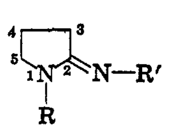
The preparation of a number of N-substituted 2-iminopyrrolidines has been undertaken. The reaction of 4-chlorobutyronitrile with primary amines was found to be a convenient synthesis of N-substituted 2-iminopyrrolidines. Nuclear magnetic resonance studies of the hydrochloride salts of these compounds showed that, in deuteriochloroform solutions, there is localization of charge, but delocalization of charge is observed in deuterium oxide solutions. The chemical-shift difference of the N substituents between the salt and free base makes it possible to determine the position of N substitution.

The nmr spectra of N-substituted methylamines in neutral and acidic media have been studied.[1-3] The N-methyl signals under both neutral and acidic conditions are useful in the determination of the nature and extent of N substitution. This article reports on the synthesis and nmr studies of some N-substituted 2-iminopyrrolidines in which one or both of the substituents are methyl or benzyl. Methyl and benzyl groups were used because of their simple and easily detectable signals.



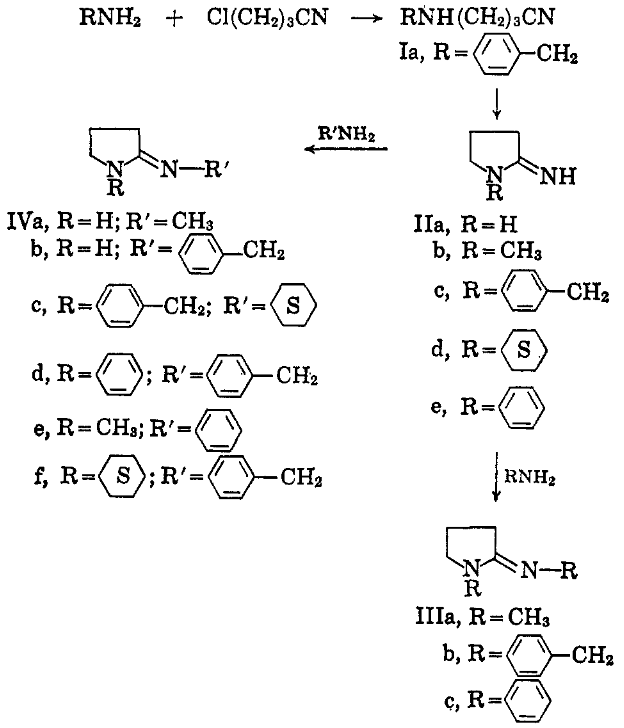
The synthesis of N-substituted 2-iminopyrrolidines has been reported by Bredereck[4] and Etienne.[5] Their methods require pyrrolidone or N-substituted pyrrolidones as starting materials. Although their methods are efficient, the limited number of N-substituted pyrrolidones is a drawback when different substituents are desired.

In view of the fact that substituted 4-dimethylaminobutyronitriles cyclized at high temperatures to form substituted 2-iminopyrrolidines,[6-9] it seemed worthwhile to investigate the cyclization of primary and secondary aminobutyronitriles.

For this purpose, 4-chlorobutyronitrile was treated with a variety of primary amines. All the reactions were exothermic after the initial heating. A mixture of 1-substituted and 1,2-disubstituted-2-iminopyrrolidines was obtained. Prolonged heating led to the disubstituted product exclusively.

Evidently, the initial alkylation step was exothermic, and enough heat was generated to cause cyclization. Further heating led to the disubstituted product through the amine exchange with the imino nitrogen. The intermediate aminonitrile (I) was not isolated under the reaction conditions, but could be prepared under milder conditions. Alkylation of benzylamine with 4-chlorobutyronitrile at room temperature gave 4-benzylaminobutyronitrile (Ia). Its hydrochloride salt was heated to 190° in the presence of dry HCl to give IIc in almost quantitative yield. Treatment of IIc with benzylamine gave IIIb (Scheme I).

SCHEME I



The 1-substituted 2-iminopyrrolidines underwent amine exchange with other primary amines to give mixed disubstituted products as IVc, IVd, and IVf. The exchange reaction proceeded equally well for both the salt and the free base.

To obtain 1-phenyl-2-iminopyrrolidine (IIe), 4-chlorobutyronitrile was refluxed with N-methylaniline. There was no amine exchange owing to the fact that secondary amine was used. The N-substituted 2-iminopyrrolidines prepared are summarized in Table I.

Subsequent to the completion of this phase of the work, Harper, *et al.*,[10] reported the cyclization of substituted secondary aminobutyronitrile to give substituted 2-iminopyrrolidine. Their secondary aminobutyronitrile was prepared from the tertiary aminobutyronitrile *via* the von Braun cyanogen bromide reaction.

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(1) J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).

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(3) M. Freifelden, R. W. Mattoon, and R. W. Kriese, *J. Org. Chem.*, **31**, 1196 (1966).

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(9) F. F. Blicke, U. S. Patent 2,513,270 (1950).

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TABLE I

PHYSICAL PROPERTIES OF N-SUBSTITUTED 2-IMINOPYRROLIDINES

Compd	Yield, %	Bp (mm) or mp, °C, of free base	Mp, °C, of HCl salt[a]	Formula	Calcd, % C	H	N	Found, % C	H	N
IIa	60	78–80[b] (sublimed)	169–171	$C_4H_8N_2HCl$	40.08	7.52	23.25	39.97	7.72	23.45
IIb	33	50–51[c] (5)	185–186	$C_5H_{10}N_2HCl$	44.61	8.24		44.83	8.41	
IIc	31	107 (0.5)	202–203	$C_{11}H_{14}N_2HCl$	62.70	7.18		62.70	7.14	
IId	70	71 (0.5)	260–262	$C_{10}H_{18}N_2HCl$	59.24	9.45	13.82	59.36	9.75	13.55
IIe	55	120–123 (0.8)	219–221	$C_{10}H_{12}N_2HCl$	61.07	6.66	14.24	60.88	6.90	14.11
IIIa	60	48 (5)	169–170	$C_6H_{12}N_2HCl$	48.48	8.81	18.85	48.57	9.02	18.61
IIIb	76	172–175 (0.5)	186–187	$C_{18}H_{20}N_2HCl$	71.87	7.33	9.32	71.92	7.50	9.03
IIIc	60	71–72 (alcohol)	...	$C_{16}H_{16}N_2$	81.32	6.83	11.85	81.61	7.17	11.60
IVa	20	92–94[d] (sublimed)	147–148[e]							
IVb	80	80–82 (sublimed)	152–153	$C_{11}H_{14}N_2HCl$	62.70	7.18	13.30	62.72	7.36	13.58
IVc	60	119–121 (0.3)	220–221	$C_{17}H_{24}N_2HCl$	69.71	8.61	9.57	70.01	8.73	9.59
IVd	73	76–77 (alcohol)	190–192[e]	$C_{17}H_{18}N_2$	81.56	7.25		81.79	7.34	
IVe		*c*	180–181	$C_{11}H_{14}N_2HCl$	62.70	7.18	13.30	62.42	7.48	13.18
IVf	75	137 (0.4)	264–266	$C_{17}H_{24}N_2HCl$	69.71	8.61	9.57	69.30	8.77	9.73

[a] All HCl salts were recrystallized from acetonitrile except IId (2-propanol–ether) and IVb (2-propanol). [b] Lit.[5] mp 84°. [c] Prepared according to the method of Bredereck.[4] [d] Lit.[5] mp 95°. [e] Too hydroscopic to analyze.

Nmr Results.—Pertinent resonance values and coupling constants are given in Table II. Chemical-shift differences between salt and free base are given in Table III. The spectra reported here are exemplified by the spectra of 1-benzyl-2-benzyliminopyrrolidine (IIIb) hydrochloride in deuteriochloroform and deuteriochloroform–deuterium oxide in Figures 1 and 2, respectively.

TABLE II

CHEMICAL SHIFTS OF R AND R′ IN DEUTERIOCHLOROFORM

Compd	Ppm R	R′	J, cps
IIIa	2.78	2.98	
IIIa salt	3.37	3.13 d[a]	5.0
IVa		2.85	
IVa salt		3.16 d[a]	5.0
IIb	2.83		
IIb salt	3.33		
IIIb	4.48	4.58	
IIIb salt	5.12	4.62 d[a]	6.0
IVb		4.39	
IVb salt		4.65 d[a]	6.5
IIc	4.45		
IIc salt	4.98		
IVc	4.52		
IVc salt	5.20		
IVf		4.50	
IVf salt		4.63 d[a]	6.0
IVd		4.52	
IVd salt		4.67 d[a]	6.0
IVe	2.95		
IVe salt	3.50		

[a] Doublet.

TABLE III

CHEMICAL-SHIFT DIFFERENCE ($\nu_{\text{salt}} - \nu_{\text{free base}}$) IN DUETERIOCHLOROFORM

Compd	Ppm R	R′
IIIa	0.59	0.15
IVa		0.31
IIb	0.50	
IIIb	0.64	0.04
IVb		0.26
IIc	0.53	
IVc	0.68	
IVd		0.15
IVe	0.55	
IVf		0.13

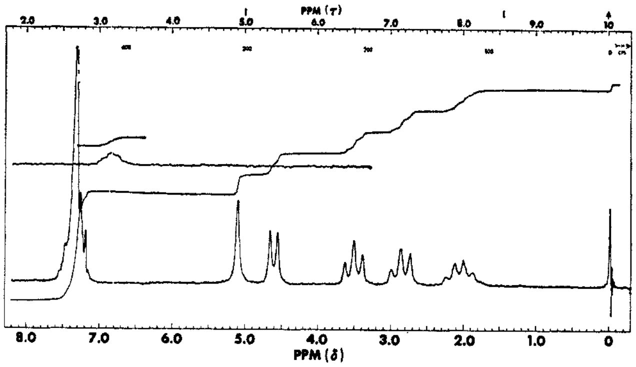


Figure 1.—1-Benzyl-2-benzyliminopyrrolidine (IIIb) hydrochloride in deuteriochloroform.

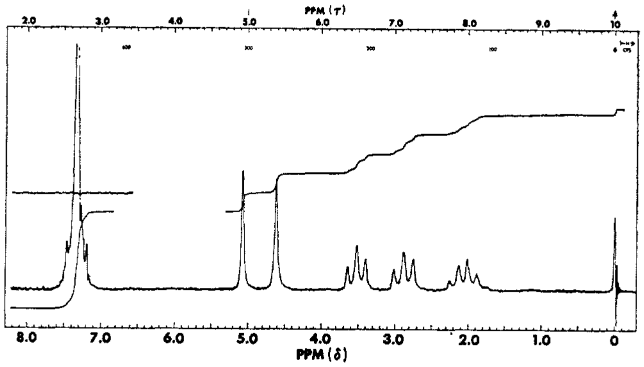
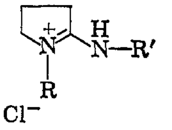


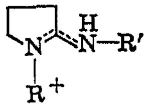
Figure 2.—1-Benzyl-2-benzyliminopyrrolidine (IIIb) in hydrochloride in deuteriochloroform–deuterium oxide.

In the disubstituted compounds IIIa and IIIb where R and R′ are the same, the signals of the substituent on the imino nitrogen R′ of the free base appear at lower field (2.98 ppm for CH_3, 4.58 ppm for $C_6H_5CH_2$) than the substituent on the amino nitrogen R (2.78 ppm for CH_3, 4.48 ppm for $C_6H_5CH_2$). This is due to the deshielding effect of the imino function. On the other hand, the spectra of the hydrochloride salts of the same compounds in deuteriochloroform show the signals for R at much lower field (3.37 ppm for CH_3, 5.12 for $C_6H_5CH_2$) than those for R′. The signals for R′ appear as doublets at 3.13 ppm for methyl in IIIa and 4.62 ppm for benzylmethylene in IIIb. The fact that R is deshielded to a much larger degree by the positive charge than R′ indicates that the charge is localized in the ring nitrogen adjacent to R. R′ is coupled to NH to give doublets (J = 5–6 cps),[11] which collapse to singlets when exchanged with D_2O. These spectral observations indicate that the hydrochloride salts of IIIa and IIIb in $CDCl_3$ solutions must have an endocyclic double bond.



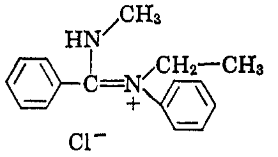
In a decoupling experiment on the hydrochloride salt of IIIb, the doublet of the benzyl methylene collapsed to a singlet on double irradiation at NH frequency. The multiplet of the NH, centered at 11.87 ppm, also collapsed to a singlet when irradiated at the frequency of the benzyl methylene.

In D_2O solutions, both R and R′ of the hydrochloride salt of IIIa and IIIb appear under one signal. The equivalence of these two signals is interpreted as the delocalization of the positive charge between the two nitrogens.



Similar behavior was also observed for the monosubstituted and mixed disubstituted compounds. The signals for R of the hydrochloride salts in $CDCl_3$ are always shifted to much lower field than those for R′. The chemical shifts are summarized in Table II.

N-Methyl-N′-ethyl-N′-phenylbenzamidine hydrochloride in $CDCl_3$ also shows the same phenomenon. The N-methyl signal appears as a doublet at 3.03 ppm, which collapses to a singlet when exchanged with D_2O. The quartet of N′-methylene appears at 4.52 ppm, indicating strong deshielding effect of the localized positive charge.



The chemical-shift difference ($\nu_{\text{salt}} - \nu_{\text{free base}}$) remains relatively constant for R in both the mono- and disubstituted compounds, but for R′ it is influenced by R as shown in Table III. When R is hydrogen as in IVa and IVb, the chemical-shift difference for R′ is larger.

Thus, it is possible to determine the position of N substitution in 2-iminopyrrolidines from the observations that the chemical-shift difference is larger for R than it is for R′ and that this large difference remains relatively constant regardless of substitution at the imino nitrogen (R′). These observations may apply to other cyclic and noncyclic amidines.

Experimental Section

Nmr spectra were recorded using a Varian HA-60 spectrometer. All the samples were run as $CDCl_3$ solutions with tetramethylsilane added as internal reference. Melting points were determined on a Thomas–Hoover apparatus and are corrected.

Reaction of 4-Chlorobutyronitrile with Amines.—The chloronitrile in excess of amine was heated slowly until exothermic reaction occurred. After the vigorous reaction had subsided, the mixture was allowed to cool, diluted with water, and treated with potassium hydroxide. The product was extracted with ether and dried. Solvent was removed under reduced pressure, and the crude product was distilled or recrystallized. For low-boiling amines, the reaction was run in an autoclave at 60–100° for 6 hr.

Reaction of 1-Substituted 2-Iminopyrrolidine with Primary Amines.—The free base or the hydrochloride salt of the 1-substituted 2-iminopyrrolidine in excess of amine was heated to reflux for 5–16 hr. The excess amine was removed and the crude product was distilled or recrystallized. For low-boiling amines, the reaction was run in an autoclave at 100° for 5 hr.

4-Benzylaminobutyronitrile Hydrochloride (Ia).—A mixture of 20 g of 4-chlorobutyronitrile and 50 ml of benzylamine was kept at room temperature for 8 days. Crystalline benzylamine hydrochloride was formed. It was diluted with ether and the precipitate was collected, washed with ether, and dried to give 24 g (87%) of benzylamine hydrochloride, mp 261–263°. The ether solution was concentrated and the residue was distilled. The product (30 g) was distilled at 106–108° (0.2 mm). Its hydrochloride was recrystallized from ethanol to give the analytical sample, mp 174–176°.

Anal. Calcd for $C_{11}H_{14}N_2 \cdot HCl$: C, 62.70; H, 7.18; N, 13.30. Found: C, 62.47; H, 7.50; N, 12.95.

1-Benzyl-2-iminopyrrolidine Hydrochloride (IIc) **from 4-Benzylaminobutyronitrile Hydrochloride** (Ia).—Dry hydrogen chloride was passed through 5.5 g of melted 4-benzylaminobutyronitrile hydrochloride (Ia) at 190–195° for 3 min. The resulting material was recrystallized from acetonitrile to give 5 g of product, mp 200–202°.

Registry No.—Ia, 754-97-0; IIa, 7544-74-3; IIa salt, 7544-75-4; IIb, 7544-76-5; IIb salt, 7544-77-6; IIc, 7544-78-7; IIc salt, 7544-79-8; IId, 7561-78-6; IId salt, 7544-80-1; IIe, 7544-81-2; IIe salt, 7544-82-3; IIIa, 7544-83-4; IIIa salt, 7544-84-5; IIIb, 7544-85-6; IIIb salt, 7544-86-7; IIIc, 7561-79-7; IVa, 7561-80-0; IVa salt, 7544-87-8; IVb, 7544-88-9; IIIb salt, 7544-89-0; IVc, 7544-90-3; IVc salt, 7550-96-1; IVd, 7544-91-4; IVd salt, 7544-92-5; IVa, 7544-93-6; IVe salt, 7544-94-7; IVf, 7544-95-8; IVf salt, 7544-96-9.

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[11] R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 60.