MECHANISM OF 1-PHENYL-1,4-DIHYDROPYRIDINE FORMATION IN REACTION OF 1-PHENYLPYRIDINIUM CHLORIDE WITH ALKALI METAL ALKOXIDES*

Josef KUTHAN, Jiří KRECHL, Martin BĚLOHRADSKÝ** and Petr TRŠKA

Department of Organic Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6

Received February 15th, 1983

Quaternary salt *Ia* reacts with sodium and lithium alkoxides to give 1-phenyl-1,4-dihydropyridine (*IIIa*) together with the unsaturated aldehyde *IVa*. The reaction mechanism for formation of compound *IVa* from the primarily arising 2-alkoxy-1-phenyl-1,2-dihydropyridines is suggested on the basis of products *IIIb* and *IVb*, arising from the 3,4,5-trideuterio precursor *Ib*.

In connection with investigation of reactions simulating biochemical redox transformations, catalyzed by alcohol dehydrogenases, we found interesting the observation of Kaválek and coworkers[1] that the reaction of sodium ethoxide with 1-phenylpyridinium chloride (*Ia*) afforded, besides the expected addition product *II* ($R = C_2H_5$), also 1-phenyl-1,4-dihydropyridine (*IIIa*). According to the cited authors, the latter compound may possibly arise by oxidation of the ethoxide ion with the starting pyridinium ion of the salt *Ia*, *i.e.* by a side reaction. If the reaction went according to the scheme

$$Ia + C_2H_5O^- \rightarrow IIIa + CH_3CHO + Cl^- , \qquad (A)$$

it would represent the first bioorganic simulation of biochemical oxidation of ethanol known to us. We reinvestigated therefore in detail the reaction of *Ia* with sodium methoxide, ethoxide, 2-propoxide and tert-butoxide and with the analogous lithium alkoxides. We performed analogous experiments with 1-phenyl-3,4,5-trideuteriopyridinium chloride (*Ib*), described in our previous communication[2]. The 1,4-dihydro derivative *IIIa*, formed in the reaction of *Ia* with sodium ethoxide, was accompanied by a red product $C_{22}H_{18}N_2O$, the product ratio ranging from 1 : 1 to 1 : 1·4 (according to HPLC and spectrophotometry) and being within experimental error independent of time. The latter compound was isolated also by the above mentioned

---

* Part LXVII in the series On Dihydropyridines; Part LVI: This Journal *48*, 3123 (1983).

** Present address: Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6.

authors[1] who, however, did not study its structure. Since we detected (GLC) no acetaldehyde or its aldolization products (acetaldol or crotonaldehyde) in any of our experiments, we conclude that the occurence of both the 1,4-dihydropyridine *IIIa* and the mentioned red product *IVa* is mutually dependent. As shown by the spectral data, compound *IVa* is 1',6-diphenyl-2-(1',4'-dihydropyrid-4'-ylidene)-6-aza-3,5-hexadienal (*IVa*) with *trans*-configuration of the double bond between $C_{(3)}$ and $C_{(4)}$. Both the IR band at 1 660 cm^{-1} and a singlet at $\delta = 9{\cdot}92$ in the ^1H NMR spectrum indicate an aldehyde group; a strong peak at m/z 77 proves the presence of a phenyl group. The ^{13}C NMR spectrum exhibits (combination of the broad-band and off-resonance proton decouplings) 16 chemically non-equivalent carbon centers occuring as 11 doublets and 4 singlets in the second type of measurement. According to data, published on similar structures[3] and the gated decoupling experiments under suppression of NOE, the molecule contains 12 tertiary and 4 quaternary carbon atoms whose probable assignment in the structure *IVa* is given in Table I. The configuration of the double bond between $C_{(3)}$ and $C_{(4)}$ follows from a proton INDOR experiment. While monitoring the $H_{(5)}$ signals it was possible to determine the $H_{(4)}$ and $H_{(3)}$ signals and thus also the coupling constant between these protons.

The products *IIIa* and *IVa* were prepared also using sodium as well as lithium methoxide, 2-propoxide and tert-butoxide, and also lithium ethoxide. Composition of the reaction mixtures was followed semiquantitatively by ^1H NMR spectroscopy and thin-layer chromatography (TLC). The compound *IVa* was also monitored spectrophotometrically in the visible region (λ_{max} 435 nm). In addition to the unequivocal ^1H NMR subspectra of compounds *IIIa* and *IVa*, we observed in some cases further proton signals ascribed[1] to the primary addition products, *i.e.* 1,2-dihydro

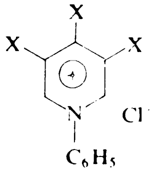
TABLE I

Assignment of chemical shifts in the ^{13}C NMR spectrum of the aldehyde *IVa*. (Measured in hexadeuteriodimethyl sulfoxide; all data given in δ-scale, internal standard tetramethylsilane)

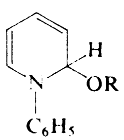
Position	δ, ppm	Position	δ, ppm
C(1)	184·8 d	C(4')	142·2 s
C(2)	107·9 s	$C_6H_5N(6)$ipso	152·8 s
C(3)	141·8 d	*o*-, *m*-	120·7 d[b], 122·5 d[a]
C(4)	120·7 d[b]	*p*-	128·5 d
C(5)	164·1 d	$C_6H_5N(1')$ipso	149·4 s
C(2')	137·5 d[a]	*o*-, *m*-	128·9 d[a], 130·1 d[a]
C(3')	113·7 d[a]	*p*-	124·5 d

[a] The signal corresponds to two centers; [b] overlapping signals of three centers.

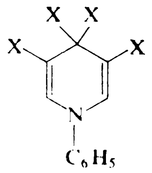
derivatives *II*. Whereas the employed alkali metal influenced only negligibly the composition of the reaction mixture, the alcohol structure (the substituent R in R—OH) had a large effect.



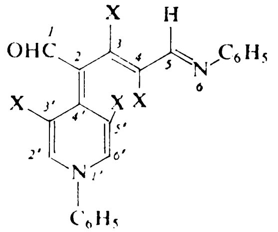
Ia, X = H
Ib, X = ^{2}H



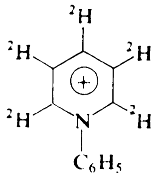
II



IIIa, X = H
IIIb, X = ^{2}H



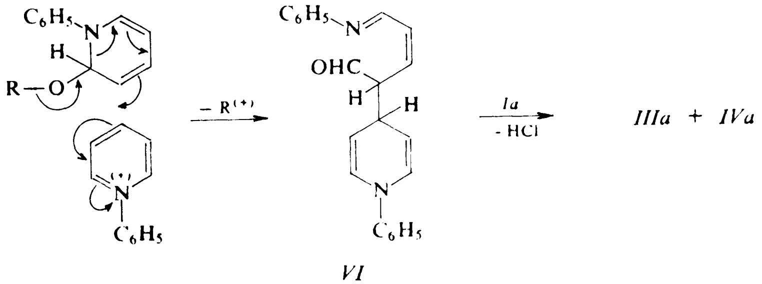
IVa, X = H
IVb, X = ^{2}H



V

In case when R = CH_3 the main product was the adduct *II* (R = CH_3) whereas only traces of compounds *IIIa* and *IVa* were detected (at the limits of the instrument sensitivity). For R = C_2H_5 comparable amounts of all the three products *II* (R = C_2H_5), *IIIa* and *IVa* arose, in accord with ref.[1]. In contrast, for R = iso-C_3H_7 and tert-C_4H_9 the 1,2-adducts *II* (R = iso-C_3H_7 and tert-C_4H_9) could not be identified with certainty in the presence of the products *IIIa* and *IVa*. The formation of the 1,4-dihydro derivative *IIIa* even in the reaction with sodium or lithium tert-butoxide confirmed at the same time that *IIIa* cannot be the sole product of reactions of the type (*A*). To clarify the origin of the reducing species, affording hydrogen equivalents in the process *Ia* + (2 H) → *IIIa* + (HCl) we utilized the 3,4,5-trideuterated substrate *Ib*. In this case, instead of compounds *IIIa* and *IVa*, treatment with all the studied sodium alkoxides afforded exclusively 1-phenyl-2,4,4,6-tetradeuterio-1,4-dihydropyridine (*IIIb*) and the 3,3',4,5'-tetradeuterio derivative *IVb* whose structures were confirmed by the ^{1}H and ^{13}C NMR spectra. The isotope distribution in compound *IIIb* shows unequivocally that sodium alkoxide cannot be the reducing agent, excluding thus the reaction (*A*) and being in accord with the mentioned behaviour of sodium and lithium tert-butoxide. The fact that *IVb* lacks two deuterium atoms indicates that they might have been transferred into the product *IIIb*.

The formation of the 1,4-dihydro derivative *IIIa* from the quaternary salt *Ia* can be regarded as a two-step process in which the primarily formed 1,2-adduct reacts with two equivalents of the starting salt *Ia* (Scheme 1). The first step represents an electrophilic substitution of the 1,2-dihydropyridine skeleton, resembling reactions known for this type of heterocycles[4,5]. The primarily formed "leuco-derivative" *VI* is obviously the sought species, reducing the quaternary salt *Ia* to the 1,4-dihydro derivative *IIIa* under simultaneous formation of the extensively conjugated "dye" *IVa*. The fate of the eliminated carbonium ion R^+ in the strongly nucleophilic reaction mixture was not investigated further. However, the fact that the products *IIIa* and *IVa* are formed less readily with decreasing stability of the ions R^+, *i.e.* tert-$C_4H_9 \approx$ iso-$C_3H_7 > C_2H_5 \gg CH_3$, speaks sufficiently for the suggested reaction mechanism. The overall reaction rate of both reaction steps in Scheme 1 is an order of magnitude lower than the rate of the alkoxide-induced isotopic exchange[2,6] in the positions 2 and 6 of the starting salt *Ia*. This conclusion follows from the observation that the 2,3,4,5,6-pentadeuterio derivative *V* affords exclusively *IIIb* and *IVb*. From the above-discussed composition of the reaction mixtures it is further apparent that character of the substituent R can strongly influence the rate of formation of compounds *IIIa* and *IVa*. It is probable that whereas the kinetics of methoxide additions are probably only negligibly affected by the subsequent formation of *IIIa* and *IVa*, we cannot for certain exclude a possible influence on the kinetics of ethoxide additions[1] to substrates of the type *Ia*. A reaction course analogous to that in Scheme 1 has been observed also for pyrylium salts[7].



SCHEME 1

EXPERIMENTAL

Temperature data are uncorrected. Spectral data were obtained on the following instruments: Specord UV-VIS (Carl Zeiss, Jena), Perkin-Elmer 625 (IR spectra), Varian XL-100 (^{1}H NMR), Tesla BS-567 (^{13}C NMR) and LKB-9000 (mass spectra, 70 eV). Gas liquid chromatography (GLC) was performed on a Chrom-3 chromatograph (poly(propylene sebacate), silicone elastomer SE-30), high performance liquid chromatography (HPLC) on a chromatograph type 501 (Laboratory Instruments, Prague; Separon; in methanol) and thin-layer chromatography (TLC) on Silufol 254 plates. Melting points were determined on a Boetius hot stage.

Solutions (0·5—1·5 mol l^{-1}) of sodium and lithium methoxide, ethoxide, 2-propoxide and tert-butoxide were prepared by reaction of the pertinent alkali metal with the corresponding amount of the alcohol at 30—60°C under nitrogen. Only freshly prepared solutions were used in the experiments.

Reaction of 1-Phenylpyridinium Chloride (*Ia*) with Sodium Ethoxide

The quaternary salt *Ia* (ref.[8,9]; 600 mg) in ethanol (3 ml) was added dropwise to a solution of sodium ethoxide (2·7 ml; 1·5 mol l^{-1}) in ethanol. The separated sodium chloride was removed by filtration and the filtrate was set aside at room temperature for 24 h. The red crystals of *IVa* were collected, washed with tetrachloromethane and dried at 60°C/200 Pa. Yield 100 mg (32%); m.p. 163—163°C (ethanol); reported[1] m.p. 164—165°C. For $C_{22}H_{18}N_2O$ (326·4) calculated: 80·90% C, 5·56% H, 8·58% N; found: 80·82% C, 5·84% H, 8·62% N. UV spectrum (ethanol), λ_{max} (nm), log ε: 204 (4·57), 260 (4·17) and 435 (4·61); IR spectrum ($CHCl_3$), $\tilde{\nu}$ (cm^{-1}): 660 w, 840 w, 985 w, 1 000 w, 1 165 s, 1 195 s, 1 280 s, 1 370 m, 1 400 s, 1 490 s, 1 510 s, 1 580 s, 1 610 s, 1 660 s, 3 020 w. ^{1}H NMR spectrum (C^2HCl_3) δ, ppm: 6·9—7·6 m (C_6H_5; =C—CH=C, 7·44 ppm, d, 15·6 Hz; N=C—CH=C, 7·04 ppm, dd, 8·3 and 15·6 Hz), 8·12 d (N—CH=CH—, 7·5 Hz), 8·28 d (—N=CH—CH=, 8·3 Hz), 9·92 s (—CH=O). ^{13}C NMR spectrum is given in Table I. Concentration of the mother liquors to 2 ml *in vacuo* afforded less pure portions of *IVa*, in which ^{1}H NMR spectrum, HPLC and TLC revealed the presence of the 1,4-dihydro derivative *IIIa* (using an independently prepared[1] standard).

In another experiment, the mixture after reaction of sodium alkoxide with *Ia* was distilled (bath temperature up to 150°C) and the distillate was collected in a receiver cooled with an ethanol–CO_2 mixture. According to GLC, the volatile products did not contain acetaldehyde, acetaldol or crotonaldehyde (comparison with standards and blank experiment in the absence of *Ia*).

Reaction of 1-Phenyl-3,4,5-trideuteriopyridinium Chloride (*Ib*) with Sodium Alkoxide

The quaternary salt *Ib* (ref.[2]; 600 mg) was treated as described in the preceding experiment, affording 95 mg of red crystals of *IVb*, m.p. 164—165°C. ^{1}H NMR spectrum (CCl_4), δ, ppm: 8·13 s (N—CH=C^{2}H), 8·28 s (N=CH—C^{2}H=C^{2}H), 9·93 s (CH=O), 6·9—7·6 m (C_6H_5). ^{13}C NMR spectrum (hexadeuteriodimethyl sulfoxide). δ, ppm: 184·4 d (1 C), 164·1 d (1), 152·8 s (1), 149·4 s (1), 142·2 s (1), 137·5 d (2), 130·1 d (2), 128·9 d (2), 128·5 d (2), 124·5 d (1), 122·5 d (2), 120·6 d (2), 107·7 s (1). After filtration of the compound *IVb*, the mother liquors were taken down and the residue was dissolved in tetrachloromethane. ^{1}H NMR spectra of this solution exhibited the following signals of *IIIb* (δ, ppm): 6·26 s (N—CH=) and 6·8—7·25 m (C_6H_5); identical with spectrum of an independently prepared standard.

Reaction of the quaternary salt *Ia* with the other alkoxides was carried out as described in the preceding experiments, the spectral data for the obtained compounds *IIIa* and *IVa* being identical with those given above.

Mass Spectra, *m/z* (relative intensity, %)

IVa: 236 M^+ (51·3), 325 (26·6), 299 (16·8), 298 (64·1), 297 (100·0), 249 (10·7), 235 (12·6), 234 (84·6), 222 (13·5), 221 (24·7), 220 (10·2), 219 (13·5), 206 (17·7), 194 (26·1), 193 (18·6), 180 (23·8), 156 (20·5), 155 (95·0), 154 (37·8), 116 (10·3), 104 (15·4), 91 (12·1), 89 (10·3), 78 (10·2), 77 (74·4). *IVb*: 330 M^+ (24·7), 331 (13·3), 329 (10·0), 303 (26·6), 302 (72·2), 301 (100·0), 300 (21·5), 239 (10·1), 238 (15·8), 200 (10·3), 199 (12·0), 159 (11·4), 158 (17·7), 157 (20·2), 156 (32·3), 155 (12·7), 94 (13·9), 93 (32·9), 92 (31·0), 77 (44·3).

REFERENCES

1. Kaválek J., Lyčka A., Macháček V., Štěrba V.: This Journal *40*, 1166 (1975).
2. Kuthan J., Krechl J., Bělohradský M.: This Journal *47*, 3283 (1982).
3. Wehrli F. W., Wirthlin T.: *Interpretation of Carbon* ^{13}C NMR *Spectra*. Heyden, London 1976.
4. Kuthan J., Kurfürst A.: Ind. Chem., Prod. Res. Develop. *21*, 191 (1982).
5. Stout D. M., Meyers A. I.: Chem. Rev. *82*, 223 (1982).
6. Macháček V., Štěrba V.: This Journal *40*, 1163 (1975).
7. Pyshchev A. I., Bokii N. G., Struchkov Y. T.: Tetrahedron *34*, 2131 (1978).
8. Kaválek J., Polanský J., Štěrba V.: This Journal *39*, 1049 (1974).
9. Marvell E. N., Shahidi I.: J. Amer. Chem. Soc. *92*, 5646 (1980).

Translated by M. Tichý.