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THE MECHANISM OF REDUCTION OF 3-CARBOXAMIDOQUINOLINIUM SALTS WITH FORMIC ACID AND TRIETHYLAMINE

Leo R. Gizzi and Madeleine M. Joullié

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania

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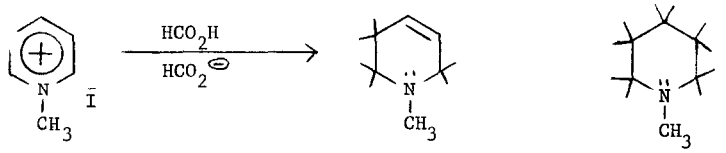
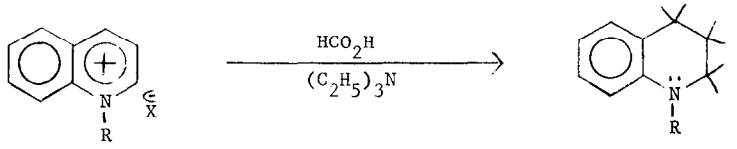
It has been shown by Stewart[1] that the mechanism of reduction of triphenyl carbonium ion by formic acid occurs by hydride transfer. A similar mechanism has been postulated by Cervinka[2] for the reduction of methylpyridinium iodide with formic acid and formate ion. Two products were formed in the reduction.



I II

Cervinka[2] showed by deuterium labeling of formic acid (HCO_2D) that N-methyl-1,2,5,6-tetrahydropyridine (I) resulted from attack of hydride ion at the 2-position while N-methylpiperidine resulted from attack at the 4-position.

Kost and Yudin[3] reported the reduction of a variety of quinolinium salts with formic acid and triethylamine to give the corresponding tetrahydroquinolines.

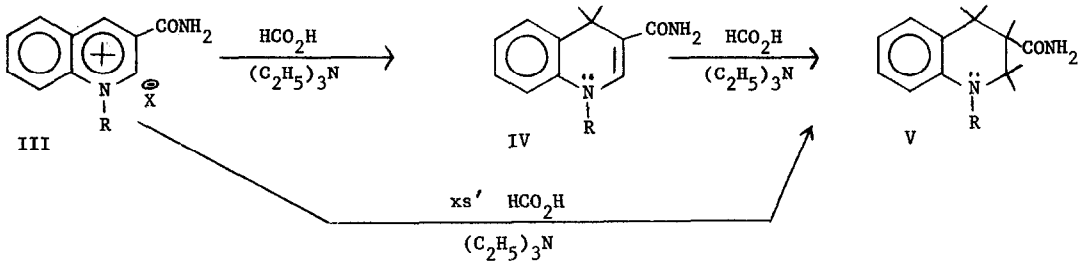


$R = -CH_3, -C_2H_5, -C_3H_7, -C_4H_9, -CH_2C_6H_5$

However, no mechanism has been postulated for this reduction to date.

Because of our interest in the reduction of quinoline analogs of model compounds for coenzyme I[4], we investigated the reduction of 1-substituted-3-carboxamidoquinolinium halides with formic acid and triethylamine. We now report the products and mechanism of these reductions. 1-Substituted-3-carboxamidoquinolinium halides (III) react with formic acid and triethylamine to yield the corresponding tetrahydroquinoline (V) which arises from a

1,4-dihydroquinoline (IV) intermediate.

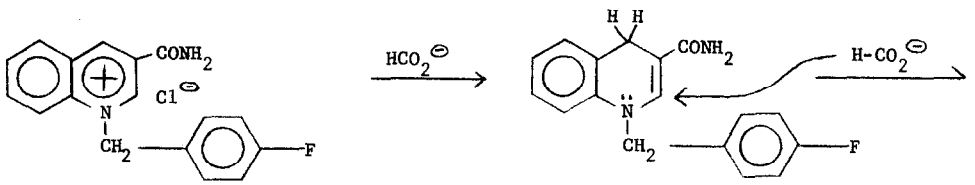


a, R = $-CH_2-C_6H_4-F$, $X^{\ominus}$ = Cl; b, R = $-C_4H_9$, $X^{\ominus}$ = Br; c, R = $-C_{12}H_{25}$, $X^{\ominus}$ = Br

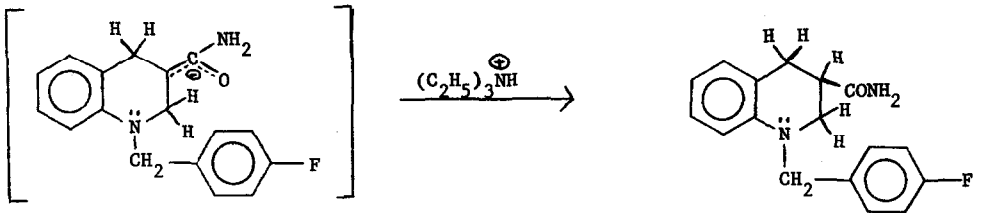
The reduction procedure of Kost and Yudin was followed.[5] N-(p-Fluorobenzyl)-3-carboxamidoquinolinium chloride was heated with formic acid and triethylamine (in a 1 : 2 : 2.5 molar ratio respectively) for five hours. The resulting solution was made basic with 10% sodium hydroxide and extracted with chloroform. The chloroform extracts were dried with sodium sulfate and the solvent was removed. The residue was recrystallized from 30 : 70 ethanol-water to yield 80% of N-(p-fluorobenzyl)-1,4-dihydro-3-carboxamidoquinoline (IVa) as a yellow crystalline solid, mp. 187-189°. Anal. Calcd. for $C_{17}H_{15}N_2OF$: C, 72.33; H, 5.36; N, 9.92; F, 6.73. Found: C, 72.30; H, 5.47; N, 9.82; F, 6.84; UV $\lambda_{max}^{CH_3OH}$ mμ (ε): 234 (8,800); 340 (5,700). NMR ($CDCl_3$) δ:7.15 (complex multiplet, 8 aromatic + 1 olefinic proton); 5.45 (broad singlet, $-NH_2$); 4.75 (singlet, $>N-CH_2-$); 3.85 (singlet, $-CH_2-$). The reaction of IVa with additional formic acid and triethylamine gave N-(p-fluorobenzyl)-1,2,3,4-tetrahydroquinoline (Va). Anal. Calcd. for $C_{17}H_{17}N_2OF$: C, 71.81; H, 6.03; N, 9.85; F, 6.68. Found: C, 71.75; H, 5.79; N, 10.02; F, 6.55. NMR ($CDCl_3$) δ: 6.90 (complex multiplet, 8 aromatic protons); 6.04 (broad singlet, $-NH_2$); 4.44 (singlet, $>N-CH_2-C_6H_4F$); 3.44 doublet, J = 5.0 cps, $>N-CH_2-CH<$); 2.97 (complex multiplet, $-CH_2-CH-CON$).

The reaction was shown to involve hydride transfer by using two deuterated forms of formic acid, HCO_2D and DCO_2H. The mechanism of this reduction may be postulated as follows:

$$HCO_2H + (C_2H_5)_3N \longrightarrow HCO_2^{\ominus} + (C_2H_5)_3\overset{\oplus}{N}H$$

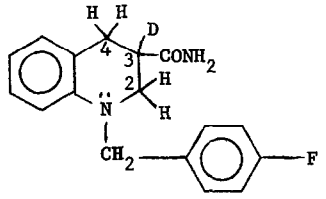


IIIa IVa

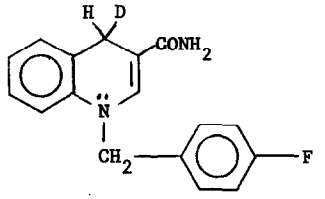


Va

When HCO_2D was used, IVa was isolated. When this compound was treated with more HCO_2D, deuteration occurred at the 3-position, and compound VI was obtained.



VI

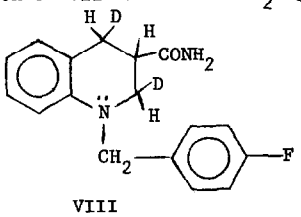


VII

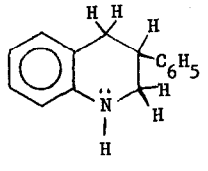
Compound VI may also be obtained directly from IIIa by using an excess of HCO_2D. This product is an amorphous off-white solid, m.p. 128-130°, yield 20%, NMR ($CDCl_3$) δ: 6.93 (complex multiplet, 8 aromatic protons); 5.92 (broad singlet, $-NH_2$) 4.43 (singlet, $\rangle N\text{-}CH_2\text{-}C_6H_4\text{-}F$); 3.43 (singlet, $\rangle N\text{-}CH_2\text{-}C(D)(H)\text{-}CON$); 2.98 (singlet, $-CH_2\text{-}C(D)(H)\text{-}CON$). The singlets at δ 3.43 and 2.98 are slightly deformed. A small complex multiplet is seen at the base of the peak at δ 2.98. The integration of this peak indicates the presence of some C-H at C-3. This is probably due to the presence of Va. If the starting materials were not absolutely dry, some exchange could take place, to produce contamination of VI with Va.

When DCO_2H was used, deuteration occurred at the 4-position to give VII. Compound VII was isolated as yellow needles after recrystallization from ethanol-water, m.p. 187-190°, yield 70%, NMR ($CDCl_3$) δ : 7.12 (complex multiplet, 8 aromatic and 1 olefinic proton); 5.47 (broad singlet, $-NH_2$); 4.73 (singlet, $\rangle N\text{-}CH_2\text{-}$); 3.83 (singlet, $-C(D)(H)$).

The reaction of VII with more DCO_2H gave a dideuterated product, VIII.



VIII

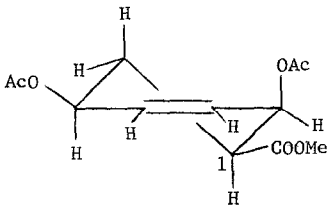


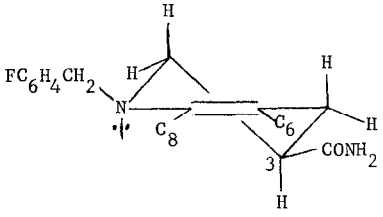
X

This off-white amorphous solid melted at 128-130°, yield, 56% NMR ($CDCl_3$) δ : 6.90 (complex multiplet, 8 aromatic protons); 6.04 (broad singlet, $-NH_2$); 4.44 (singlet, $>N-CH_2-$), 3.43 (complex, $>N-C<^{D}_{H}$); 2.91 (complex $^{D}>C<^{H}_{C-CON}$).

Hydride transfer occurs from the formate ion to the 4-position of the quinolinium salt to give a 1,4-reduced product. The dihydro reduction product can also react with another molecule of formate to give the tetrahydro derivative.

Smissman and Li[6] have shown that the methine proton (C-1) of IX appears as a six-lined pattern centered at τ = 7.2 (δ2.8), J = 11.5, 3, and 3 Hz. These coupling constants arise from one axial-axial and two axial-equitorial couplings. The NMR of Va may be compared to that of IX.





The NMR spectrum of Va shows the methine proton (C-3) as a complex set of lines centered at τ = 7.12 (δ 2.88) which could be attributed to two axial-axial and two axial-equitorial couplings.

The NMR spectra of some 1,2,3,5-tetrahydroquinolines has been studied by Booth[7]. The C-2, C-3, and C-4 protons of 3-phenyl-1,2,3,4-tetrahydroquinoline (X) were assigned to the peaks at 7.06τ (δ2.94), 8.15τ (δ1.85), and 7.24τ (δ2.76) respectively. The C-3 proton was assigned the center of a symmetrical multiplet consisting of six or more lines at 8.15τ (δ1.85).

A greater deshielding effect is observed in the case of Va. This effect is apparently due to the amide group which causes a shift of the C-3 proton downfield. This proton now absorbs in the vicinity of the C-4 proton thereby complicating the NMR spectrum.

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