Hydrogenolysis of N-Alkyl- and N-(2-Oxoalkyl)-quinuclidinium Salts

Robert J. Adamski, Robert E. Hackney, Salotu Numajiri, Larry J. Spears, and Elizabeth H. Yen

Medicinal Chemistry Research, Alcon Laboratories, Inc., Post Office Box 1959, Fort Worth, Texas 76101, U.S.A.

We report here the hydrogenolysis of a number of quaternary quinuclidine salts (1) in the presence of a palladium-on-charcoal catalyst.

\[
R-N^+\text{Br}^\circ\text{H}^\circ\text{Ac} \xrightarrow{\text{Pd-C/H}_2} R-H + \text{HBr} \cdot N^+\text{H}^\circ\text{OAc}
\]

In an effort to synthesize a series of 2-hydroxyalkyl quaternary salts, the corresponding 2-oxoalkyl derivatives (4) were prepared for subsequent catalytic reduction. Compounds 4 were prepared by refluxing, in benzene or chloroform, 3-acetoxyquinuclidine with an equimolar quantity of the appropriate α-bromo-ketone (3). Attempted catalytic reduction of 4 failed to give the desired 2-hydroxyalkyl quaternary salt but gave instead 3-acetoxyquinuclidine hydrobromide and the corresponding alcohol (5).

\[
\text{Ar-C-CH-BR} + \text{N}^+\text{H}^\circ\text{OAc} \xrightarrow{\text{Pd-C/H}_2} \text{Ar-C-CH-N}^+\text{H}^\circ\text{OAc}
\]

Investigation of the literature showed that polarographic cleavage of C—N bonds has been reported for β-trialkylammonium or aldehyde and ketonic 2-oxoalkyl-amonium salts. C—N cleavage by catalytic hydrogenation has been reported for allylic and benzyl quaternary ammonium salts\(^1\) and for 2-nitroalkylamines\(^2\) but not for 2-oxoalkyl quaternary ammonium salts.

We found that N-benzyl- and N-(2-oxoalkyl)-quinuclidinium salts were cleaved (see Table). The materials were hydrogenated in ethanol and the hydrogenation mixture checked by T.L.C. (silica gel) with appropriate standards used as controls. The 3-acetoxyquinuclidine hydrobromide in each case was isolated and compared to the known material. In the case of 3-acetoxy-1-(3-oxo-3-phenyl-2-propyl)-quinuclidinium bromide (4, Ar=\(C_6H_3\), R=CH\(_3\)), both the ketone propiophenone and its reduction product 1-phenyl-1-propanol were isolated, indicating cleavage occurred before reduction of the ketone.

Unlike polarographic reduction, catalytic reduction allows both 2-oxoalkyl tertiary and secondary amine salts to be reduced to 2-hydroxyalkyl tertiary and secondary amine salts without undergoing reductive cleavage\(^4\).

1. R. spectra were obtained on a Model IR5A Beckman spectrophotometer. T.L.C. was carried out on silica gel absorbent with fluorescent indicator, and elution was carried out with either ethyl acetate/methanol (1:1) or chloroform/methanol (8:3).
Table. Preparation and Hydrogenolysis of N-Substituted Quinuclidinium Salts (1 and 4)

<table>
<thead>
<tr>
<th>Type</th>
<th>R</th>
<th>Ar</th>
<th>Quaternary Salt†</th>
<th>Yield (°)</th>
<th>m.p.</th>
<th>Yield (°) of Hydrocarbon or Alcohol (Cleavage Product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>σ-C₆H₄Cl</td>
<td></td>
<td>84</td>
<td>165–167°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>C₆H₅CHO</td>
<td>C₆H₅-CH₂-</td>
<td>73</td>
<td>136–137.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>C₆H₂-CH₂-</td>
<td></td>
<td>49</td>
<td>181–183°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>C₆H₂-CH₂-</td>
<td></td>
<td>81</td>
<td>200–202°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CH₃</td>
<td>C₆H₅-CH₂-</td>
<td>97</td>
<td>200–201° (dec)</td>
<td>91°</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>C₆H₅-CH₂-</td>
<td>98</td>
<td>182–184°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>C₆H₅-CH₂-</td>
<td>92</td>
<td>207–209°</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Analytical results obtained were within ±0.4° of the theoretical values.

b Ketone could be isolated if hydrogenation was stopped before maximum uptake of hydrogen had occurred.

3-Acetoxy-1-[2-oxo-2-(2-naphthyl)ethyl]-quinuclidinium Bromide (Typical Quaternization Procedure):

3-Acetoxyquinuclidine (5.07 g, 0.03 mol) was added to a solution of 2-bromoacetylphenylalanine (7.47 g, 0.03 mol) in chloroform (50 ml), the mixture heated to reflux for 3 hr, and then stirred overnight at room temperature. The solvent was removed under reduced pressure and the resultant solid washed with ether and then recrystallized from methanol/ether; yield: 11.9 g (92°); m.p. 207–209°.

Hydrogenation of 3-Acetoxy-1-[2-oxo-2-(2-naphthyl)ethyl]-quinuclidinium Bromide (Typical Hydrogenolysis Procedure):

A solution of the quaternary salt (2.08 g, 0.005 mol) in absolute ethanol (150 ml) was hydrogenated in the presence of 5° palladium on carbon (0.5 g) under 3.5 atm at room temperature overnight. The catalyst and solvent were removed and the oily residue stirred with ether. The resultant colorless solid was collected and dried; yield: 1.1 g of 3-acetoxyquinuclidine hydrobromide (identified by comparison of T.L.C., I.R. spectrum, and m.p. with those of authentic material prepared from 3-acetoxyquinuclidine and hydrogen bromide). The ethereal filtrate was evaporated to dryness; yield: 0.7 g (82°) of 1-(2-naphthyl)ethanol (identified by T.L.C., I.R. spectrum, and m.p.); m.p. 71–72° (Ref.4, m.p. 71–72°).

Received: February 4, 1972

2 H. Emde, H. Kull, IX. Congr. intern. quim. pura aplicada 4, 290 (1934); C.A. 30, 2932 (1936); Arch Pharm. 274, 173 (1936).