On the Mechanism of Decarbonylation of Indole-3-glyoxyloyl Chloride

JAN BERGMAN and JAN-E. BÄCKVALL

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm 70, Sweden

We have recently observed the thermal decarbonylation of an intermediate cyclopropylmethyl isocyanate in the Favorskii rearrangement of 3-(x-haloacyl)-indoles. Since certain aryldiaddenate chlorides are known to undergo thermal decarbonylation, it appeared to us that a similar mechanism involving intermediates such as 1 and 2 might operate here. Little is known about the mechanism of such decarbonylation reactions and therefore we decided to study the thermal decarbonylation of indole-3-glyoxyloyl chloride 3. The results presented here from decarbonylation of the specifically \textsuperscript{18}O labelled compounds 3a and 3b, indicate that the main path does not involve any three-membered intermediate.

The compounds 3a and 3b were prepared as shown in Scheme 1.

The decarbonylation of 3a or 3b was performed in diglyme \([\text{CH}_3\text{OCH}_2\text{CH}_2\text{O}]\) or tetrachloroethane at 120 °C. The indole-3-carbonyl chloride and the carbon monoxide formed were analysed for their content of \textsuperscript{18}O. The results of the decarbonylations of 3a and 3b are given in Table 1. On decarbonylation, 3a gave carbon monoxide with a high enrichment of \textsuperscript{18}O, whereas 3b gave carbon monoxide with a low percentage of \textsuperscript{18}O. The content of \textsuperscript{18}O found in the indole-3-carbonyl chloride which was isolated as a cross-check in some of the experiments, is in agreement with the values obtained from measurements on carbon monoxide. Thus the results show that the carbon monoxide formed by the decarbonylation of indole-3-glyoxyloyl chloride mainly comes from the COCl group.

The fact that the carbon monoxide formed has its origin in the COCl group rather than in the keto group rules out 1 and 2 as main intermediates, which would have required a total (1) or partial (2) origin of the carbon monoxide in the keto group. A possible main path, consistent with the failure to detect radicals in the decarbonylation of phenylglyoxyloyl chloride, is formation of the indoleene compound 5, followed by decomposition to the ketene 6 (eqn. 1). A radical mechanism cannot be excluded but seems unlikely since only

* The slight systematic deviation from the expected amount of \textsuperscript{18}O in the products, assuming the carbonyl in the COCl group is lost, appears to indicate a minor involvement of three-ring intermediates 1 or 2. In fact, the figures from Table 1 from decarbonylation of 3b in tetrachloroethane are consistent with approximately 25% involvement of a path via the intermediate 2.

Table 1. Decarbonylation of indole-3-glyoxyloyl chloride.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Starting material \textsuperscript{18}O enriched( a, c ) (%)</th>
<th>Products \textsuperscript{18}O enriched( b, c ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a( d )</td>
<td>16.8</td>
<td>4.2</td>
</tr>
<tr>
<td>3b( d )</td>
<td>42.4</td>
<td>20.6</td>
</tr>
<tr>
<td>3c( d )</td>
<td>15.1</td>
<td>2.0</td>
</tr>
<tr>
<td>3d( d )</td>
<td>24.2</td>
<td>5.6</td>
</tr>
<tr>
<td>3e( d )</td>
<td>30.3</td>
<td>7.4</td>
</tr>
</tbody>
</table>

\( a \) Determined from the acid before reaction with SOCl\(_2\) by mass spectrometry. \( b \) Determined by mass spectrometry; the carbon monoxide was separated from \( N_2 \) and \( O_2 \) on a GC column connected to the mass spectrometer. \( c \) The estimated errors in Table 1 vary from ±0.1 for the small values to ±0.5 for the large values. \( d \) R=3-indolyl. \( e \) Performed at 120 °C in diglyme. \( f \) Performed at 120 °C in tetrachloroethane.

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aliphatic glyoxylate esters appear to decarbonylate via a radical chain.

**Experimental. General.** Mass spectra and IR spectra were recorded on an LKB-9000 and a Perkin-Elmer 421 spectrometer, respectively. Gas chromatographic separations were carried out at 50 °C using a 1.8 m x 3 mm column packed with molecular sieves (5A). 18O enriched H2O with a content of 20 % and 40 % 18O was used.

**Indole-3-glyoxylic acid** 3 was prepared from indole and oxalyl chloride according to Speeter and Anthony.

4a. 3 (207 mg, 1 mmol) was hydrolyzed by 18O enriched H2O (19 µl) in THF (1 ml) at 0 °C. After 1 min the solvent was rapidly evaporated in vacuo. The produced indole-3-glyoxalic acid [m.p. 218 °C (acetonitrile) lit. 216 °C] was analysed for its 18O content by mass spectrometry.

4b. Indole-3-glyoxylic acid (unlabelled, 180 mg) 18O enriched H2O (92 µl) and 8 µl conc. HCl was stirred in THF (1 ml) for 24 h at room temperature. After the reaction was completed the solvent was removed in vacuo and the acid analysed for its 18O content (MS).

3a and 3b. The appropriate labelled indole-3-glyoxylic acid 4a or 4b (189 mg) was treated with SOCl2 (250 µl) in a mixture of THF (3 ml) and ether (2 ml) for 20 h at room temperature. After this time the solvent and excess SOCl2 were removed in vacuo.

**Decarbonylation of 3a and 3b** was performed at 120 °C as described in Ref. 3, using diglyme or tetrachloroethane as solvent.

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Chemical Synthesis and Disproportionation of N-Hydroxytyrosine

**BIRGER LINDBERG MÖLLER,**
IAN J. McFARLANE * and ERIC E. CONN

Department of Biochemistry and Biophysics, University of California, Davis, California 95616, USA

In spite of the various routes reported for the chemical synthesis of N-hydroxyamino acids they remain difficult to obtain either because of instability, poor yields, or limited applicability of each of the methods. N-Hydroxyamino acids have been established as components of several naturally occurring compounds and have also, although the experimental data are weak, been postulated to be involved in the biosynthesis of several classes of secondary plant products. We were particularly interested in testing N-hydroxytyrosine as an intermediate in the biosynthesis of the cyanogenic glucoside dhurrin and this report describes its synthesis and characterization.

**Experimental.** N-Hydroxytyrosine was synthesized by a modification of the method described by Ahmad. p-Hydroxyphenylypruvic acid (20 mmol) and hydroxylamine hydrochloride (30 mmol) were dissolved in a mixture of 35 ml of H2O, 25 ml of EtOH and 45 ml of 1 M NaOH. Sodium cyanoborohydride (35 mmol) was added and pH kept at 4 by the addition of 1 M HCl. After reaction at room temperature for 24 h an additional 35 mmol of sodiumcyanoborohydride were added. After 60 h the reaction was stopped by the addition of concentrated HCl to pH ~0. The reaction mixture was evaporated to dryness at 30 °C in a rotary evaporator. The yellow residue was suspended in 50 ml of EtOH and insoluble inorganic material removed by filtration. The ethanol extract was evaporated to dryness and analytically pure N-hydroxytyrosine was obtained as white crystals in 74 % yield by re-crystallizing the residue from hot water (Found: C 54.64; H 5.70; N 7.11. Calc. for C6H5NO: C 54.82; H 5.62; N 7.10). M.p. 226–228 °C (decomp.). MS [IP 70 eV, solid probe, 140 °C]: 197 (M+), 107 (base peak). Potentiometric titration: pK1 = 2.52 and pK2 = 5.26.

**Results and discussion.** N-Hydroxyamino acids described earlier have shown considerable discrepancies in both physical and chemical properties. The main criteria used for identification and purity has been elemental analysis, providing only little information on the nature of the impurities present. In this study NMR analysis was found very suitable for analyzing

* Present address: School of Biochemistry, University of New South Wales, Kensington, New South Wales, Australia 2033.