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

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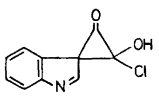
We have recently observed [1] the thermal decarbonylation of an intermediate cyclopropanone in the Favorskii rearrangement of 3-(α-haloacyl)-indoles. Since certain arylglyoxyloyl chlorides are known [2–4] to undergo thermal decarbonylation, it appeared to us that a similar mechanism involving intermediates such as *1* and *2* might operate here. Little is known



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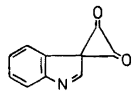

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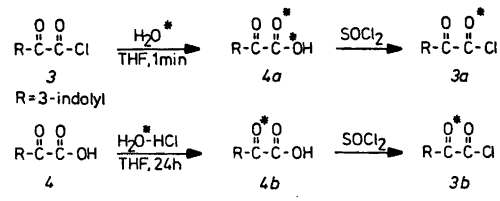
about the mechanism of such decarbonylation reactions and therefore we decided to study the thermal decarbonylation of indole-3-glyoxyloyl chloride *3*. The results presented here from decarbonylation of the specifically ^{18}O labelled compounds *3a* and *3b*, indicate that the main path does not involve any three-membered intermediate.

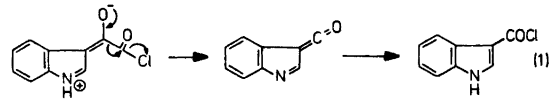
The compounds *3a* and *3b* were prepared as shown in Scheme 1.



Scheme 1.

The decarbonylation of *3a* or *3b* was performed in diglyme [$(CH_3OCH_2CH_2)_2O$] or tetrachloroethane at 120 °C. The indole-3-carbonyl chloride and the carbon monoxide formed were analysed for their content of ^{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 ^{18}O, whereas *3b* gave carbon monoxide with a low percentage of ^{18}O. The content of ^{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,[4] is formation of the indolenine compound *5*, followed by decomposition to the ketene *6* (eqn. 1). A radical mechanism cannot be excluded but seems unlikely since only



(1)

5 *6*

* The slight systematic deviation from the expected amount of ^{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.

Compound[d]	Starting material ^{18}O enriched[a,c] (%) RCO*COCl	RCOCO*Cl	Products ^{18}O enriched[b,c] (%) RCO*CO*Cl	RCO*Cl	CO*
3b[e]	16.8	4.2	1.0		6.0
3a[e]	4.2	20.6	1.4		21.0
3b[f]	15.1	2.0	0.3	10.2	3.4
3b[f]	32.4	5.6	2.7		10.9
3b[f]	30.3	7.4	3.1	27.0	12.6

[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.

aliphatic glyoxyloyl chlorides appear [4] 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 × 3 mm column packed with molecular sieves (5A). ^{18}O enriched H_2O with a content of 20 % and 40 % ^{18}O was used.

Indole-3-glyoxyloyl chloride 3 was prepared from indole and oxalyl chloride according to Speeter and Anthony.[5]

4a. 3 (207 mg, 1 mmol) was hydrolysed by ^{18}O enriched H_2O (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.[6] 216 °C] was analysed for its ^{18}O content by mass spectrometry.

4b. Indole-3-glyoxylic acid (unlabelled, 189 mg) ^{18}O enriched H_2O (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 ^{18}O content (*MS*).

3a and *3b*. The appropriate labelled indole-3-glyoxylic acid *4a* or *4b* (189 mg) was treated with $SOCl_2$ (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 $SOCl_2$ 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

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In spite of the various routes reported for the chemical synthesis of *N*-hydroxyamino acids [1–3] 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 [4,5] and have also, although the experimental data are weak, been postulated to be involved in the biosynthesis of several classes of secondary plant products.[6] 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.[3] *p*-Hydroxyphenylpyruvic acid (20 mmol) and hydroxylamine hydrochloride (30 mmol) were dissolved in a mixture of 35 ml of H_2O, 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 recrystallizing the residue from hot water (Found: C 54.64; H 5.70; N 7.11. Calc. for $C_9H_{11}NO_4$: 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: $pK_1 = 2.52$ and $pK_2 = 5.26$.

Results and discussion. N-Hydroxyamino acids described earlier have shown considerable discrepancies in both physical and chemical properties.[3] 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

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