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## Acid-catalysed Isomerization of Indol-3-yl Sulphides to Indol-2-yl Sulphides: Unexpected Intermolecular Nature of the Rearrangement

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The rearrangement of indol-3-yl sulphides (1) to indol-2-yl sulphides (4), catalysed by proton acids, unexpectedly proceeds by an intermolecular mechanism involving initial disproportionation to an indole-2,3-diyl bis-sulphide (2) and an indole (3), followed by a reaction between (2) and (3) to yield the rearranged product (4).

The acid-catalysed rearrangement of 3-substituted indoles to 2-substituted indoles, in which the migrating atom is carbon, has been known for a century,<sup>1</sup> and all available evidence indicates that such rearrangements are intramolecular in nature.<sup>2</sup> Recently, Plate and Ottenheijm<sup>3</sup> reported the first

examples of this rearrangement [in trifluoroacetic acid (TFA) at room temperature] in which the migrating atom is sulphur, and made the reasonable suggestion that this new reaction proceeds by an intramolecular mechanism as well, involving an episulphonium ion (A) ( $\mathbf{R} = alkyl$ ).

Immediately prior to the appearance of the Plate and Ottenheijm paper, we had found that this rearrangement also occurs on heating the sulphides (1) in polyphosphoric acid (PPA) at 100 °C. Upon performing the rearrangements in TFA we have discovered that the isomerization unexpectedly proceeds principally, if not exclusively, by an intermolecular mechanism with initial rapid transformation of (1) to an indole-2,3-diyl bis-sulphide (2) and an indole (3). These, in a subsequent, slower step, react to yield (4) (Scheme 1). We have also extended the rearrangement to 3-arylthio indoles and N-alkylated analogues (Table 1); in the former case this constitutes the first synthesis of 3-unsubstituted, 2-arylthio-indoles.

We also have results suggesting that the same processes occur in the PPA-promoted rearrangements, although the relative rate differences for the two steps are not so great as in TFA.

In a typical experiment, a  $0.16 \,\mathrm{M}$  solution of the substrate (1) in TFA is stirred at room temperature until the formation of (4) is optimal; this is followed either by evaporation of the TFA or quenching with water, and the product is purified by chromatography. Careful monitoring of the reaction of (1a) in TFA uncovered the unexpected sequence of events shown in Scheme 1. There was initial, rapid (~minutes) formation of an intermediate, which was slowly ( $\sim 2$  h) transformed to (4a). This intermediate was isolated and shown to be the known<sup>4</sup> 2,3-bis(phenylthio)indole (2a). Under optimized conditions, up to a 69% yield (based on the indicated stoicheiometry) of (2a) was isolated along with a 55% yield of indole isolated as a mixture of monomer and dimer.<sup>6</sup> When (2a) was treated alone in TFA only slow formation of (4a) was observed. However, the reaction of 1 equiv. of indole (3a) with (2a) gave (4a) in 67% yield within a few hours. Reaction of (1b) was even more striking, and quenching of the reaction in TFA after 4 minutes gave an 85% yield of (2b), and a 72% yield of N-methylindole, (3b), isolated as a mixture of the monomer (45%) and its

**Table 1.** Isomerization of indol-3-yl sulphides to indol-2-yl sulphides in TFA at room temperature:  $(1) \rightarrow (4)$ .<sup>a</sup>

(A)

Compound	$\mathbb{R}^1$	R <sup>2</sup>	t/h	% Yield (4)	M.p. (4)/°C
а	Н	Ph	4	56	7274
b	Me	Ph	0.5	91	71—73
с	Н	Me	2.5	16	5152ь
d	Me	Me	48	53	Oil

<sup>a</sup> All new compounds have been fully charcterized by i.r., n.m.r., m.s., and elemental analysis. <sup>b</sup> Lit.,<sup>3</sup> m.p. 47-48 °C.

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dimer (27%);<sup>6</sup> the independent reaction of (2b) and (3b) in TFA led to isolation of (4b) in 86% yield. Similar results were obtained with the alkyl sulphides (1c) and (1d) (Table 2).

We therefore conclude that the transformation of (1) to (4) proceeds mainly by initial disproportionation of (1) to an indole-2,3-diyl bis-sulphide (2) and an indole (3), followed by recombination to yield (4) (Scheme 1).

A striking demonstration of the bimolecularity of the process was provided by the following experiment: when a 1:4 molar ratio of (1a) and N-methyl indole (3b) was stirred in TFA at room temperature for 2 h, a mixture of (4a) and (4b) in a ratio of 1:4 (overall yield 48%) was obtained, thus demonstrating that a crossover process had indeed occurred (Scheme 2).

The experiments described herein indicate that the major pathway for the rearrangement of (1) to (4) involves the disproportionation shown in Scheme 1. They do not completely rule out some participation of an intramolecular pathway,<sup>3</sup> but it would appear to be minor.



Scheme 1. Reagents and conditions: (i) TFA, room temp., ca. 5 min; (ii) TFA, room temp., several hours.



Scheme 2. Reagents and conditions: (i) TFA, room temp., 2 h.

**Table 2.** Stepwise conversion of indol-3-yl sulphides in TFA at room temperature:  $(1) \rightarrow (2) + (3) \rightarrow (4)$ .<sup>a</sup>

	% Yield											
			Time/min			Time/h						
Compound	$\mathbb{R}^1$	<b>R</b> <sup>2</sup>	$(1) \rightarrow (2) + (3)$	(2)	( <b>3</b> ) <sup>b</sup>	M.p. (2)/°C	$(2) + (3) \rightarrow (4)$	% Yield				
а	Н	Ph	4	69	55	97—99°	3.5	67				
b	Me	Ph	4	85	72	107—108 <sup>d</sup>	18	86				
с	Н	Me	5	25	e	Oil	40	19				
d	Me	Me	2	63	74	Oil	24	52				

<sup>a</sup> All new compounds have been fully characterized by i.r., n.m.r., m.s., and elemental analysis. <sup>b</sup> Indoles isolated as mixtures of monomer and dimer. <sup>c</sup> Lit.,<sup>4</sup> m.p. 98–99 °C. <sup>d</sup> Lit.,<sup>5</sup> m.p. 107 °C. <sup>e</sup> Indole and its dimer detected in complex mixture.

With regard to the mechanism of the intermolecular sulphenyl transfers which must occur to give the bis-sulphides (2), we suggest that the indolenium cations resulting from 3-protonation of (1) are subject to nucleophilic attack on sulphur by an external nucleophile, either another molecule of (1), or, more likely, the solvent. The former would generate (2) and (3) directly. The latter would generate an indole (3) and a sulphenylating species, such as a sulphenyl trifluoroacetate, which would sulphenylate unreacted (1) to generate (2). A repetition of this sequence on (2) would then give rise to the observed (4). We favour a mechanism involving a sulphenyl trifluoroacetate because we consistently observe the formation of diphenyl disulphide in the reactions of (1a) and (1b), and sulphenyl carboxylates are known to decompose to disulphides.7 They are also capable of sulphenylating reactive nuclei,8 as required by this mechanism.

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