

THE ISOMERIZATION OF ORTHANILIC ACID TO SULPHANILIC ACID IN THE  
PRESENCE OF SULPHURIC ACID-S<sup>35</sup>

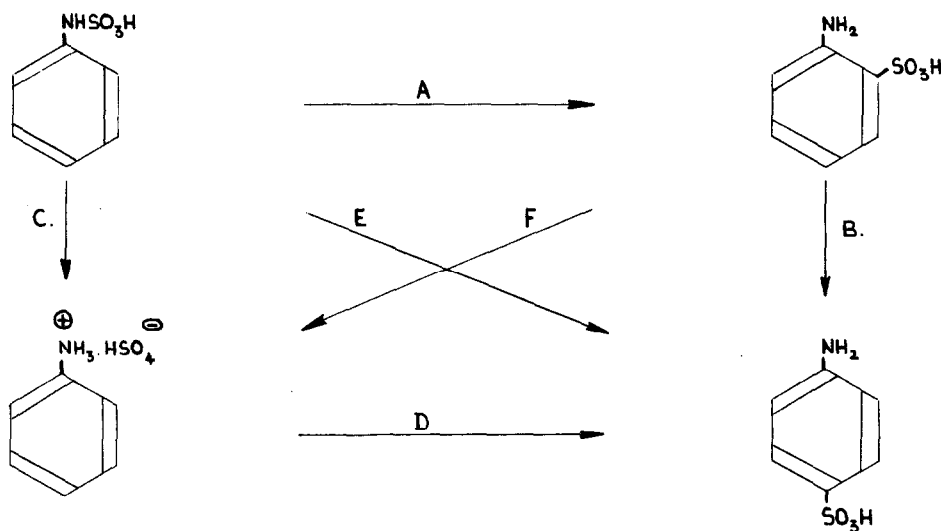
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The sequence of reactions : phenylsulphamic acid to orthanilic acid to sulph-anilic acid (Figure I) is cited as involving examples of intramolecular rearrangements in major modern texts (1). Illuminati (2) found that

FIG. 1.



reaction A in the sequence did not occur. More recently we have demonstrated (3) that reaction E, which was reported by Illuminati as taking place, did not occur in one step, but involved first hydrolysis (reaction C) and then resulphonation (reaction D). We have now examined the remaining steps in the sequence outlined in Figure I, namely, the conversion of orthanilic to sulph-anilic acid (reaction B), and again we find that it is not intramolecular but involves de-sulphonation (reaction F) followed by resulphonation (reaction D). In this way, the intramolecular character of each of these steps has been eliminated.

Reaction B has been described by Bamberger (4), who found that when orthanilic acid was heated in concentrated sulphuric acid at 180-190°C for 7 hours, it was converted into sulphanilic acid in 87% yield. We used radio-labelled ( $S^{35}$ ) sulphuric acid as medium and catalyst to examine this process further. We employed the experimental conditions described by Bamberger with slight modifications. All our runs involved heating the appropriate sulphonic acid in concentrated sulphuric acid (a sulphonic to sulphuric acid ratio of 1 : 5.6 being used) in sealed glass ampoules. In order to be able to recover some unchanged orthanilic acid (even after the isomerization had progressed for some time) we used a reaction temperature of 156°C. The work-up of each run was also standardized. The cooled ampoule was broken and its contents were added cautiously to water. The white crystalline precipitate represented (in each run) approximately 60% of the original sulphonic acid and was generally a mixture of the ortho- and para- acids. We used the difference in acidity of the two isomers ( $K_A$  for orthanilic acid,  $3.3 \times 10^{-3}$ ;  $K_A$  for sulphanilic acid,  $5.8 \times 10^{-4}$ ) to separate them on an ion-exchange resin (Amberlite-IRA (400)Cl) using hydrochloric acid (0.01N to 0.1N) as elutant. This technique was adopted after fractional crystallization of the two acids, as their S-benzylthiuronium salts, failed to separate them.

In a number of trial experiments on this technique we found that (a) an equimolar mixture of the two isomers could be separated with a 90% recovery of each component in the mixture, (b) in 9 : 1 mixtures of the two isomers, the isomer present in excess could be recovered to the extent of about 90% and the other isomer to the extent of 85% and (c) in a 9 : 1 mixture of radioactive sulphanilic acid and inactive orthanilic acid, the orthanilic acid isolated (83%) after two recrystallisations was found to be inactive; thus showing that it did not contain occluded sulphanilic acid.

In our study of the isomerization process we were not concerned with the absolute yields of each isomer but, with the specific activity of each as isolated. Table I summarizes the data we obtained in a series of runs. The sulphonic acids isolated were also characterised by formation of their S-benzylthiuronium derivatives and by their IR spectra. Table II records the specific activities (cpm/mmmole) of sulphanilic acid, which had been heated at 156°C in the presence of 5.6 molar equivalents of concentrated sulphuric acid- $S^{35}$  for (a) 60 minutes and (b) 24 hours, and of the aniline sulphate used to determine the activity of the standard sulphuric acid solution.

TABLE I

Specific Activities <sup>a,b,c</sup> of Orthanilic and Sulphanilic Acids and the % Yield of each Isomer Recovered<sup>e</sup>

Reaction Heating Time (minutes)	Products					
	Orthanilic Acid			Sulphanilic Acid		
	Specific Activity (cpm/mmole x 10 <sup>5</sup> )		Yield	Specific Activity (cpm/mmole x 10 <sup>5</sup> )		Yield
	Actual	Corrected <sup>d</sup>		Actual	Corrected <sup>d</sup>	
22	0.168	0.168 (4.1)	100	-	-	0
45	0.483	0.519 (12.6)	55 <sup>e</sup>	3.68	3.96 (97)	45 <sup>e</sup>
60	0.483	0.543 (13.4)	20 <sup>e</sup>	3.45	3.88 (95)	80 <sup>e</sup>
75	0.490	0.558 (13.6)	11	3.27	3.73 (91.0)	89
90	0.580	0.663 (16.2)	5	3.27	3.74 (91.5)	95

<sup>a</sup> Radioactive assays were carried out on a Nuclear Chicago D47Q gas flow counter with a 'Micromil Window' on samples of finite thickness with appropriate corrections for efficiency and self-absorption. <sup>b</sup> All substances (including those in Table II) were recrystallised from water to constant activity. <sup>c</sup> The figures in parenthesis represent the percentage activity of the maximum that the particular sample possessed. <sup>d</sup> These figures have been corrected to allow for dilution of the radiolabelled acid by the inactive sulphonic acid group, released as sulphuric acid by hydrolysis (see text). <sup>e</sup> Yields superscripted thus were estimated to within  $\pm 10\%$  and are currently being rechecked.

Table II

Specific Activities of Sulphanilic Acid under Isomerization Conditions and of Aniline Sulphate

Reaction Heating Time	Compound	Specific Activity (cpm/mmole x 10 <sup>5</sup> )
60 minutes	Sulphanilic Acid <sup>a</sup>	0.1105
24 hours	Sulphanilic Acid <sup>a</sup>	2.43
-	Aniline Sulphate <sup>b</sup>	4.09

<sup>a</sup> Under isomerization conditions. <sup>b</sup> The activity of the sulphuric acid stock solution was determined by the formation (in ethanol), from two moles of aniline and one mole of acid, of aniline sulphate in quantitative yield. (This sample of aniline sulphate gave an infra-red spectrum which was identical with that obtained from an authentic sample of aniline sulphate.)

These findings show that the formation of sulphanilic acid from orthanilic acid is an intermolecular process. This conclusion is based on the specific activities of the sulphanilic acid samples isolated. If the isomerization were intramolecular then the sulphanilic acid isolated should be inactive, or at least, no more labelled than any exchange of radiosulphur between the labelled and either, or both, starting material and product would produce. (Our results show incidentally that both such exchanges occur but only to a limited extent over the reaction period considered). We have found that the sulphanilic acid isolated even in the early stages of the reaction is highly labelled with up to 97% of its maximum value (a value calculated for each sample by (a) assuming first hydrolysis of the sulphonic acid to form the correct quantity of sulphate, thus diluting the overall radiosulphate concentration, followed by (b) re-sulphonation from this mixed acid to form both labelled and unlabelled sulphonic acid randomly). Thus we designate the isomerization as an intermolecular process. It is interesting to note that the isomerization of some related acids, namely, various tolyl and chlorobenzene sulphonic acids has been studied in the presence of radiolabelled sulphuric acid and both inter- and intramolecular mechanisms have been reported (5).

The mechanisms whereby the particular sulphonic acids exchange (rather than rearrange) with the labelled sulphate must also be considered. In the sulphanilic acid case, hydrolysis to aniline sulphate and resulphonation of this can explain the exchange data. We have confirmed that when aniline is heated in 5.6 molar equivalents of concentrated sulphuric acid for 75 minutes, sulphanilic acid is formed in 30% yield without the detection of any orthanilic acid (i.e. it cannot have been present to greater than 3%). However, the mechanism where the 13% incorporation of radiosulphur into orthanilic acid occurs during the isomerization reaction is unclear and remains for further study.

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