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A Study of the Reaction of *N*-Bromosuccinimide with Indomethacin

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The reaction of *N*-bromosuccinimide with indomethacin in acid medium has been studied. The purified product has been identified by TLC, elemental analysis and infra-red studies, and a reaction mechanism is proposed on the basis of the results. The reaction proceeds smoothly and consistently and can be studied kinetically so as to determine various thermodynamic parameters.

INTRODUCTION

The indole ring is found in many naturally occurring compounds and recently some synthetic indole derivatives have been reported to possess antiparkinsonian activity.[1-3] *N*-Haloimides[4-7] have been used for titrimetric determination of indole and its derivatives. But the reaction is too fast to be studied kinetically. However, indomethacin reacts with *N*-bromo-succinimide (NBS) so smoothly that it can be studied kinetically so as to trace the mechanism of the reaction based on various observations.

EXPERIMENTAL

N-Bromosuccinimide (NBS) solution was prepared by taking the exact amount of NBS (pro-analysis sample, GRS Merck) and dissolving it in minimum amount of hot water. The solution was made up to the mark in cold water. It was always prepared fresh before use and stored for use in a black coated flask. Its strength was checked by iodometric method.[8]

Aqueous solution of indomethacin was prepared by dissolving the exact weighed amount in hot water acidified with acetic acid. Aqueous solutions of mercuric acetate, succinimide, sodium perchlorate and potassium chloride were prepared as usual. Aqueous solution of sodium thiosulphate (AR, BDH) was prepared by dissolving its appropriate weight in water and a pinch of sodium carbonate (AR, BDH) was added to it.[9] It was standardised against standard copper sulphate solution by iodometric method.

Procedure

NBS solution was equilibrated with requisite amount of the acetate buffer solution, mercuric acetate and water in a water bath maintained at a desired temperature for 30 min. The reaction was initiated by adding appropriate volume of indomethacin solution maintained at the same temperature and shaking the reaction mixture vigorously. Unreacted NBS was determined iodometrically using starch as an indicator.

Stoichiometry

Stoichiometry of the reaction shows that two moles of NBS is consumed per mole of the substrate under the experimental conditions.

Product Identification

The reaction product was isolated by dissolving 100 mg of indomethacin in about 25 mL of glacial acetic acid slowly adding mercuric acetate solution in acetate buffer solution and 0.1 M *N*-bromosuccinimide with constant stirring. The reaction mixture was allowed to stand for 24 h. A precipitate was formed which was filtered off and washed with water and dried to obtain dried pale brown needles (mp = 208°C). Thin layer chromatography of this compound on silica gel G with chloroform 92%, acetic acid (95% v/v) showed a single spot. Analysis showed the presence of 2 atoms of bromine in the product molecule. Spectroscopic studies could not be made at present. However, on the basis of other parameters, the product has been identified.

RESULTS AND DISCUSSION

N-Bromosuccinimide is a mild oxidising and brominating agent. It has been suggested that the reactive species of *N*-bromosuccinimide (NBS) is the protonated molecule $NBSH^+$, which gives rise to the electrophilic bromonium ion:

$$NBSH^+ \rightarrow \text{Succinimide} + Br^+$$

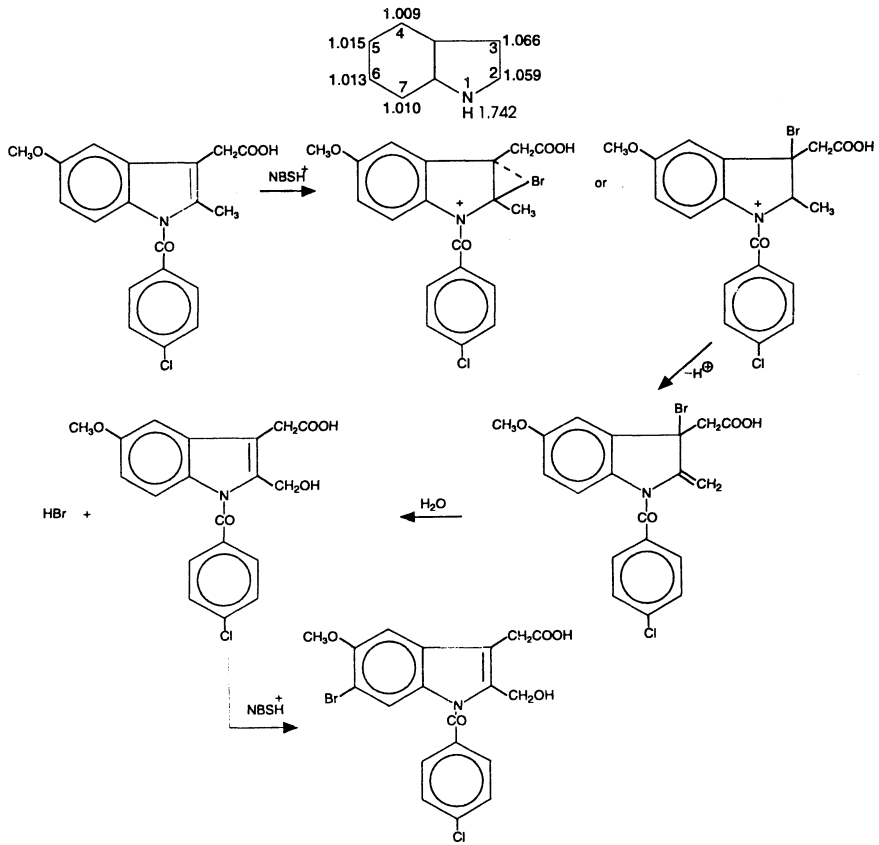
Stoichiometric study has shown that 2 moles of NBS is consumed per mole of indomethacin.The π-electron density on the indole nucleus is shown below.[10] It indicates that position 3 is the most susceptible to electrophilic attack. If, however, position 3 is already occupied, position 2 is preferably attacked and then position 5. If position 5 is also occupied, preferential position of attack is 6.

KINETIC RESULTS

$[NBS] \times 10^3$ M	[Indomethacin] $\times 10^3$ M	pH	Temp. 30°C $K_1 \times 10^5$
0.8	5.00	1.0	11.8
1.0	5.00	1.0	11.2
1.2	5.00	1.0	10.6
1.4	5.00	1.0	10.1
1.6	5.00	1.0	9.59
1.0	6.25	1.0	13.5
1.0	7.50	1.0	15.9
1.0	8.75	1.0	18.2
1.0	10.00	1.0	20.2
1.0	5.00	1.0	11.2
1.0	5.00	1.1	14.2
1.0	5.00	1.2	17.4

A close look at the structure of indomethacin reveals that positions 2 and 3 both are occupied. So the most probable intermediate appears to be a cyclic bromonium ion intermediate or a 3-bromo indolenine derivative. This undergoes hydration or loses a proton followed by hydration to give 2-hydroxy methyl indole derivative. This undergoes further bromination at position 6 leading to the formation of the final product.

On the basis of the observed stoichiometry, bromine content of the raction product and the infrared spectra, the reaction can be explained as follows:



THERMODYNAMIC PARAMETERS

Temp. (°C)	$K \times 10^4$ sec^{-1}	$A \times 10^{-9}$ sec^{-1}	ΔS^* eu	ΔH^* kcal $mole^{-1}$	ΔF^* kcal $mole^{-1}$
30	9.55	1.02	−18.4	16.2	21.8
35	15.40	1.07	−18.3	16.2	21.8
40	22.20	0.99	−18.5	16.2	22.0
45	35.50	1.05	−18.3	16.2	22.0
50	53.70	1.05	−18.3	16.2	22.0

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