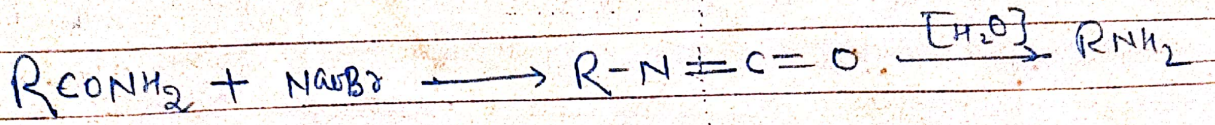


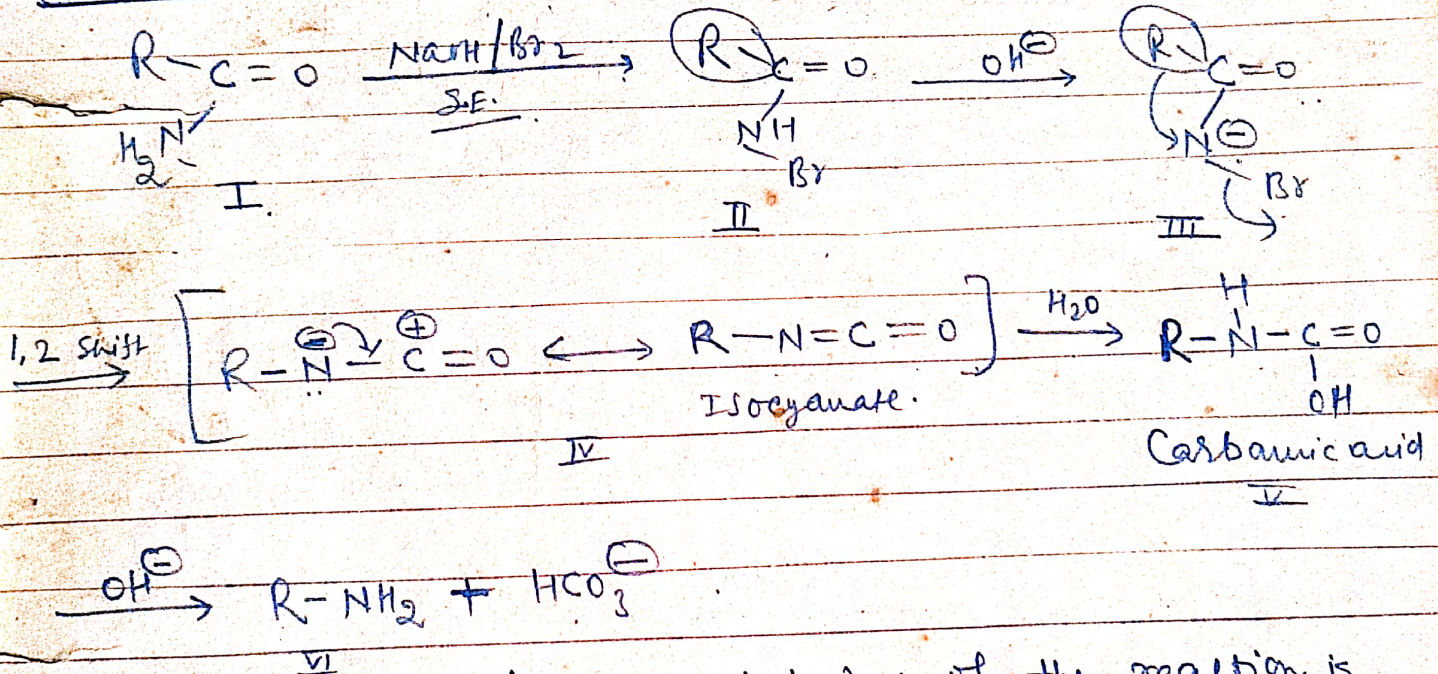
I. Hofmann Rearrangement → In the Hofmann rearrangement

an unsubstituted amide is treated with sodium hypobromide (or NaOH/Br₂, which is essentially the same thing) to give a primary amine, which has one carbon fewer than the starting material amide.

[The conversion of an unsubstituted amide to an amine containing one carbon less than the starting amide, by the action of sodium hypobromide (NaOH/Br₂) is called Hofmann reaction.]



Mechanism →



The formal end-product of the reaction is the isocyanate (IV) corresponding exactly to the ketene in the Wolff reaction, but this undergoes addition of water under reaction condition to yield the unstable carbanic acid (V) which in turn, decarboxylates to yield the amine (VI).

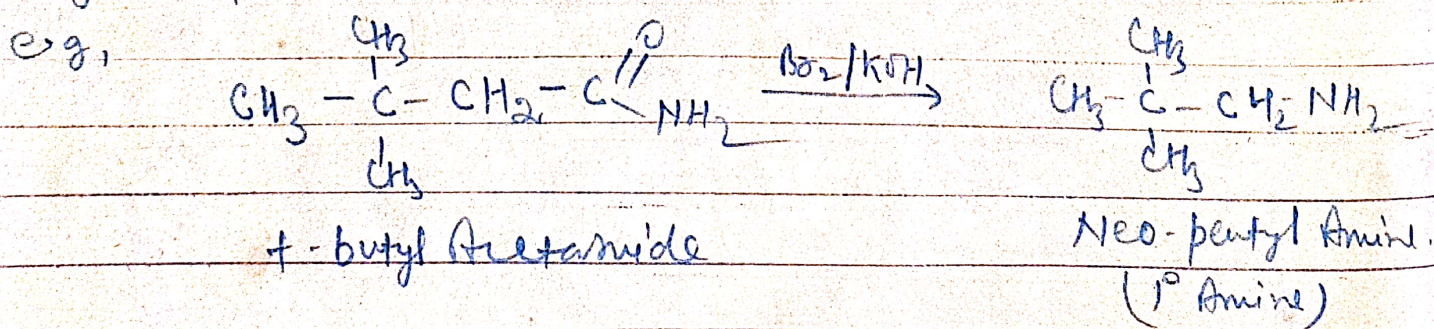
Under suitable conditions it is possible to isolate N-bromoamide (II), its anion (III), and isocyanate (IV) as intermediates, which proves the above reaction pathway is true.

The rate-limiting step is probably loss of Br⁻ from (III) & the question arises whether whether the migration of R or whether

Carbonyl nitrene intermediate $R-\overset{\text{O}}{\parallel}{C}-\dot{N}$ is formed, which then rearranges. But the formation of hydroxamic acid $R-\overset{\text{O}}{\parallel}{C}-N\begin{matrix} H \\ \diagup \\ OH \end{matrix}$ (that would be expected from attack of solvent H_2O at $R\overset{\text{O}}{\parallel}{C}-\dot{N}$) has never been detected, also it has been found that rate of the rearrangement can be speeded up by increasing electron releasing capacity of migratory group R. Both these facts support a concerted (synchronous) mechanism.

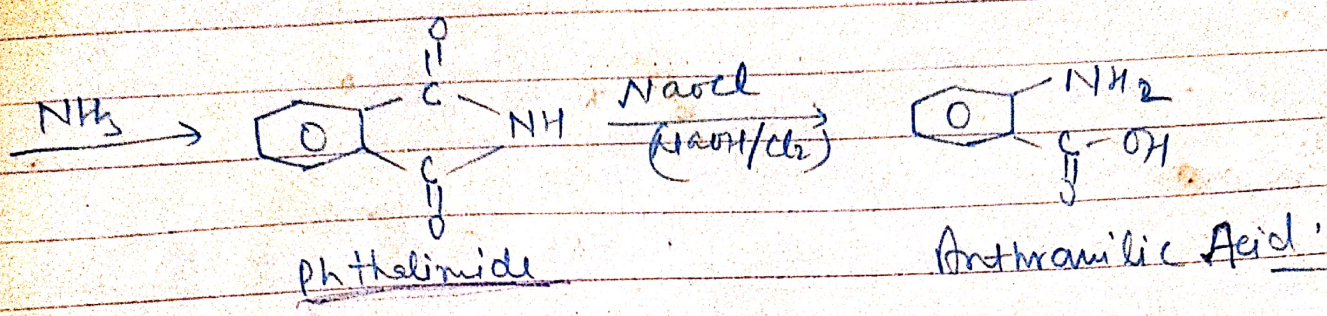
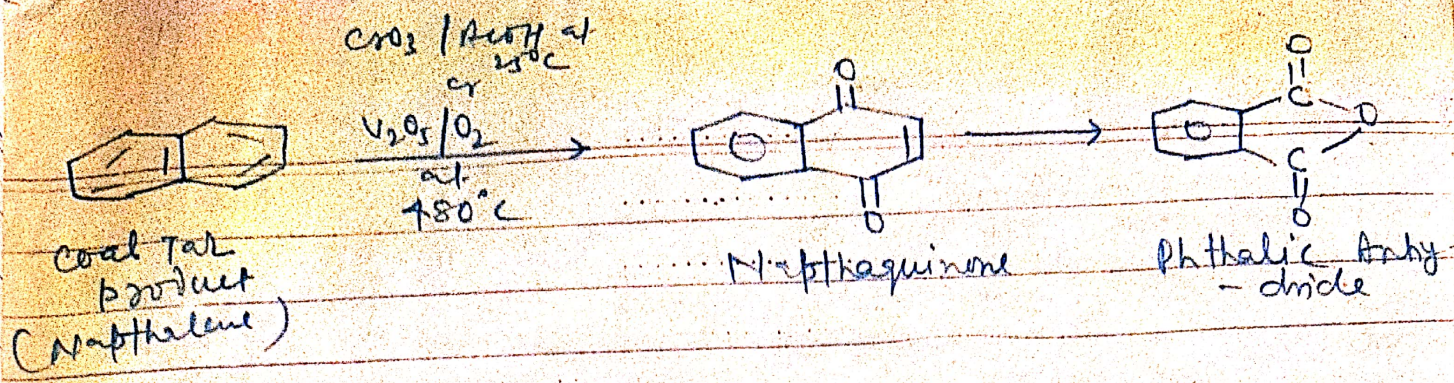
It has been also found that if migratory group R is chiral e.g., $C_6H_5-\overset{CH_3}{\underset{H}{\text{C}}}$, then it migrates with its configuration unchanged (retention). There is complete lack of racemization. This proves that R^{\ominus} does not occur as an independent species (i.e., never becomes free in solution). Hence the reaction is strictly intramolecular. This is also proved by the fact that cross over experiments lead to no mixed products.

Applications: - (i) Hofmann rearrangement is synthetically useful when 1° amine can not be prepared directly by simple S_N reaction.



Apart from this mixture formation ($1^\circ, 2^\circ, 3^\circ$ Amine) is avoided since in ~~the~~ the preparation by simple S_N or S_N2 mixtures of $1^\circ, 2^\circ, 3^\circ$ Amines are obtained).

(ii) Synthesis of β -Amino Acids: - Important industrial application of Hofmann rearrangement is the synthesis of Anthranilic Acid from phthalimide



(b) Synthesis of β -Amino pyridine: \rightarrow β -Aminopyridine is prepared from the nicotinamide (available from Natural source) as it can not be obtained in good yield via the nitration of pyridine.

