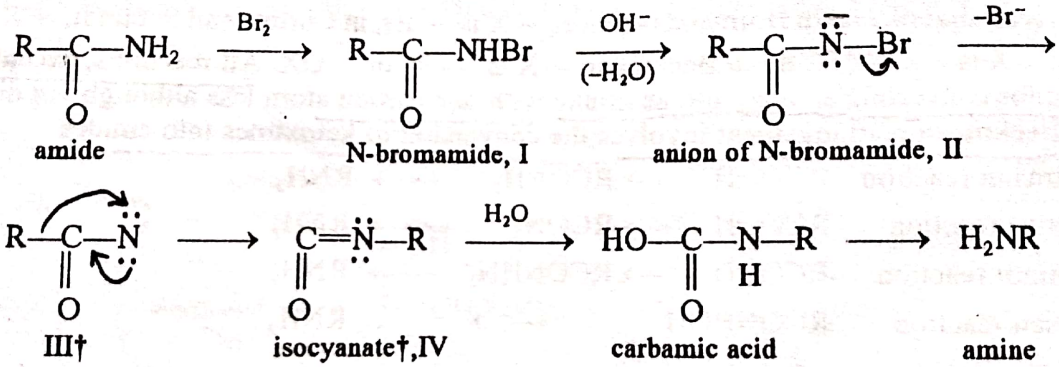
Such examples are also applicable to other rearrangements, *viz.* Hofmann, Lossen, Schmidt, etc.

1. Hofmann reaction, Hofmann degradation of amides or Hofmann rearrangement. The conversion of an amide to an amine with one carbon atom less by the action of alkaline hypohalite or bromine in alkali* is known as the Hofmann reaction. The overall reaction for this conversion may be represented as below.

$$RCONH_2 + Br_2 + 4KOH \longrightarrow RNH_2 + 2KBr + K_2CO_3 + 2H_2O$$

Mechanism. The reaction is found to follow the following path.



The formation of N-bromamide I, its anion II and isocyanate IV as the intermediate products and hence, the above mechanism for Hofmann reaction is proved by their isolation under suitable conditions. These intermediate species can undergo further reaction with the reagents to yield amine as the final product.

Note that the elimination of bromide ion from the anion of N-bromamide II forms a highly unstable neutral species $RCO\ddot{N}$, which has only a sextet of valency electrons around the nitrogen atom. This species is therefore highly electron deficient on nitrogen, and it gains some stability by the migration of the methyl

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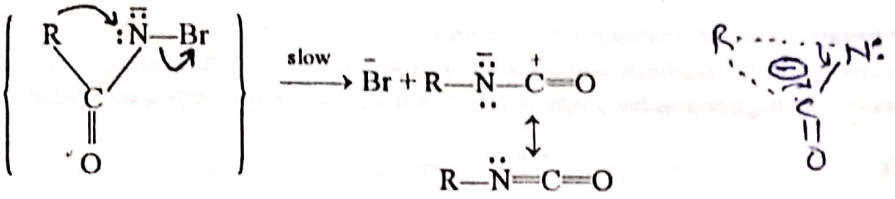
* Sodium hydroxide may be replaced by potassium hydroxide, and bromine may be replaced by chlorine.

† Note that the electron deficient atom in species III, known as acyl nitrene, corresponds to the electron-deficient carbon in the carbene II from the Wolf rearrangement and that the isocyanate, IV obtained by the rearrangement corresponds closely to the ketene obtained from the Wolf rearrangement.

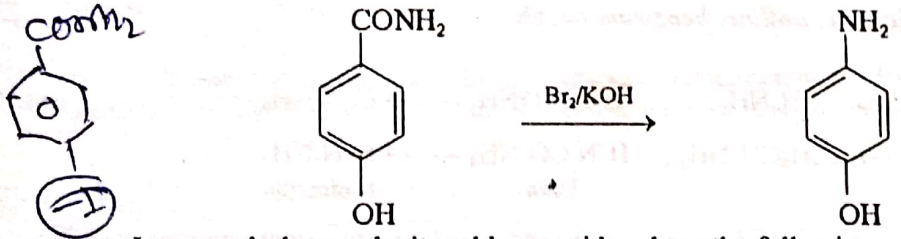
group with its pair of bonding electrons to form isocyanate. **This rearrangement of N bromamide or its anion to isocyanate is known as Hofmann rearrangement.** The isocyanate may be isolated in anhydrous conditions but as the reaction is normally carried out in aqueous or alcoholic solution, the isocyanate is converted into amine or a urethane, respectively.

$$\underset{\text{urethane}}{RNHCOOR'} \xleftarrow{R'OH} \underset{\text{isocyanate}}{R-N=C=O} \xrightarrow{H_2O} \underset{\text{amine}}{RNH_2} + CO_2$$

However, Wright (1968) by using ^{14}C– and ^{15}N– labelled compounds observed that the intermediate III (acyl nitrene) may not involve during the Hofmann, Curtius and Lossen rearrangements, and the compound II is directly converted into isocyanate *i.e.*, elimination of halide ion and migration of alkyl group take place simultaneously.



It has been observed and established that Hofmann reactions are accelerated if the migrating group R has an increased electron releasing* capacity. A strongly electron donating migrating group not only eases the departure of Br from the bromamide anion, but also enables to satisfy the electron deficiency of the residual nitrogen atom more effectively. Thus, the rate of amine formation from *p*-hydroxybenzamide is more rapid than that for benzamide itself due to the activating effect of phenolic –OH group.

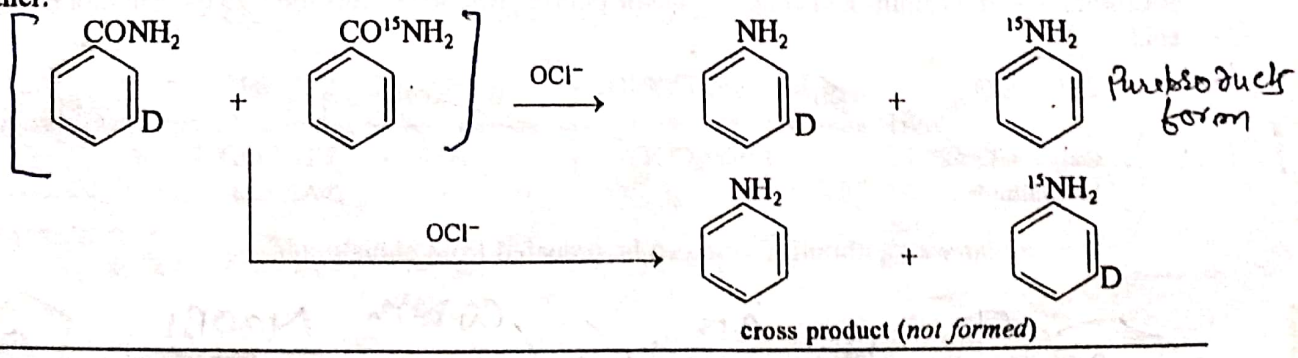


In general, the *p*-substituted benzamides show the following order of reactivity.

$$-OCH_3 > -CH_3 > -H > -Cl > -NO_2$$

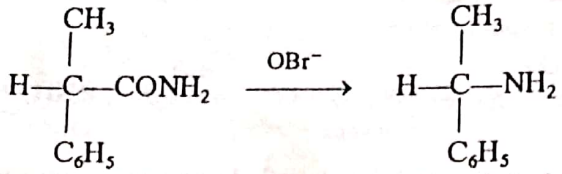
Intramolecular nature of Hofmann rearrangement. The intramolecular nature of the rearrangement can be shown by the following two experiments.

(*i*) When a mixture of *m*-deuteriobenzamide and benzamide –^{15}N are treated with alkaline chlorine, only two products (*m*-deuterioaniline and aniline –^{15}N) are found to be produced ; no cross-product is produced which would have been formed if the phenyl group from one molecule had become attached to nitrogen of another.



* This supports the formation of a bridged ion during the reaction.

(*ii*) When optically active α-phenyl propionamide undergoes the Hofmann degradation, α-phenylethyl amine of the same configuration is obtained.



(+)-α-Phenylpropionamide (+)-α-Phenylethyl amine

This reaction also indicates that the rearrangement proceeds with complete retention of configuration about the chiral centre of the migrating group.

Applications : (*i*) *Primary aliphatic and aromatic amines* : Hofmann reaction provides an efficient route for making both aliphatic and aromatic primary amines from amides containing upto seven carbon atoms, while the higher amides form cyanides which can be converted into amines by reduction.

$$RCONH_2 \xrightarrow{Br_2/KOH} RNH_2$$

where, R = CH_3— to C_6H_{13}—

$$RCH_2CONH_2 \xrightarrow{Br_2/KOH} RCN \longrightarrow RCH_2NH_2$$

where, R = > C_5H_{11}—

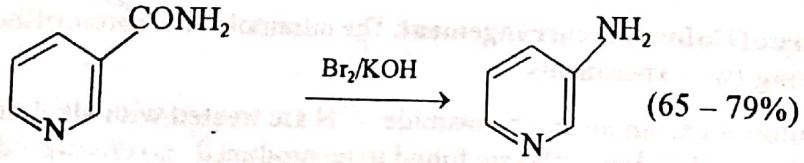
The following type of primary amines can be prepared from the reaction.

(a) *Preparation of methylamine, aniline, benzylamine,* etc.

$$CH_3CONH_2 \xrightarrow{Br_2/KOH} CH_3NH_2 \quad ; \quad C_6H_5CONH_2 \longrightarrow C_6H_5NH_2$$

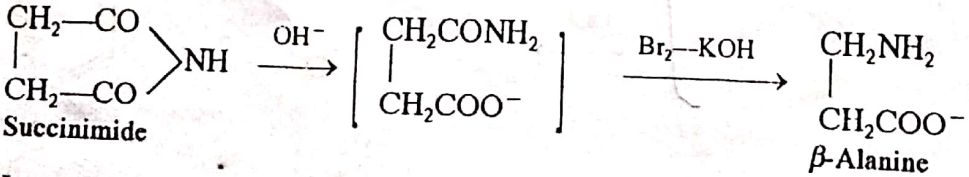
$$C_6H_5CH_2CONH_2 \longrightarrow C_6H_5CH_2NH_2 \; ; \quad \underset{\text{Urea}}{H_2N.CO.NH_2} \longrightarrow \underset{\text{Hydrazine}}{H_2N.NH_2}$$

(b) *Preparation of β-aminopyridine*: β Aminopyridine is prepared from the nicotinamide (available from natural sources), as it cannot be obtained in good yield *via* the nitration of pyridine.



(65 – 79%)

(c) *Preparation of amino acids* : β Alanine *e.g.*, can be obtained in about 45% yield by treating succinimide with bromine and aqueous caustic potash ; reaction occurs through the half amide of succinic acid.



Succinimide β-Alanine

In a similar way anthranilic acid can be prepared from phthalimide.