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OXIDATIVE DEGRADATION OF CIPROFLOXACIN BY CHLORAMINE-T IN ACIDIC MEDIUM – A KINETIC AND MECHANISTIC APPROACH

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Abstract:

The kinetics and mechanism of Ciprofloxacin [CIP] oxidation in $HClO_4$ medium with sodium N- chloro-p-toluene sulfonamide or chloramine-T (CAT) was investigated at 303 K. The rate of reaction was followed by first-order kinetics on [CAT] and [CIP] and inversely proportional to [H+] concentration. Activation parameters were assessed and the reaction was examined at various temperatures. P-toluene sulfonamide addition slows down the rate of reaction. 7-amino fluoroquinolone and p-toluene sulfonamide were the oxidation products detected, and the reaction's stoichiometry was found to be 1: 2. A mechanism and rate law have been proposed to account for the observed results.

Keywords – stoichiometry, kinetics**,** mechanism**,** Activation parameters**.**

I. INTRODUCTION

The long-term presence of various pharmaceuticals in the aquatic environment arises due to huge manufacture by pharmaceutical enterprises. The human intake and excretion of drug residues, as well as the discharge of high quantities of expired drugs by households and hospitals, is a serious issue [1,2]. As a result, the use of significant doses of antibiotics, hormones, analgesics, sedatives, medications, and various disinfectant preparations, as well as the difficulty in completely inactivating them in water treatment, has been a serious issue[3]. The use of polluted water contaminated with pharmaceutical residues and their metabolites disrupts body equilibrium and increases harmful drug resistance, causing major difficulties for human health [4].

Ciprofloxacin (1-cyclopropyl-l–6–fluoro-1,4-dihydro-4-oxo-7-(piperazinyl)–quinolone-3 -carboxylic acid) (CIP) is one of the most commonly used fluoroquinolones in hospitals, where they find their way into the various environmental compartments because there is no regulation of concentration limits for such compounds. **(Fig.1)** depicts the structure of (CIP), which contains piperazine and pyridone moieties. Several investigators have demonstrated CIP oxidation by various oxidants [5-9].

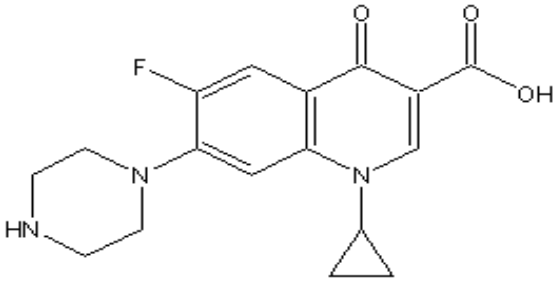


Fig. 1: Structure of Ciprofloxacin

The Sodium N-chloro p-toluene sulfonamide or chloramine –T ($p\text{-}CH_3C_6H_4SO_2NClNa.3H_2O$) or (CAT) is a prominent member of the class of N-halo aryl sulfonamides. In both acidic and alkaline situations, the redox chemistry of N-chloro p-toluene Sulfonamide, also known as chloramine-T, has been widely explored(10,11). However, more work remains to be done to separate Chloramine-T species, in aqueous acidic and alkaline conditions as an oxidant. Chloramine-T species are pH-dependent, and differentiating them in acid media is more difficult due to an interaction of such species governed by several types of equilibrium.

In general, CAT undergoes a two-electron hang in its reactions, yielding p- toluene Sulfonamide or PTS ($p\text{-}CH_3C_6H_4SO_2NH_2$) and sodium chloride as reduction products. Because hypochlorite and CAT can operate as chlorine sources, they are used in the disinfection of drinking water [12,13]. As a result, [CAT] can enter the stomachs of animals, including humans [13]. Under acidic situations in the stomach, antibacterial medications such as CIP can react with [CAT]. As a result, there is a need to understand the drug's oxidation mechanism in the acidic medium so that the study may shed light on the drug's fate in biological systems in vivo. Enzymes [14], N-aryl halo sulfonamides [15], and nanometallic reagents are among the most commonly utilized new reagents for degradation investigations. Chloramine-T (CAT) is well-known for its versatility & its oxidative activity that affects a wide range of characteristic groups to generate molecular changes [16]. Here, oxidative degradation of CIP by Chloramine-T in $HClO_4$ medium is studied. To characterize the degradation products, we used UV and IR studies as supplementary and confirmatory approaches.

II. EXPERIMENTAL

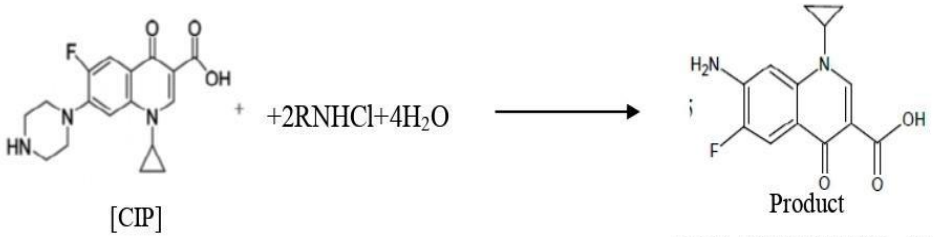
2.1 Chemicals

All chemicals used were of analytical grade. N-Chloro P-Toluene Sulphonamide [CAT] was taken as its Sodium salt (E-Merck). An aqueous solution of chloramines–T [CAT] was prepared and stored in brown bottles to prevent its photochemical degradation. Chloramine–T solution was standardized iodometrically with sufficient accuracy. The Ciprofloxacin [CIP] (Sigma Aldrich) stock solution was prepared by dissolving its requisite quantity into a particular volume of water and also stored in amber-colored glass bottles. Double distilled water was used for preparing all the solutions. Moreover, perchloric Acid ($HClO_4$), Sodium perchlorate ($NaClO_4$), and other reagents were employed as received.

2.2 Kinetic Measurements

All reaction ingredients except CAT were taken in a glass stoppered Erlenmeyer flask painted black from the outside and immersed in a water bath and thermostated at 30±0.1°C and their action was initiated by adding the requisite volume of temperature pre-equilibrated solution of chloramine–T. The process of reaction was followed by measuring the absorbance of unreacted CIP, in the reaction mixture by UV–Visible 3000^{+}(LABINDIA) spectrophotometer at $\lambda_{max=}$278nm as there is no interference of other reagents at this wavelength. After 3-4min. retardation of reaction rates is seen due to one of the reaction products PTS (p–Toluene Sulfonamide) so initial rates are calculated. Calibration curves were plotted to verify Beer's law and the absorptivity values calculated at the respective wavelength is ε=9.083x10^{3}dm^{3}mol^{-1}cm^{-1}[17]. Initial rates were calculated employing the plane-mirror method. The pseudo-first-order plots were made wherever reaction conditions permitted.

The stoichiometry of the reaction was resolved by taking excess CIP over CAT which revealed that the oxidation of each mole of CIP requires for oxidation of two moles of CAT. The final product 7-amino fluoroquinolone was obtained from dealkylation and deamination of piperazine moiety and identified by FTIR results [18] **[Fig.(2)]**. The absorbance peak at 1629 cm^{-1} shows (-C=O stretching),3059 cm^{-1}(-NH_2 stretching), and 3437 cm^{-1} (-OH stretching of –COOH group).



[CIP] Product

$$+ 2\,HCl + 4HCHO + NH_3 + 2RNH_2 \quad (1)$$

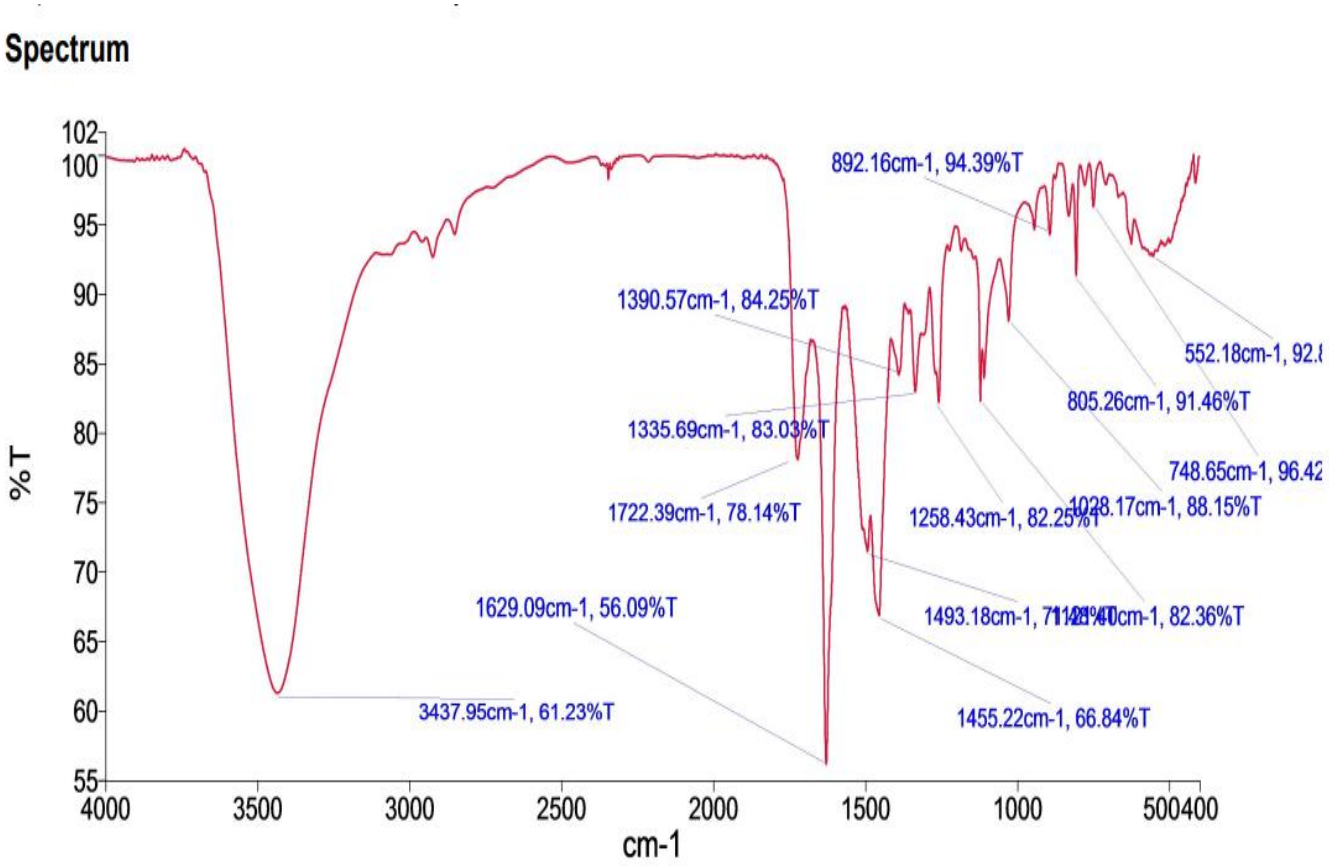


Fig.2 FTIR Spectra of Oxidation Product of CIP & CAT

III. RESULTS

3.1 Dependence on ciprofloxacin

The concentration of CIP was varied from [CIP] =$1x10^{-5}$to$7x10^{-5}$ mol dm^{-3}at two different but fixed concentrations of CAT, viz.$2.0x10^{-4}$and$3.0x10^{-4}$ mol dm^{-3} respectively. Since the rate of reaction is affected by one of their action product PTS, hence, initial rates (k_i, mol $dm^{-3}s^{-1}$) were computed to avoid its interference. The plots of initial rates versus time were prepared that yielded straight lines **(Fig.3)** indicating first-order dependence of rate concerning the drug. Second-order plots were also prepared by plotting log $[CIP]_t/[CAT]_t$ versus time. Second-order rate constants have good agreement calculated from initial rates as well as second-order plots.

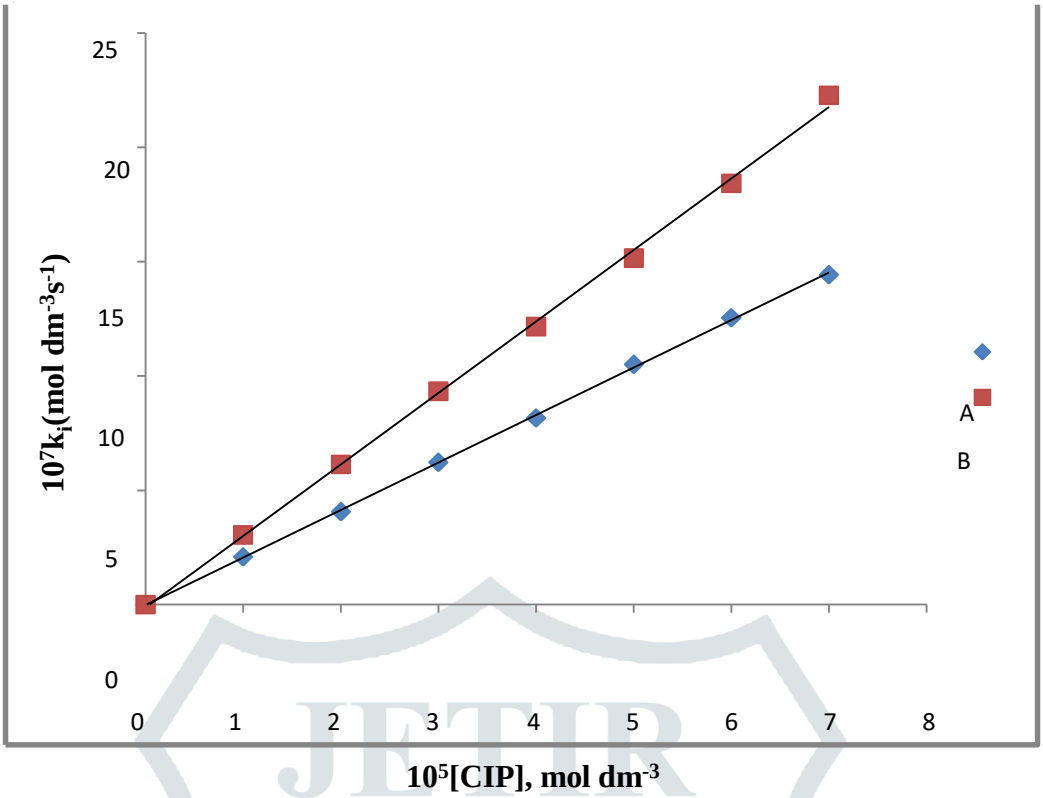


Fig 3: Variation of Ciprofloxacin

[CAT]= (A)2.0 X 10^{-4}mol dm^{-3}(B) 3.0X 10^{-4}mol dm^{-3} [H^+]=1.0 X 10^{-4}mol dm^{-3}

I=2.0 X 10^{-4}mol dm^{-3} ,Temp.= 30^{o}C

3.2 Chloramine –T Dependence

The concentration of [CAT] was varied from 1x10^{-4} to 5x10^{-4} mol dm^{-3} at two but fixed concentrations of [CIP] =4x$10^{-5}$and 5x10^{-5} mol dm^{-3} and all other constant conditions. The plots of initial rates (k_i, mol dm^{-3}s^{-1}) against the concentrations of [CAT] were prepared, which show straight lines passing through the origin these plots confirm first-order dependence of rates concerning oxidant [CAT]**.** Second-order plots were also prepared by plotting log $[CAT]_t$ /$[CIP]_t$ versus time **(Fig.4**). The second-order rate constant calculated from initial rates has good agreement with those obtained from second-order plots.

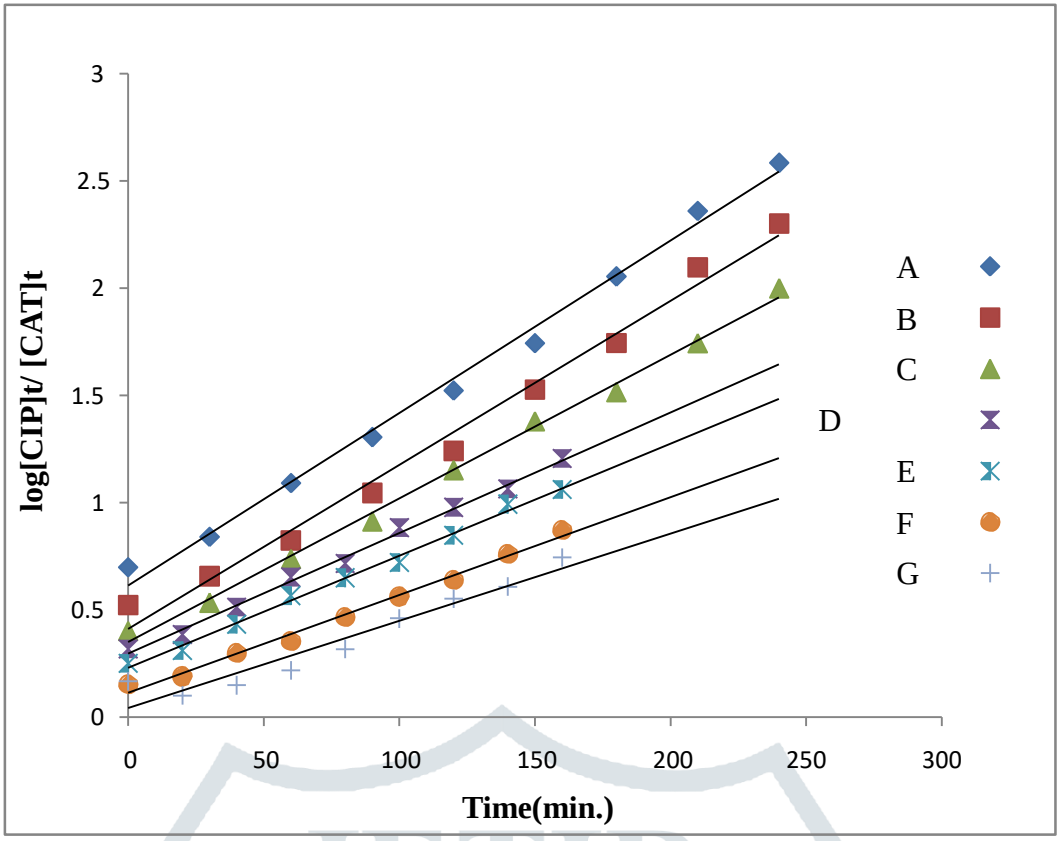


Fig. 4 : Second-order plots of chloramines–T

[CIP]=5.0 X 10^{-5}mol dm^{-3} $[H^+]$=1.0 X 10^{-4}mol dm^{-3} I=2.0X 10^{-4}mol dm^{-3} Temp.= 30°C ·
[CAT] X 10^{-4}mol dm^{-3}= (A)1.0 (B) 1.5 (C) 2.0 (D) 2.5 (E) 3.0 (F) 4.0 (G) 5.0

3.3 Hydrogen ion Dependence

The concentration of $[H^+]$ ion was varied from $[HClO_4]$=1x10^{-4}to1 x10^{-3} mol dm^{-3} at three different temperatures. The rate of reaction was found to be decreased with increasing concentrations of $[H^+]$ ion. The plots of initial rates (k_i, mol dm^{-3} s^{-1}) against the concentrations of $[H^+]$ ion at three different temperatures were prepared. The initial rates k_i are high at low $[H^+]$ ion concentrations but low at middle $[H^+]$ ion concentrations and almost steady at much lower at low$[H^+]$ ion concentrations.

3.4 Ionic Strength Dependence

At constant concentrations of reactants and other conditions, the ionic strength was varied by varying the concentrations of $NaClO_4$ from 1x10-4 to 1 x10^{-3} mol dm^{-3}. The rate of reaction is negligibly affected by ionic strength.

3.5 Effect of added product

Concentration of PTS is varied from 1x10^{-4} to 1x10^{-3}mol dm^{-3}at three different concentrations $[HClO_4]$=1x10^{-4} ,5 x10^{-4} ,1 x10^{-3} mol dm^{-3}. The initial rates were computed and plots of k_i versus concentrations of PTS were prepared at three different concentrations $[HClO_4]$. The rate of reaction decreases with an increase in concentrations of PTS**,** which is regarded to the fact that PTS is involved

with hydrolysis of chloramines-T as an equilibrium step, and due to PTS addition reverse step is increased and inhibits the rates of reaction [19]. Basically, due to this reason $k_{i,}$ the initial rates are taken into account for kinetic studies.

IV DISCUSSION:

4.1 Mechanism

Since the studies show that the rate of reaction is decreased by the PTS, which is a side product of the reaction, it seems that there is an equilibrium between CAT and PTS as well HOCl appears to be the reactive species of CAT. Retardation of rate which is associated with $[H^+]$ also shows that it is involved in a different equilibrium step. As stoichiometric studies show that two moles of CAT react with one mole of CIP, while the order of reaction for both reactants is one, the following mechanism can be suggested for the above-discussed reaction.

$$RNHCl + H_2O \underset{}{\overset{K_1}{\rightleftharpoons}} RNH_2 + HOCl \quad (2)$$

$$[CIP] + HOCl \overset{K_2}{\rightleftharpoons} [C] + [H^+] \quad (3)$$

$$[C] \overset{k'}{\underset{(slow)}{\rightleftharpoons}} [C'] + Products \quad (4)$$

$$[C'] + HOCl \overset{(fast)}{\longrightarrow} [Product] \quad (5)$$

(SCHEME: I)

Here, RNHCl refers to N- Chloro p- Toluene Sulphonamide (CAT), and RNH_2 refers to p-Toluene Sulphonamide i.e. PTS.

4.2 Rate law:

Based on the above mechanism and all the observed studies the rate law can be given below

$$\frac{-d[RNHCl]}{dt} = \frac{2k' K_1K_2 [RNHCl] [CIP]}{[RNH_2] [H^+] + K_1[H^+] + K_1K_2 [CIP]} \quad (6)$$

Since the order concerning [CIP] is unity, hence the above equation (6) can be reduced to the following equation (7)

$$-\frac{d[RNHCl]}{dt} = \frac{2k' K_1K_2 [RNHCl] [CIP]}{[RNH_2] [H^+] + K_1[H^+]} \quad (7)$$

$$-\frac{d[RNHCl]}{dt} = \frac{2k' K_1K_2 [RNHCl] [CIP]}{[H^+] ([RNH_2] + K_1)} \quad (8)$$

The above equation can be further reduced as below (9),

$$-\frac{d[RNHCl]}{dt} \Big/ [RNHCl] [CIP] = k = \frac{2k' K_1 K_2}{[H^+] ([RNH_2] + K_1)} \quad (9)$$

where 'k' is introduced as observed second-order rate constant

Finally, the reciprocal of equation (9) can lead to the rate law as below equation (10),

$$\frac{1}{k} = \frac{[RNH_2] [H^+]}{2k' K_1K} + \frac{[H^+]}{2k' K_2} \quad (10)$$

When 1/k is plotted against $[RNH_2]\,[H^+]$, it yielded a straight line with non-zero intercept). It also confirms the rate law presented as equation (10). The slope and intercept calculated can be given by equations (11), and (12) respectively

$$S = \frac{1}{2k' K_1K_2} \quad .(11)$$

$$I = \frac{[H^+]}{2\,k' K_2} \quad (12)$$

$$\frac{S}{I} = \frac{2k' K_1K_2}{2\,k' K_2\,[H^+]} = \frac{K_1}{[H^+]} \quad (13)$$

(SCHEME II)

When the plot of intercept 'I' versus $[H^+]$ was prepared at 30°C and ionic strength I = 2.0 x10^{-4} mol dm^{-3} it yielded a straight line passing through the origin. The slope calculated from this plot gives the 1 / 2 k' K2 value. The values of k', $K_{1,\text{ and}}$ K_2 calculated from equations (11) and (12) were further employed in equation (9), which were in full agreement with observed values. This also confirms the above rate law. Activation parameters and thermodynamic parameters are also calculated.

V CONCLUSION

The kinetic and mechanistic study of the oxidation of ciprofloxacin by chloramine–T in an acidic medium was investigated. The observed stoichiometry of reaction indicates that one mole of Ciprofloxacin reacts with two moles of Chloramine–T and HOCl was found to be a reactive species of CAT in reaction. The final product obtained by dealkylation of piperazine moiety of ciprofloxacin which has antimicrobial activity as having fluoroquinolone ring structure intact and hence can play an important role in wastewater treatment. The kinetic studies show first-order dependence concerning ciprofloxacin as well as chloramines-T, and H^+ plays a significant role in the rate of oxidative transformation. The value of second order rate constant was inversely proportional to $[H^+]$ as well as [PTS] concentration, and the reaction does not follow the free radical pathway. Thus, the present investigation widens the knowledge about the applicability of CAT for kinetic and mechanistic studies of oxidative transformation reactions.

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