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Research Article

PHARMACOLOGICALLY ACTIVE N-CHLOROISONICOTINAMIDE IN THE KINETIC STUDY OF OXIDATION OF P-METHYLBENZALDEHYDE DI-N-BUTYL ACETAL

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ABSTRACT

N-chloroisonicotinamide (NCIN), has been found to possess pharmacological activity. It has significant effect on locomotor activity, when compared with the standard drug Chlorpromazine. The results of gross behavioral assessment indicates that the active compound produce a depressant effect on the central nervous system. The compound, NCIN has significant anti-convulsant action against MES induced convulsion, when compared with the standard drug phenytoin. The kinetic study of oxidation of an aromatic diether, p-methylbenzaldehyde di-n-butyl acetal by the pharmacologically active N-halo compound, N-chloroisonicotinamide, has been carried out. The reaction follows first order dependence of rate on [substrate] and [oxidant]. The rate increases with the decrease in dielectric constant of the medium. Variation of ionic strength and the addition of isonicotinamide has significant effect on the reaction rate. The stoichiometry and product analysis have been carried out. From the effect of temperature on the reaction rate, the Arrhenius and thermodynamic activation parameters have been calculated.

Keywords: N-chloroisonicotinamide, locomotor activity, anti convulsant action, acetal, kinetics.

INTRODUCTION

N-chloro compounds are synthesized, characterized and used as versatile reagents in kinetic studies and organic synthesis. The compound N-chloroisonicotinamide (NCIN), prepared by the chlorination1 of isonicotinamide, offers many advantages like easy method of synthesis, easy handling, low toxicity and mild nature with appreciable stability. N-chloroisonicotinamide, the oxidant in the present study, has been found to possess pharmacological activity. The pharmacological activity of NCIN and the subsequent utility as an oxidant for the organic compounds have not been reported so far. Hence a general review involving isonicotinamide had been given as a background for the present study. A comparative rate study on the oxidation[2] of nicotinamide and isonicotinamide by permanganate in acidic medium has been carried out . The oxidation of nicotinamide is reported to be faster than the oxidation of isonicotinamide. It has been reported that the presence of–CONH2 group at meta- position activates the ring nitrogen more for oxidation than the presence of this group at para-position. It has been reported3,4that N-cyanomethyl-2-chloroisonicotinamidederivative induces a broad range of disease resistance in rice and tobacco andN-phenylsulphonyl-2-chloroisonicotinamide shows high protective systemic activity against rice blast when applied in granulated form. Crystallization5 of α,ω-alkane dicarboxylic acids with isonicotinamide (INA) in1:2 and 1:1 stoichiometry has been studied. Supramolecular synthons6 in phenol-isonicotinamide adducts have also been studied. Experimental thermo chemical study[7] of the enthalpies of

formation and sublimation of isonicotinamide, picolinamide, nicotinamide, isonicotinamide-N-oxide andnicotinamide-N-oxide have been studied.

Acetals play a vital role in bio-organic research in exploring biological activities8 (antimalarial, antiviral etc.). The most stable form of glucose in solution is its cyclic hemiacetal. Acetaldehyde diethyl acetal is an important flavouring compound in distilled beverages. Acetal polymers (polyacetals) are tough and hard plastics used as substitutes for metals. Acetals are sometimes used as protecting group for carbonyl groups in organic synthesis as they are stable with respect to hydrolysis by bases. Acetal molecules are used as intermediates for the production of polymers, vitamins, carotenoid pigments, dyes, pharmaceuticals, pesticides, corrosion inhibitors, fragrances and perfumes. The acetal group plays an important role in glycoside and in the side-chain of steroids. Simple acetals do not seem to occur in nature.

The pharmacological activity of NCIN and the kinetic study of oxidation of p-methylbenzaldehyde di-n-butyl acetal by NCIN has been carried out in the present investigation.

Pharmacologically active NCIN in the kinetic study of oxidation

Materials and methods

Pharmacological evaluation of the N-chloroisonicotinamide (NCIN) wascarried out in the Department of Pharmacology, Periyar College ofPharmaceutical Sciences for Girls, Trichy, Tamil Nadu, India. Animal facilityof this institute is approved by CPCSEA (Reg. No. 265/CPCSEA). Theexperimental protocols for the antidiabetic, antiulcer, anti-inflammatory,diuretic, local anaesthetic, sedative and hypnotic, locomotor, antianxiety andantiepileptic activities have been approved by the Institutional Animal EthicsCommittee and conducted according to the guidelines of Indian NationalScience Academy for the use and care of experimental animals. The animalswere maintained at a well ventilated, temperature controlled animal room forseven days prior to the experimental period and provided with food and water.The animals were acclimatized to laboratory conditions before the test. Eachanimal was used only once. The animals were allowed free access to food andwater and were housed at room temperature. All the test compounds were administered via intra peritoneal injection in distilled water with Tween 80solution. For the kinetic study of oxidation of p-methylbenzaldehyde di-n-butyl acetal by the pharmacologically active oxidant, N-chlorosisonicotinamide, acetonitrile was used as a solvent. The oxidant, N-chloroisonicotinamide was prepared by the chlorination of isonicotinamide. NCIN was characterized by 1H-NMR spectra.

Acetals are gem-dialkoxy compounds9,10and they are formed by the nucleophilic addition of the alcohol to the carbonyl group of an aldehyde producing a hemiacetal which reacts further with another molecule of alcohol to give the acetal in the presence of a catalyst.

The substrate p-methylbenzaldehyde di-n-butyl acetal was prepared by the method described in the literature11,12. The required quantities of the acetal solution, sodium perchlorate and acetonitrile-water mixture were pipetted out in a clean dried reaction bottle, kept in thermostat for about half an hour, set at the desired temperature. The reaction was started by pipetting out the required quantity of NCIN solution, which had also been thermostated for nearly half an hour. The total volume of the reaction mixture was always 25 ml. About 3 ml of reaction mixture was pipetted out into the conical flask and the progress of the reactionwas followed iodometrically.

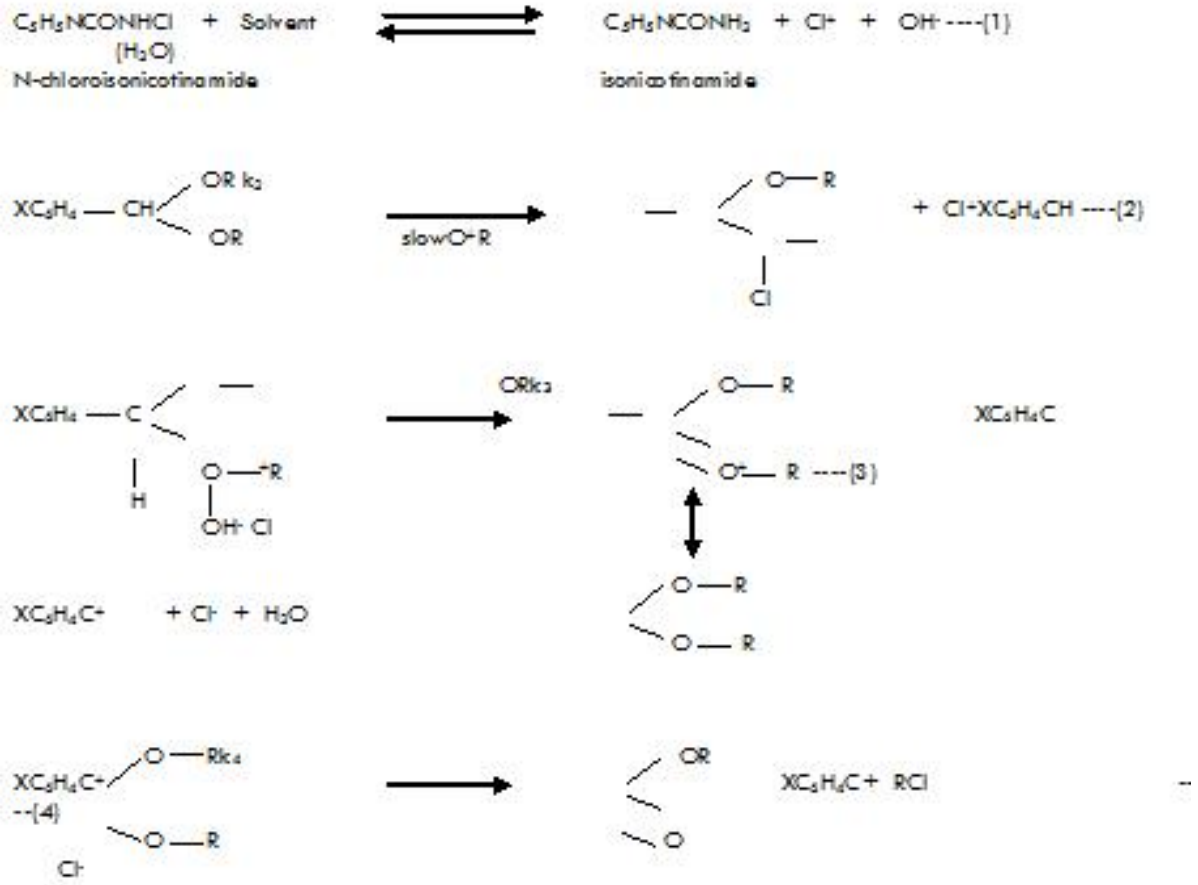
The stoichiometry was found to be 1:1. The product of oxidation, the corresponding ester was confirmed by TLC and 1H-NMR spectrum.

RESULTS

Locomotor activity

Most of the central nervous system acting drugs influence the locomotoractivities in man and animals. The central nervous system depressant drugs such as barbiturates and alcohol reduce the locomotor activity while thestimulants such as caffeine and amphetamine increase the activity. In otherwords, the locomotor activity can be an index of wakefulness (alertness) ofmental activity. The locomotor activity (horizontal activity) can be easily measuredusing an actophotometer13 which operates on photoelectric cells which areconnected in circuit with a counter. When the beam of light falling on thephotocell is cut off by the animal, a count is recorded. Actophotometer couldhave either circular or square area in which the animal moves. Both rats andmice can be used for testing in this equipment. Actophotometer

Figure 1 Mechanism for the kinetic study of oxidation of p-methylbenzaldehyde-di-n-butyl acetal by NCIN



R = n-butyl, X = *p*-CH3

Assuming Cl^+ as the effective oxidizing species, the rate law is given as follows:

$$\frac{-d[NCIN]}{dt} = \frac{k_1 k_2 [XC_6H_4CH(OR)_2]\,[NCIN]}{k_{-1}[NA]}$$

The above rate law accounts for the first order dependence on [NCIN] and [acetal]. This also explains the retardation in the rate by the addition of isonicotinamide.

Table 1 Effect of NCIN on locomotor activity

S. No	Drug Used	Before Administration	After Administration
1.	Vehicle 5 ml/kg	48.0 ± 1.22	46.28 ± 1.18
2.	Chlorpromazine HCl (3 mg/kg)	44 ±1.18	7.22 ± 1.02
3.	Test drug (30 mg/kg)	52.2 ± 1.04	22 ± 1.12

Table 2 Effect of NCIN on anti-convulsant activity

S.No.	Treatment	Phase of Convulsions				Recovery / death
		Flexor (Sec)	Extensor (Sec)	Clonus (Sec)	Stupor	
1.	Vehicle	6 ±0.18	15 ± 0.012	22 ± 0.18	211 ± 0.18	Recovered
2.	Phenytoin (25 mg/kg)	2 ± 0.10	--	8 ± 0.08	72 ± 0.12	Recovered
3.	Test compound (30 mg/kg)	4 ± 0.12	2 ± 0.10	18 ± 0.04	81 ± 0.12	Recovered

Table 3 Effect of variation of [substrate], ionic strength and solvent composition on the rate of the reaction

$X\text{-}C_6H_4\ CH(OC_4H_9)_2\ x10^2$ (M)	$[NCIN]x10^3$(M)	$[NaClO_4.H_2O]x10^3$ (M)	$CH_3CN - H_2O$% (v/v)	Temp. (K)	$k_1\ x10^4\ (s^{-1})$
4.0	6.0	1.0	90-10	323	3.55
6.0	6.0	1.0	90-10	323	5.37
8.0	6.0	1.0	90-10	323	7.89
10.0	6.0	1.0	90-10	323	9.68
12.0	6.0	1.0	90-10	323	11.82
8.0	6.0	1.0	88-12	323	4.49
8.0	6.0	1.0	89-11	323	5.92
8.0	6.0	1.0	90-10	323	7.89
8.0	6.0	1.0	91-09	323	8.88
8.0	6.0	1.0	92-08	323	10.49
8.0	6.0	1.0	90-10	323	7.89
8.0	6.0	2.0	90-10	323	9.21
8.0	6.0	3.0	90-10	323	11.40
8.0	6.0	4.0	90-10	323	12.58

Table 4 Effect of temperature on the rate of oxidation of p-methylbenzaldehyde-di-n-butyl acetal by NCIN andevaluation of Arrhenius and thermodynamic activation parameters

$[X\text{-}C_6H_4\ CH(OC_4H_9)_2$ = $8.0x10^{-2}$ M $[NaClO_4.H_2O]$ = $1.0\ x10^{-1}$ M
[NCIN] = $6.0\ x10^{-3}$ M Solvent (v/v) = 90% CH_3CN - 10% H_2O

$X\text{-}C_6H_4\ CH(OC_4H_9)_2$	$k_2\ x\ 10^3(s^{-1})$				Ea (kJ mol^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J $K^{-1}mol^{-1}$)	$\Delta G^{\neq}$ (kJ mol^{-1})	log A
	318 K	323 K	328 K	333 K					
X = p-CH_3	6.76	9.86	13.80	19.86	62.80	60.11	-42.51	73.84	8.15

was used to evaluate the locomotor activity. The Swissalbino mice (20-25 g) were divided into eight groups each consisting of sixanimals. The test compound was injected intraperitoneally (i.p). One groupreceived standard Chlorpromazine 3mg/kg and one group receivedvehicle (normal saline 5 ml / kg i.p). All the remaining six groups received N - chloroisonicotinamide (30mg/kg) intraperitoneally. The locomotor activityscore of all the animals was noted by placing the animals in the square area ofthe instrument for ten minutes. Each mouse was retested for activity score afterthirty minutes of the test drug administration. The difference in the activitybefore and after the administration of standard and test compounds was noted (Table 1).

Anti-convulsant activity

The animals were weighed and numbered. They were divided in to three groups, each consisting of six rats. The animals were held properly, corneal electrode was placed on the cornea and the prescribed current is applied. The different stages of convulsions14 i.e., tonic flexor, tonic extensor phase, clonic convulsions, stupor and recovery or death were noted. The same was repeated with other animals of control group. Phenytoin was injected intraperitoneally to the second group and test drug (30 mg/kg) was injected to third group. After thirty minutes, the animals were subjected to electro convulsions as described. The reduction in time or abolition of tonic extensor phase of MES-convulsionswas noted (Table 2).

Kinetic study of oxidation of p-methylbenzaldehyde di-n-butyl acetal by NCIN

The kinetic and mechanistic aspects of the oxidation of acetalby N-chloroisonicotinamide have been examined. Alkyl benzoate is the major product of oxidation. Kinetics is followed by iodometric procedure, i.e. by following the disappearance of NCIN iodometrically in aqueous acetonitrile medium at constant ionic strength. The reactions have been followed under the condition, where the concentration of the acetal is in large excess compared to that of NCIN.

The kinetics of oxidation of acetals by NCIN in aqueous acetonitrile medium at a constant ionic strength corresponding to 0.1 M NaClO4.H2O is investigated at several initial concentrationsof the reactants. Linear plots of log [NCIN]t vs time shows first order dependence of the rate on [NCIN].

The dependence of rate on acetal concentration has been determined by measuring the first order rate constants for NCIN disappearance for a wide range of acetal concentrations at 50 oC. The pseudo-first order rate constants are found to increase (Table 3) linearly with the increase in [acetal]. Plots of log k1 vs log [acetal] give straight line with unit slope confirming the first order dependence of rate on [acetal].

The influence of solvent dielectric constant on the rate of NCIN oxidation of acetal has been studied in various solvent mixtures of acetonitrile and water. The rate of oxidation increases with the increase in acetonitrile content of the solvent mixture (Table 3). The plots of log k1 vs 1/D are linear.

The influence of variation of ionic strength on the rate of oxidation has been studied by varying the concentrations of [NaClO4.H2O]. The reaction rate increases (Table 3) with the increase in ionic strength of the medium. The effect of one of the products of the reaction on the rate of oxidation has been studied by adding various concentrations of isonicotinamide, keeping the concentrations of acetal and NCIN constant. There is a decrease in the reactivity with the increase in the initially added concentration of isonicotinamide.

The oxidation of acetal has been studied at four different temperatures (318 K to 333 K). The temperature dependence on the rates of oxidation is determined by plotting log k2 against reciprocal of temperature. The second order rate constants at differenttemperatures at constant ionic strength for the NCIN oxidation of acetals underinvestigation are recorded in Table 4. The Arrhenius activation energy,pre-exponential factor, entropy, enthalpy and free energy of activation havebeen evaluated for all the acetals and the values are listed in Table 4.Addition of the reaction mixture to acrylonitrile do not initiatepolymerization, showing the absence of free radical species.

DISCUSSION

N-chloroisonicotinamide has significant effect on locomotor activity when compared to the standard drug. The results of gross behavioral assessment indicated that the active

compounds produced a depressant effect on the central nervous system. The animals were still responsive and did not exhibit any prominent muscle relaxation. This may be responsible for the modification of mesolimbic system15.

The given sample produced the loss of extensor phase in MES induced electro convulsion as like standard phenytoin and also time spent by the animals in different phases of convulsion is also reduced when compared to control. Hence, it indicates that the given sample has significant anti-convulsant action against MES induced convulsion16.

It seems that the results of NCIN oxidation of acetal in the present investigation can be accounted for, by identifying the rate-determining step in the Deno and Potter17 mechanism for the oxidation of ether by bromine and

Pharmacologically active NCIN in the kinetic study of oxidation introducing slight modification to Gopalakrishnan et al[18] mechanism for the oxidation of alcohols by N-bromosuccinimide. A probable mechanism may involve electrophilic attack of the positive part of oxidising species on the electron – rich oxygen atom of acetal rather than on the electron – deficient aldehydic hydrogen.The mechanism has been proposed assuming Cl+ as the oxidizing species.

Solvent consists of a mixture of acetonitrile and water. The reactive oxidizing species may be Cl+ or solvated Cl+. The reactive species formed in the above equilibrium step attacks the acetal molecule in the rate-determining step (2).

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