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Spectral and biological characterization of N,N-diethyl-2-hydroxyethanaminium 5-(5-chloro-4,6-dinitro)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate hemihydrates

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Abstract:-- **A new type of barbiturate (a pyrimidine derivative) has been prepared through one pot synthesis from the ethanolic solution of 1,3-dichloro-4,6-dinitrobenzene, pyrimidine-2,4,6 (1H,3H,5H)-trione and N,N diethylhydroxylamine. The mechanism of the formation of the reported barbiturate involves an intermediate sigma complex formation and proton abstraction reactions. The barbiturate has been characterized spectrally through (UV–VIS, IR, ^{1}H NMR, ^{13}C NMR, mass) and elemental analysis. Qualitative tests have been carried out to infer the presence of nitrogen and nitro groups and also chlorine atom in the barbiturate.The anticonvulsant activity of the complex has been studied. The complex uniquely dissolve in water freely possess high LD50 (>1500 mg/kg) and extraordinarily stable.**

Key words: **1,3-dichloro-4,6 -dinitrobenzene , pyrimidine-2,4,6 (1H,3H,5H)-trione , N,N- diethyl hydroxylamine Anticonvulsant activity Hypnotic activity.**

I. INTRODUCTION

The unique chemistry nitro group has led to the use of several nitro aromatic compounds in the synthesis of many diverse products including drugs[1-3] dyes [4,5]and high energy explosives [6,7]. These nitro aromatic compounds are electro-deficient and undergo reaction with electron rich species readily during which intense colour is obtained.This article focuses on a new type of carbanionic sigma complexes derived from 1,3-dichloro-4,6-dinitrobenzene (DCDNB) and barbituric acid (BA) in the presenceof N,N diethylhydroxyamine . Epilepsy (convulsion) the second most common neurological disorder after stroke, which is characterized by recurrent seizures affecting atleast 50 million persons worldwide [8]. Barbiturates (derivatives of barbituric acid) were widely used clinically for a range of indications including treatment of anxiety, insomnia, seizure disorders, sleep disorders, muscle spasm and they have proven useful in anesthesia and in localizing brain dysfunction prior to neurosurgery. These drugs have enjoyed a central place in the pharmacopoeia of CNS drug current clinically available drugs have shown significant side effects, narrow therapeutic indices and are difficult to formulate [9,10] . Hence, the search for new antiepileptic drugs continues to be an active area of medicinal chemistry research. The newly synthesized carbanionic sigma complexes of the present investigation are barbituric acid derivatives (barbiturates) exhibiting anticonvulsant activity even at low concentration (25 mg/ kg).

EXPERIMENTAL
MATERIALS AND INSTRUMENTATION

All the chemicals used were of pure grade. 1,3-dichloro-4,6-dinitrobenzene (*DCDNB*) [11] was synthesized according to the reported procedures.[12] The UV-Visible data were obtained on a Shimadzu *UV/VIS* 1800 spectrophotometer. The *IR* spectra were recorded using Perkin-Elmer RXI infrared spectrophotometer using KBr pellets. *^{1}H NMR* and *^{13}C NMR* spectra were obtained from Bruker DRX-500 MHz spectrometer with (*DMSO-d_6*) as a solvent and TMS as an internal reference.

Preparation of N,N-diethyl-2-hydorxyethanaminium 5-(5-chloro-2,4-dinitrophenyl)-2,6-dioxo-1,2,3,6 –tetrahydropyrimidin-4-olate:
DCDNB (2.37g, 0.01mol) in 15 ml absolute ethanol was mixed with barbituric acid (1.28g, 0.01 mol) in 30ml of absolute ethanol. N,N-diethyl ethanolamine (2.36g,0.02 mol) was added to the above mixture at 313 k and shaken well for

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Vol 2, Issue 12, December 2017

5-6 hrs. The solution was filtered and kept as such atroom temperature for 48 hrs. On standing maroon red colour crystals come from the solution. The crystals were powdered well and washed within copious amount of ethanol and dry ether and recrystallized from absolute alcohol (yield of pure crystals 80 % , m.p. 503 K). Good quality crystals (maroon red for single crystal X-ray studies were obtained by slow evaporation of ethanol at room temperature.

SPECTRAL DATA:

Red crystalline solid; yield: 80%; m.p. 230·C; ^{1}H NMR (500 MHz, DMSO – d^{6}) 9.70 (s, 2H, two N–H protons), 8.91 (br, s, 1H) N–H of N,Ndiethyl-2-hydroxyethanaminium cation), 8.38 (s, 1H, ring proton), 8.33 (s, 1H, ring proton), 5.33 (s, 1H, -OH proton of N,N-diethyl-2-hydroxyethanaminium cation), 3.71 (t, 2H, -CH2 protons of CH_2 OH of N,N-diethyl-2-hydroxyethanaminium cation), 3.14 (br, s, 6H, -CH_2 protons of N,N-diethyl-2-hydroxyethanaminium cation), 1.19 (t, 6H, –CH3 protons of N,N-diethyl-2-hydroxyethanaminium cation); ^{13}C NMR(500 MHz, DMSO-d ^{6}), δ (ppm): 163.6, 151.5, 144.9, 134.1, 127.8, 123.2, 86.2, 55.6,), δ (ppm): 163.6, 151.5, 144.9, 134.1, 127.8, 123.2, 86.2, 55.6, 53.3, 47.3, 8.9; IR (KBr) (cm^{-1}) 3500-2200 (br, characteristic of amine salt), 1701(s, sh, –C=O str.), 1602 (s, sh, NO_2 group asym. str.), 1353 (s, sh, NO_2 sym. str.), 1147 (s, sh, C–O str.), 800(s, sh, C–Cl), 528 (s, sh, torsional oscillation – cation moiety); UV-Vis: DMSO (485 nm), ethanol (430 nm), water (397 nm); solubility in water (1.9 g/100 mL). HRMS calcd.for $C_{16}H_{20}N_5O_8Cl$ [M+K] +: 484-0637, found: 484.0652.

RESULT AND DISCUSSION

Spectral Characterization of N,N-diethyl-2-hydorxyethanaminium 5-(5-chloro-2,4- dinitrophenyl)-2,6-dioxo-1,2,3,6 –tetrahydropyrimidin-4-olate:

The reaction between DCDNB and barbituric acid in presence of tertiary amine are depicted in the mechanism. As barbituric acid contains active methylene compound it readily yields a carbanion in presence of base . The carbanion readily attacks the carbon atom which bears chlorine atom of electron-deficient chloronitroaromatic compound (DCDNB). The good leaving ability of chlorine atom is the main driving force of such attack. This aromatic nucleophilic substitution reaction an electron withdrawing chloronitrophenyl moiety is introduced at the 5 position of barbituric acid is made highly acidic . Abstraction of this proton results in the carbanionic sigma complexes .The synthesized carbanionic sigma complex comprises of anion and cation entities and thus molecular salts since they are derivatives of barbituric acid also known as barbiturates.

The carbanionic sigma complex derived from DCDNB and barbituric acid in thepresence of N,N-diethyl-2-hydroxyethanamine is also coloured maroon red and shows absorption at a longer wavelength (430 nm) than DCDNB (255 nm). In the IR spectrum of N,N-diethyl-2-hydroxyethanamine a broad band characteristics of –OH stretching mode, involved in intermolecular hydrogen bonding, appears at −3367 cm^{-1} Whereas in the carbanionic sigma complex a broad band characteristics of amine salts[12] appears between 2200-3500 cm^{-1}.The sharp band at 528 cm^{-1}corresponds to torsional oscillation of amine salt . The sharp band at 1051 cm^{-1} corresponding to C-N stretching frequency of N, N-diethyl-2-hydroxyethanamine is shifted to frequency region 1072 cm^{-1} may probably due to protonation of the nitrogen atom of N,N-diethyl-2-hydroxyethanamine function during the formation of carbanionic sigma complex. In the PMR spectrum of N,N-diethyl-2-hydroxyethanamine, the methyl proton signal appears at δ 0.9 whereas in the carbanionic sigma complex it is shifted to low field (δ 1.19). The protons of methylene group attached to nitrogen atom of N,N-diethyl-2-hydroxyethanamine appears at δ 2.4, however ,in the sigma complex they are shifted to down field (δ 3.14) evidencing the protonation of nitrogen atom of N, N-diethyl-2-hydroxyethanamine during the formation of sigma complex . Due to the interaction with neighbouring quadrupole atom (N), the signal appears broad. In the PMR spectrum of the carbanionic siogma complex a signal corresponding to –OH group appears at δ 5.33 indicating that –OH group is protonated during the formation of the complex. In the ^{13}C NMR spectrum of carbanionic sigma complex four lines are observed corresponding to the cation. The peak at δ 86.27 is that of newly formed carbon [13]. In the high resolution mass spectrum of cabanionic sigma complex. The molecular ion peak is observed at m/z 484 (M+39) explicitly indicates the formation of carbanionic sigma complex.

Anticonvulsant activity of carbanionic sigma complexes (barbiturates) against maximal electroshockinduced convulsion in albino rats

S. No	Treatment	Time (sec) in various phases of convulsion				
		Flexor	Extensor	clonus	stupor	Recovery/ death
1.	Control Normal Saline (5ml/kg)	12 ± 1	21 ± 1.5	35 ± 2.5	168.3 ± 4.13	Recovered
2.	25mg/kg		2.0±0	13±2.	197±6.	Recovere

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		3±0.5	.7	4	3	d
3.	Phenobarbitone 20 mg/kg	2.2±0.08	--	16.5±0.23	58.14±2.34	Recovered

Mean ± S.E.M, N = 6, P< 0.001 Vs standard

Hypnotic action of carbanionic sigma complex (barbiturate)

S. No	Sample	Dose (mg/kg)	Time of Administration (mins) (a)	Time of loss of reflex (mins) (b)	Time of Recovery (mins) (c)	Onset of action (mins) (b-a)	Duration of action (mins) (c-b)
1.	**Control (Saline)**	0	--	--	--	--	--
2.	**Complex**	100	0	37.90 ± 4.4	116.8 ± 4.6	37.90 ± 4.4	78.9
3.	**Pentobarbitone**	20	0	26.8 ± 1.42	168.36 ± 6.4	26.8 ± 1.42	131.56

Mean ± S.E.M, N = 6, P< 0.001 Vs standard

PHARMACOLOGY

In Maximal electroshock method [14, 15], the reduction or abolition of various phases of convulsion (flexor, extensor, clonus and stupor) is taken as the measure of anticonvulsant activity. In the present investigation among the carbanionic sigma complexes derived using N, N-diethyl-2-hydroxyethanamine have quiet appreciable amount of anticonvulsant activity as they abolish the clonus phase of convulsion even at low concentration (25 mg /kg). This implies that only the barbiturate anion part but also the cation part plays an important role in the modulating the chloride ion channels, resulting in the enhanced anticonvulsant activity.

ACUTE TOXICITY

Acute toxicity studies on the carbanionic sigma complex fall under class 4 (LD50>1500mg).
The animals did not show any behavioral changes.

CONCLUSION

Aromatic nucleophile substitution results in the formation of molecular slat from 1, 3-dichloro-4, 6-dinitrobenzene, barbituric acid and N, N-diethyl-2-hydroxyethanamine.The product formed in appreciable amounts with high purity through one pot synthesis. Well-developed good quality crystals were obtained by slow evaporation of alcohol. They are non-hygroscopic solids, very stable at room temperature and soluble in water.

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