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Review Article

# Chemistry Of Mesoionic Sydnones As Versatile Heterocyclic Compounds

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**Abstract**

Sydnones are mesoionic heterocyclic aromatic compounds. They have been widely studied for some important biological activities like antiviral, antitumor, antimicrobial, anti-inflammatory, anticancer, analgesic, anthelmintic and antihypertensive activities. The aim of the present article is to review the available information on sydnones and the derivatives of sydnones and also a look at the future perspectives. Sydnone can be defined as a five-membered pseudo-aromatic heterocyclic molecule. Classically, 1,2,3-oxadiazole forms the main skeleton of sydnone. The molecule has delocalized balanced positive and negative charges. The five annular atoms share the positive charge and the enolate-like exocyclic oxygen atom bears the negative charge. The hydrogen atom at the position C4 was proved to have acidic and nucleophilic functionalities making the sydnone ring reactive towards electrophilic reagents. These unique chemical features enable sydnones to interact with biomolecules resulting in important therapeutic effects like anticancer, antidiabetic, antimicrobial, antioxidant and anti-inflammatory. Consequently, we aim from the current article to review the available chemical and pharmacological information on sydnone and its derivatives.

**Keywords:** Sydnone, Mesoionic, Heterocycles, imines, biological activity.

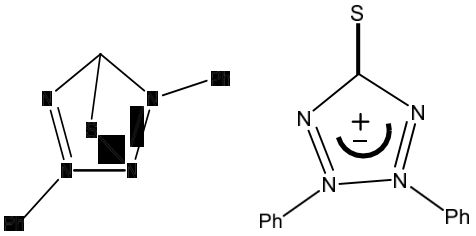
## Introduction

Sydnones are mesoionic heterocyclic chemical compounds possessing a 1,2,3-oxadiazole core with a keto group in the 5 position.[1-3] Like other mesoionic compounds they are di-polar, possessing both positive and negative charges which are delocalized across the ring. Recent computational studies have indicated that sydnones and other similar mesoionic compounds are nonaromatic, "though well-stabilized in two separate regions by electron and charge delocalization."[4]A sydnone imine in which the keto group of sydnone (=O) has been replaced with an imino (=NH) group can be found as a substructure in the stimulant drugs feprosidnine and mesocarb. Sydnones are the most studied compounds amongst the mesoionic family due to their interesting structures, chemical properties, synthetic utility and biological activities. Many reports stated that one covalent structure is not sufficient to represent the sydnone molecule satisfactorily. However, 1,2,3-oxadiazolium bearing a carbonyl function has recently been the major representative of sydnones because FTIR spectroscopy showed a carbonyl stretch frequency attached to C5 of the ring like in 4-acetyl-3-tolylsydnone which exhibited a strong band at 1783 $cm^{-1}$. X-ray analysis revealed a bond length of 1.196 Å which corresponds to an exocyclic C=O double bond. Classically, the sydnone ring can be prepared from the cyclization of *N*-nitroso amino acids with acetic Anhydride[5]. Later, many attempts were employed to improve the yield of cyclization by using a stronger dehydrating agent such as trifluoroacetic acid anhydride or thionyl chloride[6]. Since their first preparation, sydnones attracted the attention of medicinal chemists and pharmacologists to investigate their biological applications. Their distinguished chemical structure enables them to bind and deactivate a variety of biomolecules like DNA and enzymes. A vast range of therapeutic properties has been demonstrated including antimicrobial, anti-inflammatory, anti-cancer, antioxidant and antidiabetic[7]. The present review demonstrates the important chemical and biological data on

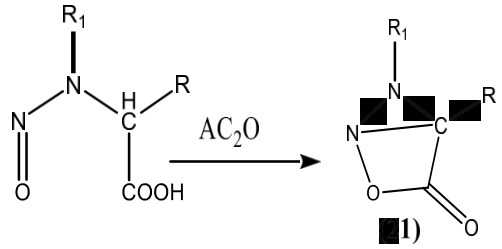
sydnones starting from their early discovery in 1935 until today.

**Chemistry of Sydnone**

Over 120 years ago, Emil Fischer oxidized dithizone; yielding an orange, crystalline compound he entitled dehydrodithizone. Fischer assigned the bicyclic structure to this species however, better understanding of the nature of such species was gained as time progressed and more advanced analytical techniques became available. In 1946, Baker, Ollis, and Poole coined the term mesoionic (mesomeric/ionic) to describe the monocyclic, dipolar nature of compounds such as dehydrodithizone. In 1955, these three authors published a paper in Chemistry and Industry which specifically defined the term mesoionic. Using their definition, dehydrodithizone is considered the first known mesoionic species and is assigned the dipolar, monocyclic structure.[8] A significant portion of the research in heterocyclic chemistry has been devoted to sydnones containing different moieties, as evident from the literature.[9-10] Sydnones have played a crucial role in the development of theory in heterocyclic chemistry and have been used extensively as synthons in organic synthesis. Sydnone are unique, dipolar, heteroaromatic member of the general class of mesoionic compound. Their derivatives are associated with an array of physiological activities. It is also reported that the ionic resonance structures of the hetericyclic ring of sydnones promote significant interactions with biological molecules, which also fulfill many of the spatial and electronic requirements ascribed to their biological activities.

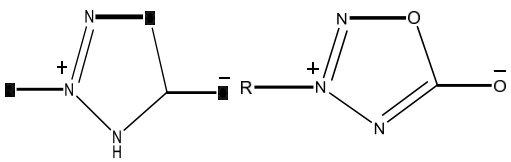



The lactone, which is a 1,2,3-oxadiazole-5-one heterocycle was named as Sydnone in honour of University of Sydney (Sydney + lactone) where it was prepared for the first time by Earl and Mackney in 1935. Earl and Mackney reported that treatment of *N*-nitroso-*N*-phenylglycine.



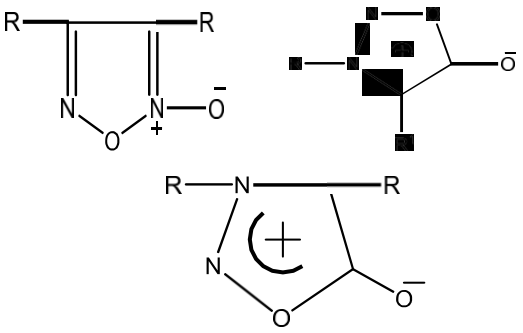

(structure 20,R=H, R'=Ph) with acetic anhydride afforded a neutral, anhydro derivative to which the bicyclic structure (structure 21, R=H, R=Ph) was assigned.

Baker, Ollis and Poole showed that the assigned structure for sydnones was incorrect and that they were actually monocyclic, dipolar oxadiazolone derivatives with many resonance forms contributing to the resonance hybrid, designated using representation. With regard to the cyclodehydration step, Earl and Mackney originally employed acetic anhydride at room temperature for six days. Since then, several modifications have been forthcoming and now include: heating in acetic anhydride or thionyl chloride, treatment with phosphorus pentoxide or the use of trifluoroacetic anhydride (TFAA). The reaction with TFAA has become the method of choice since it usually occurs rapidly (<15 minutes), at low temperature (-5 °C to 0 °C) and in high yields (> 90% for N-phenylsydnone). The only foreseeable drawback to its use is the far greater cost of this reagent compared to the others. Some alkyl sydnones with a functional group in the side chain are extensively decomposed by hot acetic anhydride. Hahn et al. Synthesized sydnone compounds by the ultrasonic technique in 1987. Two main types, depending formally upon the origin of the electrons in the system, have been identified, they are exemplified by compound (22) and (23).



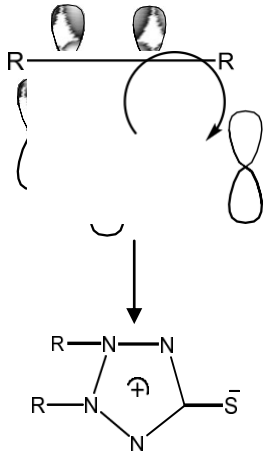

In structure the nitrogen and oxygen atoms, 1,3 to each other, are shown as donating two electrons each other to the total of eight electrons in the whole π systems, where as in structure the two middle nitrogen atoms, 1,2 to each other, are the two electron donors. The term "satisfactorily" in the definition refers to the fact that the charge in the ring cannot be associated exclu-

sively with one ring atom. Thus these compounds are in sharp contrast with other dipolar structures, such as ylides (for example, structure, and such compounds are not considered mesoionic. Mesoionic compounds are most commonly represented as follows compound (22) as structure (25) and compound (23) as structure(26).



The circle represents six π electrons, the positive charge is shared by all the rings atoms.

The unequal electron densities of the atoms lead to the different natures of N(3) and C(4). In general it is believed that C(4) possesses negative character and N(2) is positive, based on their orientation and calculations. Thus the syndone ring demonstrates the electron-withdrawing character on N(3) and electron-donating properties on C(4) and is also confirmed by various calculations. Some fundamental aromatic reactions such as bromination, nitration, acylation and sulfonation occur at the 4$^{th}$ position of the sydnone ring and also functionalized by various functional groups, such as phosphino, silyl, alkyls, halides etc. Oxadiazole derivatives, which belong to an important group of heterocyclic compounds, have been the subject of extensive study in the recent past. Numerous reports.



**Overlap of p-orbitals in sydnone ring (27)**

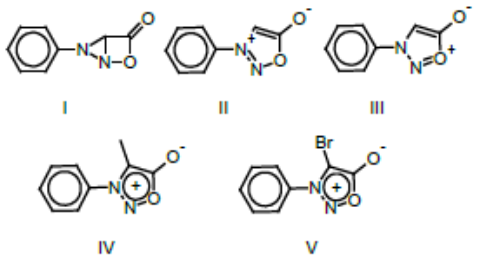
organic Light Emitting Diodes. The oxadiazole ring is electron deficient, resulting in poor hole transport but good electron transport properties. Sydnones are derivatives of 1,2,3-oxadiazole. The IUPAC name of sydnone is 1,2,3-oxadiazolium-5-olates. Sydnone is a typical mesoionic compound and its chemical properties are unique. Sydnone compounds seem to be fairly different from other aromatic compounds in both reactivity and stability. The aromaticity of the ring is explained by the classical sextet theory. Total of seven 2Pz electrons are contributed by the five atoms of the ring with one 2Pz electron on the exocyclic atom. A sextet of electrons will be obtained when one of the seven 2Pz electrons is paired with the single electron on the exocyclic atom. The circle indicates the delocalization of six electrons which is detected as ring current by $^{1}$H-NMR spectroscopy.

This polarization of charges is evidenced by large dipole moments (4-6 D) for the mesoionic rings. The ring will be positively charged, balanced by the negative charge on the exocyclic atom. Sydnones have played a crucial role in the development of theory in heterocyclic chemistry and have been used extensively as synthons in organic synthesis. The photo chromic properties of sydnone were first observed by Tien and Hunsberger. Some of the sydnone derivatives changed their color on exposure to light.Sydnone halogen derivatives change their color irreversibly under the influence of UV light ($\lambda$ < 400 nm). The chemical and spectroscopic properties of molecules containing the sydnone ring have been interpreted to indicate a six-electron aromatic system, delocalized over the five atoms of the ring. The uncommon chemical property of sydnones is that the reaction between 3-aryl sydnone and Lawessan reagent to form 1,4-diaryl-1,4-dihydro- 1,2,4,5-tetrazines, instead of expected product 3-aryl-1,3,4-oxadiazole-5- thion. Aryl sydnones are generally less toxic and more active than alkyl sydnones. Also chalcone analogues are known to have antimicrobial activity, Sydnones are stable compounds those exhibit considerable polarity. Sydnone ring itself is sensitive to acids, bases and heat. Hence the synthesis must be carried out with careful consideration of temperature, reaction path, the order of addition of reagents etc. Sydnone compounds are sometimes decomposed during reaction and/or work up. Sydnones on acid hydrolysis yield the corresponding monosubstituted hydrazines. A general method for the introduction of hetero atoms

at 4th position of a sydnone ring developed by Fuchigami *et al*. 4th position of sydnone ring undergoes substitution with a wide variety of electrophiles, with retention of the ring, typical of aromatic substrates. No method to introduce electron- releasing groups such as amino, hydroxyl and alkoxyl groups at 4th position of the sydnone ring has been found. It seems to be possible to substitute the 4th position by electron releasing groups in interposition of a methylene group. Thus, sydnones are mesoionic compounds, defined to be planar five- membered heterocyclic betains with dipole moments around 6D. The electronic structure of sydnones has been investigated by semi empirical and ab initio methods. Although their geometry can be predicted by ab initio methods, the calculated charge distributions do not agree with experimental results.

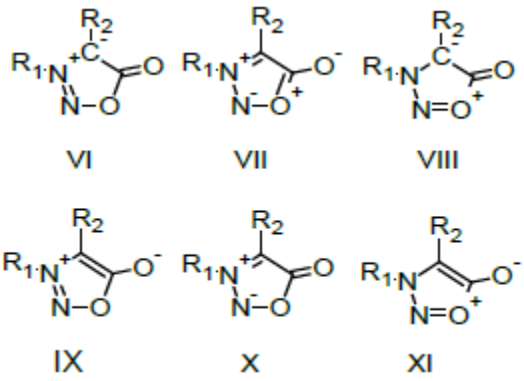
**Biological Importance:**

Many sydnone compounds have been found to have biological and pharmacological activities. Kier and Roche[52] reported in detail the biological importance of various mesoionic compounds. A vast array of sydnone derivatives have been found to show varied biological properties, such as Antibacterial, Antidepressant, Antitumor, Antihypertensive, Antifungal, Antimalarial and Anticonvulsant. Sydnones show liquid crystalline properties and also used in battery applications. The *N*-methyl sydnone having a high dielectric constant was used as a solvent for lithium battery electrolyte. The word sydnone was originated from the phrase "University of Sydney" where this class of compounds was first prepared by Earl and Mackney in 1935. They suggested the formation of fused three-and four-membered ring product (I) from the action of acetic anhydride on *N*-nitrosophenyl glycine which was later considered wrong by other chemists. Firstly, a fused ring system is unlikely to be formed by a simple intramolecular rearrangement and would be a highly strained unstable structure due to the existence of a β-propiolactone group. Therefore, Baker and his collaborator omitted the bridge bond and recommended a partially aromatic five-membered ring (II and III) which was a hybrid of many zwitterionic forms [8]. Secondly, acid hydrolysis decomposes sydnone into hydrazine, carboxylic acids and carbon dioxide while hot aqueous sodium hydroxide can revert the sydnone into the starting *N*-nitroso compound. These two facts indicate that the bicyclic system proposed by Earl is improbable. Thirdly, other researchers proved that acetic anhydride can convert the dextro-rotary *N*-nitroso-*N*-phenylalanine into the optically inactive *N*-phenyl-*C*-methylsydnone (IV). The loss of optical activity implies either racemization or a change in the hybridization of C4 from a chiral $SP^3$ state into a chiral $SP^2$. The oxygen atom attached to C5 was proved to be in an enolate form due to the rapid formation of a mono-bromo derivative (V) in glacial acetic acid and bromine [11].

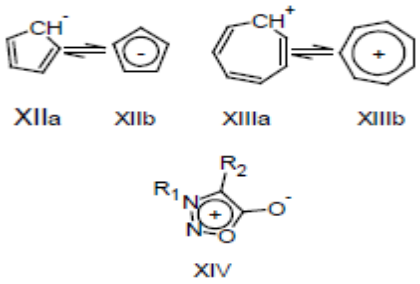



To put a limit to the previous debate, Baker and Ollis extensively reviewed all proposed structures of sydnone and suggested more clear description as follows:

A single covalent structure from the preceding suggestions does not fairly describe sydnone. In other words, the sydnone molecule should be considered as a hybrid of bipolar and tetrapolar forms (VI-XI) whose contribution to the hybrid ring is not equal. Consequently, sydnones are described as mesoionic compounds.



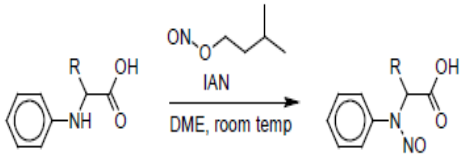

Compared to cyclopentadienyl anion (XIIa, XIIb), tropylium cation (XIIIa, XIIIb), furan, Pyrrole and pyridine, the sydnone ring has all requirements to develop aromatic properties. The exocyclic oxygen atom provides an electron to the ring to complete the sextet of π electrons. Moderately satisfied, they came up with the formula XIV to represent the sydnone structure.




After all, they defined sydnone as a mesoionic compound consisting of a five-membered aromatic heterocyclic ring mainly 1,2,3-oxadiazole or a six-membered ring in some cases. The molecule is neutral and has a positive charge in common between the annular atoms balanced by a negative charge borne on an exocyclic atom(s). Even though there is no single polar or covalent structure for sydnone, the structure XIV is being used as a representative in the majority of literature.

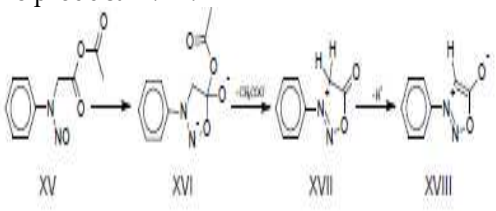
**Synthesis of sydnone**

Primarily, sydnone was prepared by Earl and his colleague by the cyclodehydration effect of acetic anhydride on the *N*-nitroso derivatives of amino acids. They reported that the dissolution of *N*-nitroso-*N*-arylglycine in excess acetic anhydride at room temperature resulted, after 24 h, in a nitroso-free, crystalline and stable heterocyclic product which was later referred to as sydnone. The preparation of the *N*-nitroso intermediate was accomplished by the conventional nitrosation of the amino group of *N*-phenylglycine by the nitrous acid generated from the reaction of sodium nitrite and hydrochloric acid. The *N*-nitrosation of *N*-phenylglycine in neutral conditions was described later by Applegate and Turnbull using isoamyl nitrite (IAN) in dimethoxyethane (DME) at room temperature (Scheme 1). They claimed that IAN was successfully used to prepare the *N*-nitroso derivative of *N*-(2-acetylphenyl) glycine with high yield compared to the acid-based method which led to the formation of *C*-nitroso glycine.




**Scheme 1: Preparation of *N*-nitroso analogues in neutral conditions**

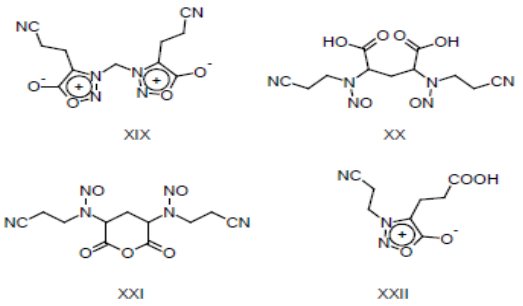
Later, Baker *et al.* deduced the mechanism of cyclization of the *N*-nitroso starting material by losing a water molecule which involves four steps as presented in Scheme. Firstly, a mixed anhydride intermediate XV will be formed from the effect of acetic anhydride on the free nitroso acid whose carbonyl group will evolve strong cationic properties. Of interest, it was found that using a potassium salt of the *N*-nitroso-*N*-phenylglycine will drastically slow down the development of the intermediate. Secondly, a nucleophilic attack of the nitroso oxygen on the acid carbonyl group will lead to ring closure (XVI). Thirdly, an acetate group is lost, and a double bond between the two nitrogen atoms is formed (XVII). Lastly, loss of proton and formation of enolic oxygen will produce the final sydnone product XVIII.



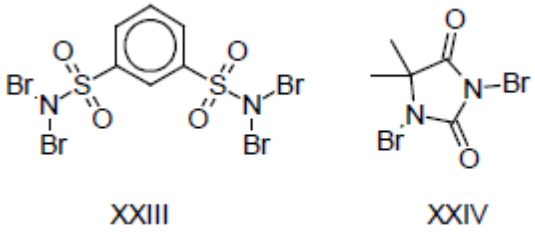

**Scheme 2: Mechanism of ring closure and sydnone formation**

However, Eade and Earl found that the preparation of some sydnone analogues such as nitro-containing sydnone took a long time up to 7-30 d at room temperature with low to moderate yields. They claimed that heating accelerated the formation of sydnone ring, even though it reduced the yield due to rapid hydrolysis of the product by the hot acidic reaction medium. Therefore, Baker and his colleagues reported for the first time an instant and complete separation of *N*-arylsydnone in 90% yield when they used trifluoroacetic anhydride (TFAA) as a dehydrating agent. The later synthetic route had been successfully utilized to prepare some complicated sydnones such as *N,N*-polyaliphatic *bis*-sydnone at a yield of 70-80%. Moreover, heat-labile sydnone such as 3-(2-methoxycarbonylphenyl) sydnone was prepared in a considerable yield of 75% within one hour using TFAA in dichloromethane at 5C. Many alternative reagents were also employed to prepare the sydnone system. In 1950, Baker et al. used thionyl chloride. They reported that the conversion of *N*-nitroso amino acids into sydnone took place within a few minutes using thionyl chloride in dry ether at room temperature giving a low yield of 28%. On the other hand, using thionyl chloride in a mixture of cold dioxane and pyridine resulted in an improved yield (75%) within 25 min. Some special structures of sydnones were reported as unexpected products of the cyclodehydration of the *N*-nitroso derivatives of $\alpha\alpha'$-iminodicarboxylic

acids. For example, 4, 4'-methylene bis [3-(2-cyanoethyl) sydnone] XIX was obtained from the effect of acetic anhydride on the diastereo isomeric mixture of αα′-*di*-(*N*-2-cyanoethyl-*N*-nitrosoamino) glutaric acid XX. On the contrary, the individual α and β forms gave mainly the cyclic anhydride; *N*-2-cyanoethyl-*N*-nitroso-L-glutamic anhydride XXI. Likewise, the hydrolysis of the latter cyclic anhydride in water at room temperature led to an intramolecular rearrangement giving 3-(2-cyanoethyl)-4-(2-carboxyethyl) sydnone XXII with 35% yield.



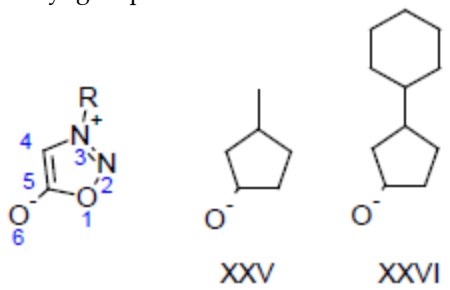

Recently, *N,N,N′,N′*-tetrabromobenzene-1,3-disulfonamide XXIII (TBBDS) and 1,3-dibromo-5,5-dimethylhydantoin XXIV (DBH) were employed as catalysts for the one-pot conversion of *N*-arylglycines into the corresponding sydnone in a neutral medium. Stirring of *N*-arylglycine, TBBDS, sodium nitrite, and acetic anhydride in dichloromethane (DCM) at 5 °C was sufficient to bring about the formation of the sydnone ring in a very satisfactory yield during 5-8 h. Similarly, DBH efficiently promoted the cyclization within 10-16 h. Worth mentioning, sydnones containing nitrophenyl groups were prepared in a yield of 80-88% using the previous reagents compared to 5-30% by the classic Earl's method.




**Physicochemical properties of sydnone**

**The electronic structure of sydnone ring**

Using a new method of molecular orbital calculation named as ω -technique modified from Hückel framework, Kier and Roche calculated reasonable values of charge densities and bond orders for 3-methylsydone and 3-phenylsydone. The calculated bond order value of C5-O6 bond in structure XXV and XXVI along with the X-ray structure of 3-(*p*-bromophenyl) sydnone, 3-(*p*-ethoxyphenyl) sydnone and 3-(*p*-tolyl)sydnone pointed out a carbonyl-like double bond characters of the C5-O6 bond of the sydnone ring. Moreover, it can be noticed that the exocyclic oxygen O6 is highly negative charged (-0.53) even stronger than the carbonyl oxygen of butyrolactone (-0.38) indicating a very polarizable carbonyl group.



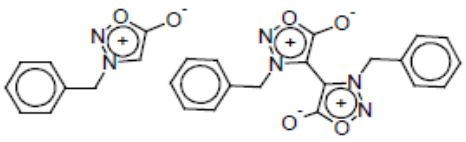

The delocalized positive charge of the ring which has been previously proved to be unevenly distributed is mainly borne on the number three nitrogen especially when an electron withdrawing group is attached to the nitrogen such as a phenyl ring. This suggests an iminium-type nature of this nitrogen and therefore has an electron withdrawing impact which will deactivate the attached aryl substituents towards all electrophilic reagents. Even though, the calculated bond order of the N-O was 1.22 Å which was close to 1.14 Å of the double bond N=O, the X-ray confirmed its single bond nature. Interestingly, the high electron density of C4 in structures XXV and XXVI was later supported by the finding of Greco and O'Reilly who reported a strong acidity of 3-phenylsydnone with $pK_a$ value of 18-20. Consequently, sydnone is an electron donating reagent and the electrophilic substitution at this position is possible. However, more recent studies by Fan and his lab-mates gave a better insight into bond length and nature, atomic charges and electron density distribution for thirteen different sydnone compounds. Ring aromaticity is gained from the unequally delocalized π-electrons with higher density on both N2-N3 and N3-C4. The calculated bond length of C5-O6 (1.80-1.85 Å) and the experimental value (1.19-1.22 Å) illustrated undoubtedly its double bond nature. On the other hand, C5-O1, N2-O1 and C4-C5 were mainly single bonds. The other bonds of the ring, N2-N3 and N3-C4 were found partially double bonds. The net atomic charges were summarized as follows: neutral (N2, N3), positive (C5) and negative (O1, C4, O6) with the

highest negative potential (-84.6 kcal/mol) was deposited at O6. Conjugation between sydnone ring and the aromatic system substituted at N3 was not essential for the stability of sydnones because the resonance between the two systems was minor.

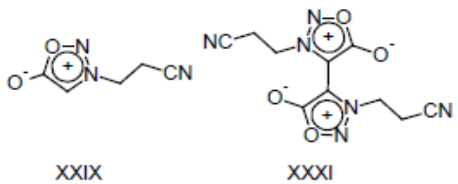
**Sydnones spectral studies**

**Ultraviolet (UV) spectroscopy**

The properties of the ultraviolet spectra of sydnones were well reviewed by Stewart and Kier and Roche (24). Briefly, absorption maxima in the range 290-340 nm was considered as a proof of the presence of the aromatic ring of sydnone. Alkyl sydnone absorbs at the lower wavelength (<300 nm). For example, 3-methylsydnone, 3-*n*-butyl sydnone and 3-cyclohexylsydnone showed their UV absorption maxima at 290, 289.5 and 292 nm, respectively. A bathochromic shift was observed for 3-arylsydnone due to conjugation as in 3-phenylsydnone and 3-(1-naphthyl) sydnone which absorb at 310 and 315, respectively. Many factors can remarkably affect the UV spectra of sydnones: Conjugation: An aromatic system substituted at C4 of the sydnone ring has a stronger bathochromic effect such as 3-methyl-4-phenylsydnone whose UV maxima was at 317 nm. Similarly, 4-acetylated sydnone absorbs at a longer wavelength such as 4-acetyl-3-phenylsydnone and 3-phenylsydone absorb at 324 and 310 nm. Steric factors can retard the conjugation due to the disturbance of the planarity of the molecule. The UV maxima of 3-(2, 6-methylphenyl) sydnone was found to be at 255 nm even shorter than that of 3-alkyl sydnone which lacks conjugation. Electrostatic interaction in *bis*-sydnone system makes the co-planarity system more rigid and therefore the UV absorption wavelength is unusually high like in XXVII, XXVIII, XXIX and XXXI whose maximum absorptions were at 292, 350, 292 and 303, respectively.



XXVII XXVIII



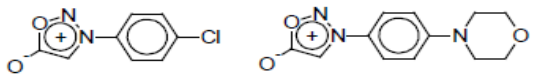
XXIX XXXI

**Infrared (IR) spectroscopy**

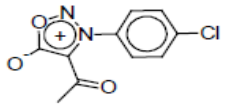
A survey of the literature since their early preparation until today revealed two characteristic IR bands for sydnones. The stretch of sydnone carbonyl (C5-O) ranges from 1740 to 1770 $cm^{-1}$ while the absorption band of carbon-hydrogen (C4-H) was more than 3000 $cm^{-1}$. However, electrophilic substitution at C4 led to the loss of the carbon-hydrogen band and an increase in the wave number of the carbonyl up to 1780-1830 $cm^{-1}$. For example, acetylation of 3-(4-chlorophenyl) sydnone resulted in up shifting the CO band from 1750 $cm^{-125}$ to 1786 $cm^{-13}$.

**Nuclear magnetic resonance (NMR) spectroscopy**

Lawson *et al.* observed an unusually high field resonance of the sydnone ring proton in a series of 3-alkylsydnone and 3-arylsydnone when compared to the normal olefinic hydrogen. They confined this deshielding phenomenon to the electron-withdrawing effect of the adjacent nitrogen and oxygen atoms along with the anisotropy effect of the nearly coplanar phenyl ring. Likewise, the positive charge and the aromatic features of the sydnone ring resulted in deshielding the phenyl ring protons, especially the hydrogen atoms on the carbon $\alpha$ to the sydnone ring. Another characteristic component of the sydnone NMR spectra is the peak of the carbon C5 which appears in the lowest field of $^{13}C$ NMR spectrum, *i.e.* the carbonyl region. The chemical shift of sydnone CO peak changes within a narrow range from 160-170 ppm regardless of the nature of the substituent at C4. As examples, compounds XXXII, XXXIII, XXXIV have their CO peaks at 169.19 ppm , 165.80 ppm and 163.20 ppm.



XXXII XXXIII



XXXIV

**Chemical properties of carbon C4 of the sydnone ring**

**Acylation and formylation of sydnone ring**

Greco and his co-workers reported unsuccessful attempts to acylate the sydnone ring in the con-

ventional Friedel-Crafts reaction using many catalysts such as aluminum chloride, stannic chloride, and phosphoric acid. However, they successfully prepared a variety of 4-acylsydnone derivatives when phosphorous pentoxide (3 equiv) was refluxed with one molar equivalent of carboxylic acid and sydnone. Later, other chemists speculated that the failure of Friedel-Crafts acylation was due to the coordination between Lewis acid and the exocyclic oxygen of the sydnone which eventually yielded a sydnone-containing fused ring compounds rather than the desired acylated product as shown.

**Conclusion**

Sydnones are mesoionic heterocyclic aromatic compounds. They have been widely studied for some important biological activities like antiviral, antitumor, antimicrobial, anti-inflammatory, anticancer, analgesic, anthelmintic and antihypertensive activities. With respect to their functionalisation, modern techniques such as metal catalysed cross-coupling and direct arylation processes have been found to be as directly applicable to these unusual compounds as they are to the more common heteroaromatic substrates. The cycloaddition of alkynes consistently gives pyrazole products. These all have the potential to furnish some very interesting molecular moities. The new sydnone functionalisation methods in conjunction with the aforementioned cycloaddition reactions will provide the focus of future research in the development of sydnone drugs.

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