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INFLUENCE OF SUBSTITUENTS ON THE SPECTRAL DATA OF SYDNONES

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The sydnones are among the first discovered mesoionic stable compounds. Their structure allows an interesting behavior making these compounds useful as drugs or as synthons for drug synthesis. The potential biological activity is influenced by the molecular geometry of the compound. Thus, a study of the molecular shape of some sydnones seems of interest. The spectral data (UV-Vis, IR and NMR) are proper tools for such investigation.

Keywords: sydnones, IR and UV-Vis spectral data, molecular geometry

1. Introduction

The sydnones are heterocyclic compounds discovered by Earl and Mackney [1] and have interesting properties due to their mesoionic structure which allows interaction with biological important compounds (proteins, DNA, etc.) as well as the capability to cross membranes [2]. These properties explain their application as drugs for different diseases [3-6].

Sydnones are synthons for the preparation of numerous compounds due to their high reactivity [7].

The interest for the synthesis and characterization of such compounds has been developed longtime ago in the laboratories of the “C.D. Nenitzescu” Centre of Organic Chemistry, the first paper on the subject being published in 1965 [8]. Starting from there a number of sydnones have been synthesized and studied. Also, their cycloaddition reactions, leading to new heterocyclic with nitrogen were investigated. Such compounds are of interest due to their potential biological activity as antibacterial, antifungal and even antitumor agents [9-12]. Some of the papers describing the work of our laboratory are mentioned here [13-15].

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The structure of studied sydnones **1-5** is of interest, due to the conjugation reflected in the resonance structures accepted for these compounds. Thus, the UV-Vis spectra of a number of sydnones have been performed and the experimental results are explained using also other information revealing their molecular geometry (IR and NMR spectra, crystallographic data).

2. Experimental

The analyzed sydnones have been synthesized in the laboratory of Centre of Organic Chemistry and the experimental details of their preparation presented elsewhere [16].

The UV-Vis spectra were performed in solutions of analytical grade solvents (CH_2Cl_2 and C_2H_5OH).

The UV-Vis spectrophotometer is a Helios Beta type with Vision soft, having a spectral window 200-800 nm. The solution absorption has been determined in 1 cm path length quartz cell.

The values for the characteristic absorption (λ, ε) were presented in Table 1.

3. Results and Discussion

The sydnones are generally prepared starting from *N*-substituted glycine, by nitrosation followed by cyclization. The sydnones have stable conjugated structures, with a number of resonance forms, as presented before [17]:

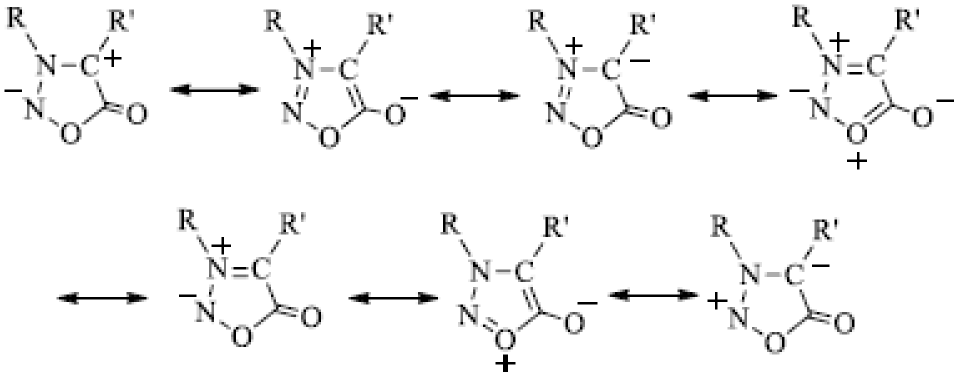


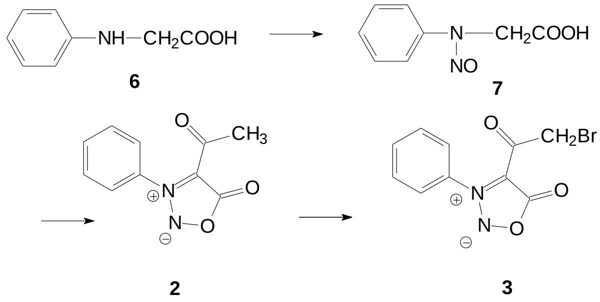
Fig. 1. Limited structures of sydnones

The presence of the *N*-substituent, (R = aryl or alkyl) is compulsory, otherwise, due to prototropy neutral species are obtained.

The *N*-phenylsydnone **1** has been synthesized according to the experimental procedure of Thoman and Voaden [18].

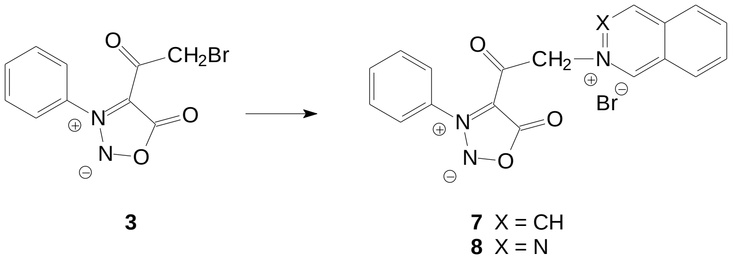
The sydnones **2-5** have been prepared, as previously described [16]. Starting from the same *N*-phenylglycine (**6**) by nitrosation (compound **7**) followed by one pot cyclization and acetylation leading to compound **2.** By bromination with bromine in acetic acid the sydnone **3** was prepared (see Scheme 1)

Scheme 1



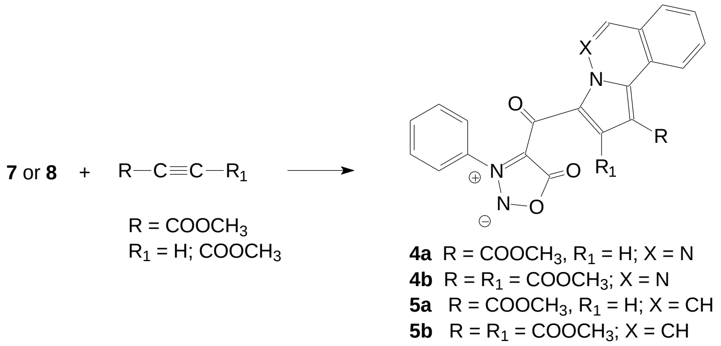
The sydnone **3** is the precursor for the synthesis of two sydnone *N*-ilydes **7** and **8** by treatment with the corresponding heterocyclic compounds (see Scheme 2).

Scheme 2



From the ilydes **7** and **8**, the compounds **4** and **5** have been prepared by the well-known Huisgen 1-3 cycloaddition reaction [19] (see Scheme 3).

Scheme 3



All the new synthesized sydnones have been purified and characterized by elemental analysis, IR and NMR spectra. For the compound **5a** the X-ray structural conformation was previously described [16].

The compounds obtained by these syntheses have different substituents into the 4 position of sydnone ring fact leading to changes into the molecular geometry.

Some information about the molecular geometry of these compounds may be obtained by performing their UV-Vis spectra. Thus, the planarity of the molecules is suggested by the possible extended conjugation, identified through the λ values characteristic for each of these sydnones. Besides, the change of solvent polarity may give information concerning the molecular geometry of the mesoionic compounds. Thus, the UV-Vis spectra have been performed in CH_2Cl_2, C_2H_5OH, two solvents with different polarity as well as solvation capacity.

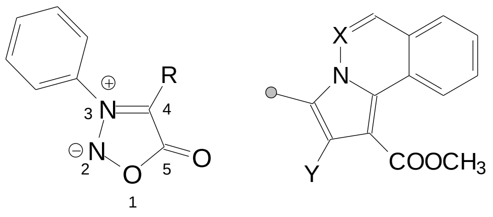
The experimental results of spectral data for the studied sydnones are presented in Table 1.

Table 1

Spectral data of sydnones 1-5

Compound	CH_2Cl_2	C_2H_5OH	ν_{CO} (cm^{-1}) endo/ exocyclic	NMR (exocyclic CO)
	λ (nm)/ ε(M^{-1}cm^{-1})	λ (nm)/ ε(M^{-1}cm^{-1})		
1 (R=H)	$313/6.8\cdot10^3$	$311/6.8\cdot10^3$	1755/-	-
2 (R=-$COCH_3$)	$324/8.13\cdot10^3$	$323/9.5\cdot10^3$	1797.3 /1666.2	184.1
3 (R= -$COCH_2Br$)	$331/8.5\cdot10^3$	$328/8.3\cdot10^3$	1790/1680	178.1
4a (R= $COHet_1$)	$280/1.8\cdot10^4$ $315/1.2\cdot10^4$ 365/3.558 382/2.415	$275/3.2\cdot10^3$ $315/1.2\cdot10^4$ $364/2.010^3$	1776/1709	168.8
4b (R= $COHet_2$)	$260/2.3\cdot10^4$ $266/2.2\cdot10^4$ $313/1.24\cdot10^4$ $345/1.5\cdot10^4$ $372/1\cdot10^4$	$267/1.6\cdot10^4$ $273/1.6\cdot10^4$ $313/5.3\cdot10^3$ $340/5.5\cdot10^3$	1726/1709	170.2
5a (R= $COHet_3$)	$270/2.1\cdot10^4$ $328/1.2\cdot10^4$ $408/1.4\cdot10^4$ $422/1.02\cdot10^4$	$269/1.3\cdot10^4$ $325/5.3\cdot10^3$ $399/8.0\cdot10^3$	1758/1700	169.0
5b (R= $COHet_4$)	$268/2.1\cdot10^4$ $334/1.34\cdot10^4$ $415/1.9\cdot10^4$ $425/1.6\cdot10^4$	$265/2.2\cdot10^4$ $332/3.23\cdot10^3$ $404/4.3\cdot10^3$	1760/1711	170.6

The values of wavelength (λ) and the corresponding molar absorptivity (ε) for the π electrons transitions are presented for a number of seven compounds. The structures of these compounds are as follows:



Het$_1$: X = N; Y = H
Het$_2$: X = N; Y =COOCH$_3$
Het$_3$: X = CH; Y = H
Het$_4$: X = CH; Y = COOCH

The change of the solvent has no significant influence on the values of the absorption wave lengths, the solvent polarity does not seem so important for the stabilization of the fundamental state as well as for the excited state of these molecules. In most of the cases a small hipsochromic effect is observes in ethanol, due most probably to the lower polarity of this solvent [20].

The ε values (10^3- 10^4) suggest $\pi - \pi^*$transitions, types B and E [20].

The λ_{max} value for compound **1** discloses a conjugation of the sydnone ring with the phenyl, generating new limited structures than those mentioned above (see Fig.2.) [21]:

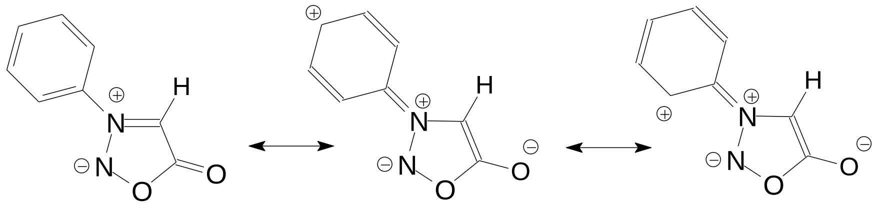


Fig. 2. Structures showing the conjugation of sydnone with the phenyl ring in 3-phenyl sydnone

Such conjugation explains the bathochromic effect observed by comparison with 3-alkyl sydnones characterized by a λ_{max} value of 290 nm [22].

The C_4 acetylation leads also to a bathochromic shift, most probably due to the extended conjugation of the sydnone ring with the external (exo) CO group, as shown in Fig. 3.

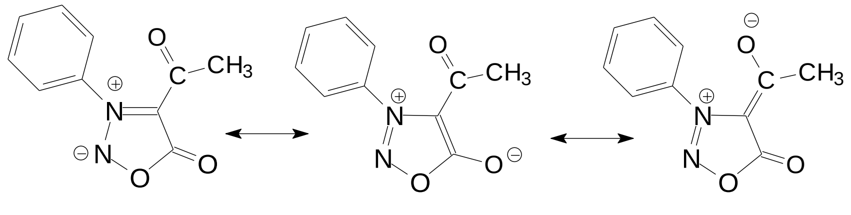


Fig. 3. Structures showing the conjugation in compound **2**

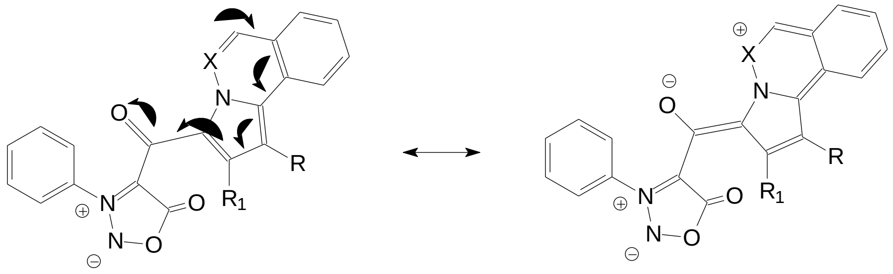
As expected, the presence of the bromine atom (possessing n electrons) in compound **3** enhances the bathochromic shift. The planarity of the sydnone ring and of the bromoacetyl group, compulsory for conjugation, has been confirmed by the crystallographic study of this molecule [23]. In sydnones **2** and **3,** the phenyl group makes, most probably, a dihedral angle of 55^o with the acetyl sydnone moiety like in the similar 4-acetyl-3(*p*-anisyl)sydnone [24]. Thus, in compounds **2** and **3** no conjugation with the phenyl ring, such as in 3-phenyl sydnone (**1**) occurs.

The values of the IR stretching bands for the exocarbonyl group [16, 21, 25] are similar with those of substituted acetophenone [26]. The results agree with the previously observed inductive effect of the phenyl substituent in similar molecules [27].

The insertion of complex heterocyclic groups, by the reactions presented in Scheme 2 and 3, extends the conjugation chain, fact reflected into higher bathochromic shifts observed for compounds **4a**, **4b**, **5a** and **5b**.

The geometry of these molecules allows the conjugation, the carbonyl group being situated in the same plane with the heterocyclic moieties. As for the compounds **2** and **3** and other similar sydnones, the phenyl ring is deviated from this plane [16].

The aspect of the UV spectra for these compounds is complex, with a number of absorption maxima generated most probably by partial or total conjugation. The longest conjugation chain, characteristic to molecules **4a**,**b** and **5a**,**b** is presented in the following figure (see Fig. 4.).



4a R = $COOCH_3$, R_1 = H; X = N
4b R = R_1 = $COOCH_3$; X = N
5a R = $COOCH_3$, R_1 = H; X = CH
5b R = R_1 = $COOCH_3$; X = CH

Fig. 4. Conjugation chain in compounds **4a,b** and **5a,b**

The supplementary absorption peaks in dichloromethane may be attributed to a charge transfer band between the n electrons of the carbonyl oxygen and the phenyl ring. Such assertion is confirmed by the fact that in ethanol these absorption peaks are not observed, most probably due to the n-electrons involved in the hydrogen bonding with the hydroxyl group of the solvent [27].

6. Conclusions

Based on the analysis of the spectral data, the molecular geometry of studied sydnones depends on the substituent from position 4. A hydrogen substituent leads to conjugation sydnone-phenyl. Starting with acetyl the phenyl ring is deviated from planarity conjugation involving in this case the sydnone ring and the RCO part.

The complex structures of compounds **4** and **5** generate a number of absorption of $\pi - \pi^*$ type. The n-electrons of oxygen carbonyl may be involved in a charge-transfer complex with the neighboring phenyl ring these absorptions being evidenced in the non-hydroxylic solvent.

REFERENCES

[1]. *J. C. Earl and A. W. Mackney,* The action of acetic anhydride on N-nitrosophenylglycine and some of its derivatives, *J. Chem. Soc.* **1935**, 899-900.

[2]. *G. Clazer Halila, M. B. Martinelli de Oliveira, A. Echevarria, A. Carneiro Belem, M. E.Merlin Rocha, E. G. Skare Carnieri, G. R. Martinez, G. Rodrigues Noleto, and S. M. Suter Correia Caden,* Effect of sydnone SYD-1, a mesoionic compound, on energy-linked functions of rat liver mitochondria, Chem. Biol. Interact., 2007, **169**,160–170.

[3]. *K. Butkovic, Z. Marinić, and M. Sindler-Kulyka,* Synthesis of 3-(*o*-stilbenyl)sydnone and 3-(*o*-stilbenyl)-4-substituted-sydnone derivatives and their antitumor evaluation, ARKIVOC, **2011**, 1-15.

[4]. *R. J. Soares-Bezerra, L. L. Leon, A. Echevarria, C. M. Reis, L. Gomes-Silva, C. G. Agostinho, R. A. Fernandes, M. M. Canto-Cavalheiro and M. S. Genestra,* In vitro evaluation of 4-phenyl-5-(40-X-phenyl)-1,3,4-thiadiazolium-2-phenylaminide chlorides and 3[N-40-X-phenyl]-1,2,3-oxadiazolium-5-olate derivatives on nitric oxide synthase and arginase activities of *Leishmania amazonensis*, Exp. Parasitol., 2013, **135**, 50–54.

[5]. *S. T. Asundaria, C. Pannecouque, E.De Clercq and K. C. Patel,* Sydnone Sulfonamide Derivatives as Antibacterial, Antifungal, Antiproliferative and Anti-Hiv Agents, Pharm. Chem. J., 2014, **48**(4), 260-268.

[6]. *M. A. Rahiman, G. N. Ravikumar, M.S.Anantha and H. Makari,* Synthesis of 4-Aryl-2-[3-arylsydnolydine-4-hydrazono-] thiazoles as Possible Antimicrobial Agents, A J B P R, 2013, **3**(3), 17-24.

[7]. *A. Schmidt, S. Wiechmann, and T. Freese,* Recent advances in neutral and anionic N-heterocyclic carbene – betaine interconversions. Synthesis, characterization, and applications, ARKIVOC, **2013**, 424-469.

[8]. *N. Suciu, Gh. Mihai, M. Elian and E. Stroescu,* Sydnones : Reaction of lithium phenylsydnone with phosgene, Tetrahedron, 1965, **21**(6), 1369-1371.

[9]. *V. K.Akbari, N. J. Chothani, Y. M. Patel and K. C. Patel,* Synthesis, anti-bacterial, and anti-fungal activity of sydnone-based aromatic compounds, Indian J. Chem. B, 2015, **54**, 93-102.

[10]. *T. Taj, R. R. Kamble, P. P. Kattimani and B. V. Badami*, Synthetic utility of sydnones: synthesis of pyrazolines derivatized with 1,2,4-triazoles as antihyperglymic, antioxidant agents and their DNA cleavage study, Med. Chem. Res., 2012, **21**, 3709–3719.

[11]. *T. Taj, S. V. Raikar and R. R. Kamble,* Synthetic utility of sydnones to couple pharmacologically important heterocycles for antitubercular activity, Arab. J. Chem., 2014, **7**, 900–905.

[12]. *G. Clazer Halila, M. B. Martinelli de Oliveira, A. Echevarria, A. Carneiro Belem, M. E. Merlin Rocha, E.G. Skare Carnieri, G. R. Martinez, G. Rodrigues Noleton and S. M. Suter Correia,* Effect of sydnone SYD-1, a mesoionic compound, on energy-linked functions of rat liver mitochondria, Chem.-Biol. Inter., 2007, **169** ,160–170

[13]. *F. Dumitrascu, C. Draghici, D. Dumitrescu, L.Tarko and D. Raileanu*, Direct Iodination of Sydnones and Their Cycloadditions to Form 5-Iodopyrazoles, Liebigs Annalen, **1997,** 2613-2616.

[14]. *F. Dumitrascu, C. I. Mitan, D. Dumitrescu, C. Draghici and M. T. Caproiu*, Steric effects on the sydnones reactivity. New sydnones and pyrazoles, ARKIVOC, **2002**, 80-86.

[15]. *F. Dumitrascu, C. Draghici, D. Vuluga and M. T. Caproiu*, New Pyrazoles by 1,3-Dipolar Cycloaddition Reactions Between Sydnones and Activated Alkynes, Rev. Roum. Chim., 2006, **51**(4), 255-260

[16]. *F. Albota, C. Draghici, M. R. Caira and F. Dumitrascu,*1,3-Dipolar cycloaddition between acetylenic dipolarophiles and sydnone-N-ylides as bis(1,3-dipoles), Tetrahedron, 2015, **71**, 9095-9100.

[17] *K. Butkovic, Z. Marinic, and M. Sindler-Kulyk*, Synthesis of 3-(*o*-stilbenyl)sydnone and 3-(*o*-stilbenyl)-4-substituted-sydnone derivatives and their antitumor evaluation, ARKIVOC 2011 (x) 1-15

[18]. *C. J. Thoman and D. J. Voaden*, 3-Phenylsydnone, In*: Organic syntheses, coll.* Willey and sons, New York, 1973, **vol. 5**, pp 962–965.

[19]. *R. Huisgen* , 1.3-Dipolar Cycloaddtion. Past and Future., Angew. Chem . Int. Ed., 1963, **2**(10), 565–632.

[20]. *R. M. Silverstein, G. C. Bassler, T. C. Morrill,* Spectrometric Identification of Organic Compounds, 5th edition, J. Wiley & Sons, New York, 1991, pp.289-314.

[21]. *F. H. C. Stewart*, The Chemistry of the Sydnone, Chem. Rev., 1964. **64**(2), 129-147.

[22]. *D. L. Hammick and D. J. Voaden*, Chemical and Physical Properties of Some Sydnones, J. Chem. Soc**.**, **1961**, 3303-3308.

[23]. *H.-K. Fun, T. S. Chia, N. Chandra, B. Kalluraya and S. Shetty*, 4-Bromoacetyl-3-phenyl sydnone, Acta Cryst., 2012. **E68**, o2103.

[24]. *H.-K. Fun, W.-S. Loh, N. Chandra and B. Kalluraya*. 4-acetyl-3(*p*-anisyl)sydnone, Acta Cryst., 2011,**E67**, o1489.

[25]. *H. Tien, K. Kanda, A. Chinone and M. Ohta*, Reactions of 4-acetylsydnones, Bull. Soc. Chim. Jpn., 1973, **46**, 3304-3306.

[26]. *N. Jones, W. F. Forbes and W. A. Muelller*, The Infrared Carbonyl Stretching Bands of Ring Substituted Acetophnones, Canadian J. Chem., 1967, **35**, 504-514.

[27] *S. Nespurek and M. Sorm,* Photochromic properties of 4-isopropenyl-3-phenylsydnone and its dimer, Czech. J. Phys. B, 1975, **25**, 1051-1062