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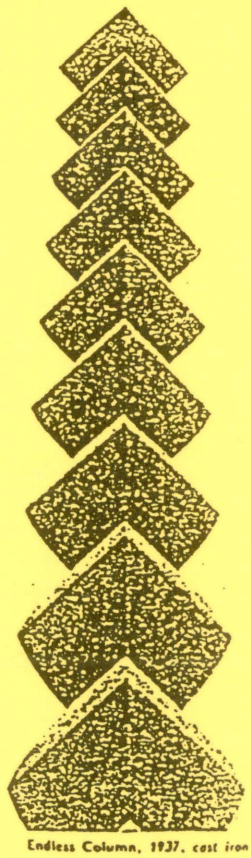

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SOUTHERN BRAZILIAN, JOURNAL OF CHEMISTRY
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STRUCTURAL AND ELECTRONIC PROPERTIES OF BRIDGED BITHIOPHENE S-OXIDES (BTO) WITH S, S=O, O, SiH_2 and BH_2 BRIDGE: SEMI-EMPIRICAL AND AB INITIO STUDY.

Banjo Semire[a*1], Isaiah Ajibade Adejoro[b], Olusegun Ayobami Odunola[a*]

[a]Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.
[b]Department of Chemistry, University of Ibadan, Ibadan, Nigeria.

ABSTRACT

In this paper, we theoretically studied the geometries, stabilities, electronic and thermodynamic properties of bridged bithiophene S-oxide (BTO-X) derivatives (with X= BH_2, SiH_2, S, S=O and O) by using semi-empirical methods, ab initio and Density functional theory. The geometries and thermodynamic parameters calculated by PM3 were in good agreement with that of B3LYP/6-31G(d). The band gap calculated by B3LYP/6-31G(d) ranged from 3.94eV (BTO-O) – 3.16eV (BTO-BH_2). The absorption λ_{max} calculated using B3LYP/6-31G(d) shifted to longer wavelength with X= BH_2, SiH_2 and S=O due to enhancement of π-conjugated system whereas, BTO-S and BTO-O shifted to shorter wave lengths as compared to dimmer thiophene S-oxide (2TO).

Keywords: Density functional theory (DFT), Semi-empirical (PM3), Bridged bithiophene S-oxides.

RESUMO

Este trabalho apresenta os resultados obtidos por nossos estudos teóricos das geometrias, estabilidades e propriedades eletrônicas e termodinâmicas de S-óxidos de derivados de bitiofenos (BTO-X) com pontes, (X=BH_2,,SiH_2 ,S=O e O) usando métodos semi-empíricos, ab-initio e teoria funcional de densidade. Os parâmetros geométricos e termodinâmicos calculados por PM3 concordaram bem com aqueles de B3LYP/6-31G(d). O intervalo de banda calculado com B3LYP/6-31G(d) variou entre 3.94eV (BTO-O) e 3.16eV (BTO-BH_2). A banda máxima de absorção calculada com o mesmo método deslocou-se para comprimentos de onda maiores com X=BH_2, SiH_2 e S=O devido ao sistema de elétrons pi conjugados. No caso de BTO-S e BTO-O o deslocamento foi para comprimentos de onda menores em comparação a tiofeno S-óxido.

Palavras Chave: Teoria DFT,Método semi-empirico PM3 , S-óxidos de bitiofeno

[1] Corresponding e-mail: semireban@yahoo.com, odunola@yahoo.com

1. INTRODUCTION

Since their discovery, conjugated polymers have attracted considerable interest during recent years because of their promising electronic applications such as in batteries [1,2], electroluminescent devices [3], field-effect transistors [4] and photovoltaics [5]. Oligothiophenes are perhaps the most thoroughly investigated and well-characterized systems [7-9]. These one-dimensional semiconductors are potentially important candidates for a broad range of applications in the ever-growing field of molecular electronics including molecular wires and switches, for example as light emitting diodes and field-effect transistors [10–12]. However, monitoring the decrease in band gap as a way controlling of the electric properties of polythiophenes are strongly governed by the intramolecular delocalization of π-electrons along the conjugation chain [6]. Thiophene related molecules such as thiophene 1,1-dioxide and thiophene S-oxide have been investigated [13], this includes the synthesis, reactivity as dienes in Diels-Alder reactions [14], photochemical and electrochemical behavior [15]. The orbital energies and electrochemical properties of monomer of thiophene S-oxides have been theoretically studied using PM2/6-31G* [16].

In regard to reduce energy band gaps, the geometric and electronic structures of some bridged octamer of oligothiophenes have been theoretically studied with bridging containing electron-accepting groups are C=O, C=S and $C=C(CN)_2$ [17-19]. In this paper, we will theoretically investigate the structure, electronic and thermodynamic properties of bridged bithiophene S-oxide (BTO-X) with bridge X = S, S=O, O, SiH_2 and BH_2. The results will be compared to un-bridged thiophene S-oxide dimmer (2TO).

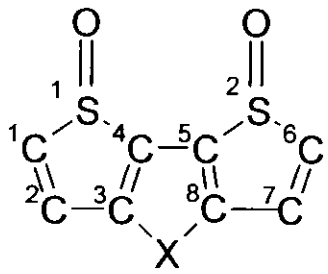

Fig.1 The structure and atomic numbering of bithiophene S-oxide (BTO); X=S, for BTO-S, X= S=O for BTO-SO, X=O for BTO-O, $X=SiH_2$ for BTO-Si and $X=BH_2$ for BTO-B.

2. COMPUTATIONAL METHODS

All calculations to study the un-bridged and bridged bithiophene-S-oxide (BTO) derivatives were performed by Spartan 06 program [20] implemented on an Intel Pentium M 1.7GHz Computer. The geometries of 2TO and bridged bithiophene S-oxide (BTO) derivatives have been full optimized at Semi-empirical methods (AM1 and PM3), ab initio (Hatree Fock and Density Functional Theory (Beckes's Three Parameter Hybrid [21] Functional) using the Lee, Yang and Parr correlation Functional B3LYP [22]). The basis set 6-31G(d) was used for all atoms in ab initio methods. We have also examined HOMO and LUMO levels; the energy gap is evaluated as the difference between the HOMO and LUMO energies. All optimizations were without symmetry restrictions.

3. RESULTS AND DISCUSSION

3.1 Geometries and Stabilities

The optimization of the geometrical structures of the bithiophene S-oxide derivatives was carried out with both semi-empirical and DFT quantum mechanical methods. Generally, the bond lengths calculated by B3LYP/6-31G(d) are slightly different from those calculated by PM3. For instance, the value of C_4-C_5 calculated by PM3 and DFT are 1.445 and 1.422Å for BTO-B, 1.442 and 1.445Å for BTO-Si, 1.411 and 1.408Å for BTO-S, 1.435 and 1.431Å for BTO-SO, 1.418 and 1.419Å for BTO-O and 1.440 and 1.433 for 2TO respectively. The overall mean deviations of bond lengths calculated by PM3 as compared DFT are 0.014, 0.032 and 0.018Å for BTO-S, BTO-SO and BTO-O respectively, but both BTO-B and BTO-Si is deviated by 0.015Å. However, the bridge X has profound effect on the geometries on the bridged bithiophene S-oxide derivatives as compared to 2TO (Table 1). The mean deviation with respect to bond angles in bridged BTO derivatives calculated by PM3 are 1.00°, 1.18°, 1.27°, 1.02° and 0.57° for BTO-B, BTO-Si, BTO-S, BTO-SO and BTO-O respectively. The largest difference in bond angles between PM3 and B3LYP/6-31G(d) is in $C_1C_2C_3$ ($C_6C_7C_8$) for BTO-B, BTO-S, BTO-SO and BTO-O and $C_3C_4C_5$ ($C_7C_5C_4$) for BTO-Si and 2TO.

Generally, the dihedral angles of bridged BTO-X derivatives with X= BH_2, SiH_2, S, S=O and O bridge show distortion from planarity, although insertion of X to 2TO increase the planarity. There are differences in dihedral angles calculated by both theoretical methods. For instance, the dihedral angles $C_1S_1C_4C_5$ ($C_2C_3C_4C_5$) calculated by PM3 are -178.29° (178.37°), -178.52° (179.82°), -178.53° (179.48°), 178.64° (-179.06°), 178.37° (179.88°) and -175.04° (176.69°) for BTO-B, BTO-Si, BTO-S, BTO-SO, BTO-O and 2TO respectively, while those calculated by B3LYP/6-31G(d) for the same dihedral angles are -177.68° (177.57°), 177.86° (-177.20°), 175.40° (-176.93°), 173.55° (-176.25°), 164.63° (-172.70°) and -175.15° (178.91°) for BTO-B, BTO-Si, BTO-S, BTO-SO and BTO-O respectively.

In the process of calculation of energies, both HF/6-31G(d) and B3LYP/6-31G(d) are employed. However, the energies calculated show that the predictive order of stability

by HF/6-31G(d) and B3LYP/6-31G(d) are the same, although DFT predicted lower energies. For instance, the energies calculated by B3LYP/6-31G(d) method for BTO-SO, BTO-S, BTO-Si, BTO-O and BTO-B are -1727.23au, -1652.09au, -1544.59au, -1329.10au and -1279.91au respectively as compared to -1255.10au for 2TO.

Table 1. Calculated geometries of bridged BTO-X derivatives with BH_2, SiH_2, S, S=O and O by means of PM3 and B3LYP/6-31G(d) methods: Bond lengths are in Å, bond angles and Dihedral angles in degree.

	2TO		BTO-B		BTO-Si		BTO-S		BTO-SO		BTO-O	
	PM3	B3LYP/6-31G(d)	PM3	B3LYP/6-31G(d)	PM3	B3LYP/6-31G(d)	PM3	B3LYP/6-31G(d)	PM3	B3LYP/6-31G(d)	PM3	B3LYP/6-31G(d)
C_1-S_1 (C_6-S_2)	1.783	1.784	1.803	1.816	1.788	1.794	1.795	1.814	1.788	1.801	1.813	1.822
C_4-S_1 (C_5-S_2)	1.812	1.826	1.793	1.808	1.796	1.805	1.787	1.812	1.789	1.811	1.774	1.807
C_1-C_2 (C_6-C_7)	1.346	1.352	1.369	1.364	1.350	1.353	1.348	1.349	1.351	1.354	1.351	1.350
C_2-C_3 (C_7-C_8)	1.461	1.449	1.431	1.435	1.446	1.452	1.452	1.450	1.448	1.442	1.448	1.440
C_3-C_4 (C_5-C_8)	1.355	1.363	1.374	1.386	1.371	1.372	1.398	1.382	1.378	1.365	1.401	1.337
C_4-C_5	1.440	1.433	1.445	1.422	1.442	1.445	1.411	1.408	1.435	1.431	1.418	1.419
C_3-X (C_8-X)	-	-	1.574	1.607	1.835	1.888	1.717	1.747	1.787	1.822	1.374	1.366
$C_1S_1C_4$ ($C_5S_2C_6$)	89.17	90.18	88.29	86.85	88.89	89.15	88.87	88.67	88.79	89.06	88.76	88.72
$C_1C_2C_3$ ($C_6C_7C_8$)	113.28	114.04	113.11	114.21	112.59	113.76	111.88	111.83	111.98	111.67	109.57	110.01
$C_2C_3C_4$ ($C_7C_8C_5$)	113.08	114.15	111.70	110.38	113.42	112.66	111.33	114.94	113.45	115.66	115.78	117.49
$C_3C_4C_5$ ($C_7C_5C_4$)	124.64	128.99	110.49	111.49	115.45	117.52	111.44	112.66	112.40	113.68	105.42	105.51
$C_1S_1C_4C_5$ ($C_6S_2C_5C_4$)	-175.04	-175.15	-178.29	-177.68	-179.52	177.86	-179.53	175.40	178.63	173.55	178.37	164.63
$C_2C_1S_1C_4$ ($C_7C_6S_2C_5$)	-7.25	-13.12	-7.07	-9.89	-6.77	-11.81	-6.34	-10.31	-7.03	-11.24	-6.68	-11.59
$C_1C_2C_3X$ ($C_6C_7C_8X$)	-	-	178.60	176.78	178.53	179.75	178.81	-178.75	172.83	171.02	179.83	-174.82
$C_2C_3C_4C_5$ ($C_7C_8C_5C_4$)	176.69	178.91	178.37	177.57	179.82	-177.20	179.48	-176.93	-179.06	-176.25	179.88	-172.70
$C_1C_2C_3C_4$ ($C_6C_7C_8C_5$)	0.07	0.22	-0.12	0.78	0-03	0.22	-0.23	0.01	-0.13	1.95	-0.29	0.47
$C_4C_3XC_8$ ($C_5C_8XC_3$)	-	-	0.26	0.04	-0.37	-0.89	-0.09	-0.76	-8.09	-12.06	0.03	-1.39

3.2. Opto-Electronic Properties

The HOMO, LUMO and energy band gaps (ΔE_g) calculated by semi-empirical (AM1 and PM3) and ab initio (HF/6-31G(d) and B3LYP/6-31G(d)) methods are displaced in Tables 2.. To further understand the properties of bridged BTO derivatives, some frontier molecular orbitals levels obtained from B3LYP/6-31G(d) are shown in Figure. 2. In BTO-B structure, the HOMO-1 and HOMO-3, and LUMO+2 and LUMO+3 are doubly degenerate respectively. In the case of BTO-S, HOMO and HOMO-3 are doubly degenerates, whereas in BTO-SO, HOMO-1 and HOMO-3 are doubly degenerate. However, in BTO-O and BTO-Si electronic orbitals levels are HOMO-1 degenerate; HOMO-1, LUMO+2 and LUMO+3 are degenerate in 2TO (Figure 2).

There is a systematic change of the HOMO and LUMO energies as X (X= BH_2, SiH_2, S, S=O and O) are introduced to bridge thiophene S-oxide dimmer. The ΔE_g of bridged BTO derivatives containing X (X =S and O) are less than that of 2TO, hence there is a more localization of π-electrons in BTO-S and BTO-O. However, BTO-BH_2, BTO-Si and BTO-SO are lower in ΔE_g than 2TO. The ΔE_g calculated by B3LYP/6-31G(d) ranged from 3.94eV (BTO-O) – 3.16eV (BTO-BH_2) as compared to 3.45eV for 2TO. The order of decrease in ΔE_g is BTO-BH_2 < BTO-SO < BTO-Si < 2TO < BTO-S < BTO-O.

Table 2. Calculated HOMO(eV), LUMO(eV), Band gap (ΔE_g), λ_{max} (nm) and Oscillator strength (OS) BTO derivatives by various methods.

Compound	Calculation method	HOMO	LUMO	ΔE_g	*Shift in ΔE_g	λ_{max} (OS)
2TO	AM1	-9.29	-1.45	7.84	-	-
	PM3	-9.51	-.1.43	8.08	-	-
	HF/6-31G(d)	-9.05	1.30	10.35	-	-
	B3LYP/6-31G(d)	-6.12	-2.67	3.45	-	360.95 (0.26)
BH_2	AM1	-9.49	-2.34	7.15	-0.69	-
	PM3	-9.60	-2.64	6.96	-1.12	-
	HF/6-31G(d)	-9.62	0.32	9.94	-0.41	-
	B3LYP/6-31G(d)	-6.55	-3.39	3.16	-0.29	536.21 (0.05)
SiH_2	AM1	-9.26	-1.71	7.55	-0.23	-
	PM3	-9.26	-1.60	7.66	-0.42	-
	HF/6-31G(d)	-8.67	0.56	9.23	-1.12	-
	B3LYP/6-31G(d)	-6.24	-3.00	3.24	-0.21	411.97 (0.20)
S	AM1	-9.21	-1.48	7.73	-0.11	-
	PM3	-9.36	-1.89	7.47	-0.62	-
	HF/6-31G(d)	-8.78	1.06	9.84	-0.54	-
	B3LYP/6-31G(d)	-6.36	-2.55	3.81	+0.36	341.79 (0.23)
S=O	AM1	-9.62	-2.20	7.42	-0.42	-
	PM3	-9.66	-2.35	7.31	-0.77	-
	HF/6-31G(d)	-9.32	0.07	9.39	-0.96	-
	B3LYP/6-31G(d)	-6.66	-3.39	3.27	-0.18	478.60 (0.04)
O	AM1	-9.25	-1.42	7.83	-0.01	-
	PM3	-9.49	-1.58	7.91	-0.17	-
	HF/6-31G(d)	-8.71	1.38	10.09	-0.26	-
	B3LYP/6-31G(d)	-6.34	-2.40	3.94	+0.48	328.53 (0.30)

*The shift in band gap (eV) is the differences in the bridged BTO-X and 2TO

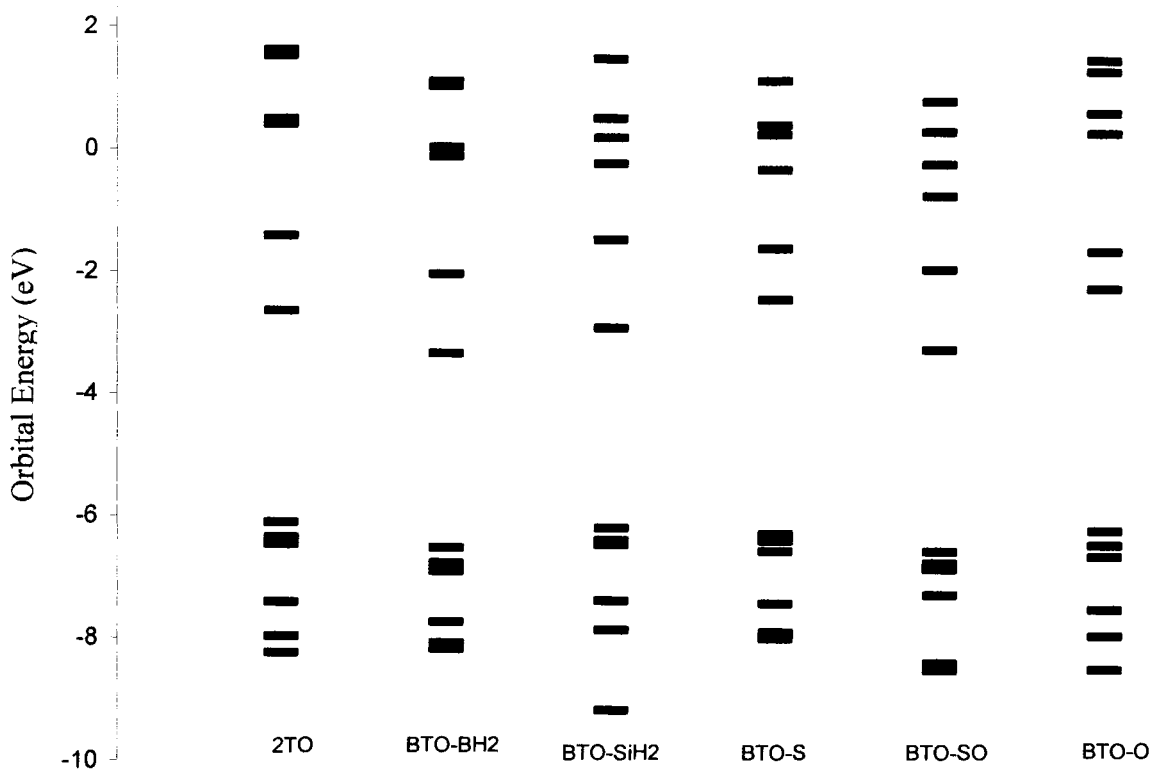

Fig. 2. Partial molecular orbital energy diagram for bridged BTO-X and 2TO calculated by B3LYP/6-31G(d) method.

The electronic spectra involving transition of valence electrons that occur in the UV-visible absorption was studied theoretically in order to investigate the effect of 2TO and the X bridged derivatives (X= BH_2, SiH_2, S, S=O and O) are shown in Table 2. It is found that with X= BH_2, SiH_2 and S=O, the λ_{max} shifted to a longer wavelength due to enhancement of π-conjugated system whereas, BTO-S and BTO-O shifted to shorter wave lengths as compared to BTO-CH_2 analogue. For example, the calculated λ_{max} for BTO-BH_2 and BTO-O are 536.21 and 328.53nm respectively as compared to 360.95nm for 2TO, there is in accordance with calculated Shift in band gaps by DFT method.

33. The Thermodynamic Properties

The standard thermodynamic properties at 298K calculated from all methods used are listed in Table 3 to determine the thermodynamic of insertion of X to bridged 2TO. It is observed that the results obtained from PM3 are in good agreement with that of DFT calculation [23] except in BTO-B and BTO-Si, this may be due to poor parameterization of boron and Silicon in PM3 method. For instances, the values of G° calculated by PM3

(DFT) for 2TO, BTO-S, BTO-SO and BTO-O are 217.48 (218.64), 167.82 (166.45), 170.90 (167.70) and 167.82 (175.74) respectively. The heat of formation for 2TO, BTO-B, BTO-Si, BTO-S and BTO-SO are higher than that of AM1 (Table 3).

Table 3. Standard enthalpy (H°), Standard entropy (S°) and Standard Gibb's free energy (G°) calculated by various methods at 298K.

Cdp	Calculation method	H° (kJ/mol)	S° (J/mol)	G° (kJ/mol)	H_f (kJ/mol)
2TO	AM1	355.94	419.73	230.80	119.07
	PM3	345.66	429.92	217.48	144.58
	HF/6-31G(d)	373.24	424.65	246.57	-
	B3LYP/6-31G(d)	346.63	429.26	218.64	-
BH_2	AM1	363.96	429.91	225.78	343.50
	PM3	342.83	439.76	211.72	346.38
	HF/6-31G(d)	366.81	423.89	240.43	-
	B3LYP/6-31G(d)	346.74	444.52	214.43	-
SiH_2	AM1	347.84	441.36	216.25	128.10
	PM3	336.15	448.89	202.31	169.38
	HF/6-31G(d)	365.56	431.28	236.97	-
	B3LYP/6-31G(d)	340.35	452.86	205.33	-
S	AM1	305.66	422.00	179.84	130.50
	PM3	296.96	433.13	167.82	186.53
	HF/6-31G(d)	318.92	417.68	194.39	-
	B3LYP/6-31G(d)	296.13	434.98	166.45	-
S=O	AM1	316.74	448.13	186.55	84.05
	PM3	307.46	457.90	170.94	125.77
	HF/6-31G(d)	331.81	448.32	198.14	-
	B3LYP/6-31G(d)	307.40	468.55	167.70	-
O	AM1	313.16	414.47	189.58	106.20
	PM3	304.61	421.81	178.85	82.08
	HF/6-31G(d)	326.57	405.90	205.55	-
	B3LYP/6-31G(d)	302.87	427.09	175.54	-

4. CONCLUSION

The geometrical and electronic structure, UV-visible absorption band, change in thermodynamic parameters of standard enthalpy, standard entropy and standard Gibb's free energy of bridged bithiophene S-oxide (BTO-X) derivatives have been investigated through quantum chemistry calculations using semi-empirical (AM1 and PM3), Hatree Fock (6-31G(d)) and B3LYP/6-31G(d) methods. The mean deviations of bond lengths calculated by PM3 as compared DFT are 0.014, 0.032 and 0.018Å for BTO-S, BTO-SO and BTO-O respectively, but both BTO-B and BTO-Si is deviated by 0.015Å. However, the bridge X has profound effect on the geometries on the bridged bithiophene S-oxide derivatives as compared 2TO. The values of thermodynamics parameters calculated by

PM3 and B3LYP/6-31G(d) are in good agreement except in BTO-B and BTO-Si due to poor parameterization of boron and silicon in PM3 method. The UV-visible absorption λ_{max} shifted to longer wavelength in BTO-B, BTO-Si and BTO-SO whereas in BTO-S and BTO-O the λ_{max} shifted to short wavelength.

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SYNTHESIS, SPECTRAL CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF SUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES

Anees A Siddiqui[1], Asif Husain[1], M Shaharyar[1], Mohd Rashid[1], Ravinesh Mishra[11], Jaseela Majeed[1] and Bhawana Sati[2]

[1]Department of Pharmaceutical Chemistry,
Faculty of Pharmacy, Jamia Hamdard
Hamdard University, New Delhi -110062, India.

[2]Krupanidhi College of Pharmacy,
Chikka Bellandur, Carmelaram Post, Varthur Hobli,
Bangalore - 560 035, India

ABSTRACT

1,3,4-oxadiazoles are important because of its versatile biological actions. In the present study, several 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives **(IIIa-j)** have been synthesized by the condensation of 8-hydroxy quinoline acetyl hydrazide **(II)** with various aromatic acids in presence of phosphorus oxychloride. The structures of the newly synthesized compounds have been established on the basis of elemental analysis, UV, IR and 1H NMR spectral data. The synthesized compounds were screened for their *in vitro* growth inhibiting activity against different strains of bacteria and fungi viz., *S. aureus, E. coli, P. aeruginosa, C. albicans, A. flavus,* and *A. fumigates* and the results were compared with the standard such as Ampicillin (50µg/ml) and Fluconazole (50µg/ml) using agar diffusion technique. Compounds **IIIc** and **IIIf** was found to be equipotent as ampicillin when tested against the strains of E. coli where as tested compounds **IIIc, IIIf** and **IIIi** showed good antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa* and *C. albicans*.

KEYWORDS

1,3,4-oxadiazole, Ampicillin, Fluconazole, Antibacterial and Antifungal activity

RESUMO

Os compostos da classe 1,3,4-oxadiazol são importantes por causa de sua atividade biológica versátil. O presente trabalho descreve a síntese de vários derivados de 2-(quinolino-8-iloximetil)-5-aril-1,3,4-oxadiazol. As estruturas dos novos compostos foram estabelecidas através de técnicas de UV, IR e RMN. A atividade biológica dos novos compostos foi comprovada contra várias bactérias e fungos, i.e., *S. aureus, E. coli, P. aeruginosa, C. albicans, A. flavus,* e *A. fumigates* e comparada com compostos padrão como Ampicilina (50µg/ml) e Fluconazol (50µg/ml).

PALVRAS CHAVE: 1,3,4-oxadiazol, Ampicilina, Fluconazol, Atividade antibacteriana e antifúngica

[1] **Corresponding author:** Ravinesh Mishra, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi-110062, India. Tel.: +919990031907; E mail: ravi_kcp@rediffmail.com

INTRODUCTION

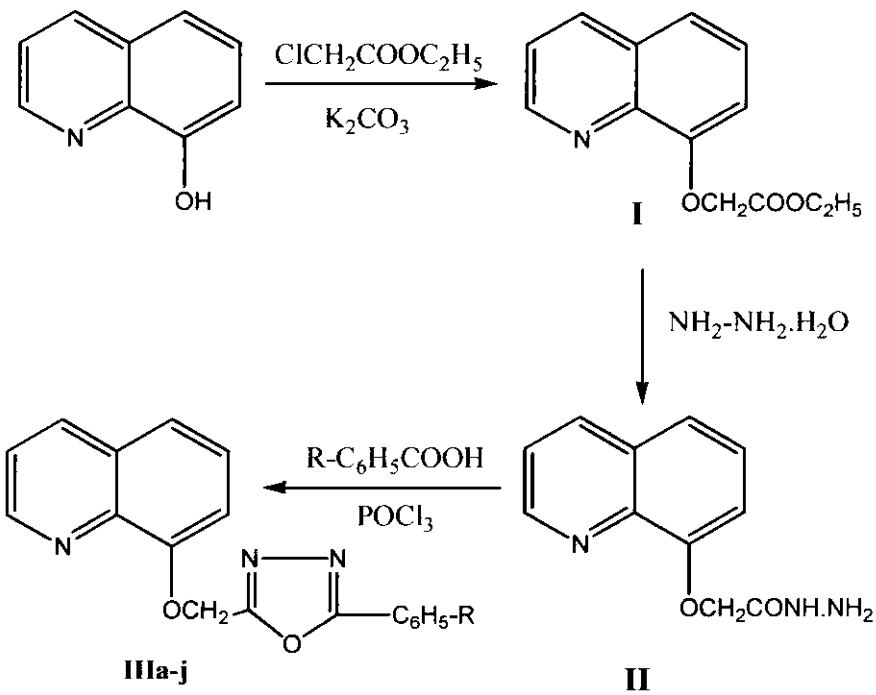
The compound 1,3,4-Oxadiazole is a versatile lead molecule for designing potential bioactive agents. The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial[1], anti-HIV[1], antitubercular[2], antimalarial[3], analgesic[4], anti-inflammatory[5], anticonvulsant[6], hypoglycemic[7] and other biological properties such as genotoxic studies[8] and lipid peroxidation inhibitor[9]. The development of antifungal agents has lagged behind that of antibacterial agents[10-13]. This is a predictable consequence of the cellular structure of the organisms involved. This difficulty complicates experiments designed to evaluate the *in vitro* or *in vivo* properties of a potential antifungal agent. 1,3,4-Oxadiazoles show various biological activities and have been synthesized from different compounds. 1,3,4-oxadiazole is popularly known for its antimicrobial[14], anti-inflammatory[15], pesticidal[16] and antihypertensive[17] activities. It is well known that the synthesis of heterocyclic compounds tend to contain multi-structure in a molecule. In this study, it was planned to incorporate the oxadiazole ring system into quanoline ring.

The earliest evidence of successful chemotherapy is from ancient Peru, where the Indians used bark from the Cinchona tree to treat malaria. Modern chemotherapy has been dated to the work of Paul Ehrlich in Germany, who sought systematically to discover effective agents to treat trypanosomiasis and syphilis. Ehrlich postulated that it would be possible to find chemicals that were selectively toxic for parasites but not toxic to humans[18].

Progress in the development of novel antibacterial agents has been great, but the development of effective, nontoxic antifungal and antiviral agents has been slow. Amphotericin B, isolated in the1950s, remains an effective antifungal agent, although newer agents such as fluconazole[19] are now widely used. An antimicrobial is a substance that kills or inhibits the growth of microbes such as bacteria (antibacterial activity), fungi (antifungal activity) and viruses (antiviral activity). Any attempt to discuss the chemotherapeutic properties[20] of heterocyclic compounds must, of necessity, be confined to a limited aspect of the subject.

EXPERIMENTAL

The protocol of compounds synthesized **(IIIa-j)** is given in Figure 1.



Compd.	R	Compd.	R
IIIa	4-Br	IIIf	4-OH
IIIb	4-NH_2	IIIg	3-Cl
IIIc	3-OCH_3	IIIh	4-Cl
IIId	3,4-OCH_3	IIIi	3-NO_2
IIIe	3,4-Cl	IIIj	2,4-OH

Figure 1. Schematic diagram for the synthesis of 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives **(IIIa-j)**

The chemicals were supplied by E. Merck (Germany) and S.D Fine chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene-ethylacetate-formic acid (5:4:1) and benzene-methanol (8:2), the spots were located under iodine vapours and UV light. IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). ^{1}H-NMR spectra were recorded or a Bruker AC 300 MHz spectrometer using TMS as internal standard in DMSO-d_6/$CDCl_3$ and Mass spectra

under electron impact conditions (EI) were recorded at 70 ev ionizing voltage with a VG Prospec instrument and are presented as m/z. Microanalysis of the compounds was performed on a Perkin-Elmer model 240 analyzer.

Synthesis of Ethyl-2-(quanoline-8-yloxy)acetate (I):

A mixture of 8-hydroxy quanoline (0.01 mol) ethyl chloro acetate (0.01 mol) and anhydrous potassium carbonate (0.01 mol) in dry acetone were refluxed on a water bath for 6hr and poured into ice-cold water. Solid product obtained was filtered and recrystallized from ethanol. Yield 76%.

Synthesis of 8-hydroxy quinoline acetyl hydrazide (II):

A mixture of compound 1(0.01 mol) hydrazine hydrate (99%, 0.07 mol) in methanol was refluxed for 5 hr. From the resultant mixture excess of ethanol was removed by distillation. On cooling, white needle crystals separates out. It was recrystallized with ethanol. The yield was 71%.

Synthesis of 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives (IIIa-j):

A mixture of compound 2 (0.01 mol) and various aromatic acid (0.01 mol) in $POCl_3$ were refluxed for 6 hr. The content was cooled and poured into ice-cold water, then neutralized with $NaHCO_3$ solution, until a solid was obtained. The solid separated by filtration and recrystallized with ethanol.

2-(quinoline-8-yloxymethyl)-5-(4-bromophenyl)-1,3,4-oxadiazole (IIIa): Yield: 66%; Mp. 135-137°C; R_f : 0.50 (toluene: ethylacetate: formic acid ; 5: 4: 1) FTIR (KBr, cm^{-1}) 3050 (C-H), 1578 (C=N), 1508 (C=C), 1206 (C-O-C), 575(C-Br); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ 7.5-8.5 (m,10H, Ar-H), 4.87 (s, 2H, OCH_2); MS: m/z 318(M^+); Anal. Calcd for $C_{18}H_{13}N_3O_2Br_1$: C,73.23; H, 5.04; N, 9.23. Found: C, 73.20; H, 5.02; N, 9.21.

2-(quinoline-8-yloxymethyl)-5-(4-aminophenyl)-1,3,4-oxadiazole (IIIb): Yield: 62%; Mp.190-192°C; R_f : 0.62 (toluene: ethylacetate: formic acid; 5: 4: 1); FTIR (KBr, cm^{-1}) 3550 (N-H), 1550 (C=N), 1480 (C=C), 1070 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.5-8.5 (m, 10H, Ar-H), 5.8 (s, 2H, NH_2), 4.8 (s, 2H, OCH_2); MS: m/z 318 (M^+); Anal. Calcd for $C_{18}H_{15}N_4O_2$: C, 68.05; H, 5.04; N, 13.05. Found: C, 68.02; H, 5.04; N, 13.01.

2-(quinoline-8-yloxymethyl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (IIIc): Yield: 70%; Mp.170-171°C; R_f : 0.55 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3050 (C-H),1560 (C=N), 1580 (C=C), 1030 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.5-8.0 (m, 10H, Ar-H), 3.8(s, 2H, OCH_2), 2.9 (s, 3H, OCH_3); MS: m/z 335 (M^+); Anal. Calcd for $C_{19}H_{16}N_3O_3$: C, 72.23; H, 5.04; N, 10.23. Found: C, 72.20; H, 5.02; N, 10.21.

2-(quinoline-8-yloxymethyl)-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole (IIId): Yield: 75%; Mp.175-177°C; R_f : 0.62 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3040 (C-H), 1630 (C=N), 1450 (C=C), 1170 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 6.8-8.2 (m, 9H, Ar-H), 5.6 (s, 2H, OCH_2), 3.8 (s, 6H, OCH_3); MS: m/z 364 (M^+); Anal. Calcd for $C_{20}H_{18}N_3O_4$: C, 72.05; H, 5.61; N, 9.01. Found: C, 72.0; H, 5.60; N, 9.01.

2-(quinoline-8-yloxymethyl)-5-(3,4-dichlorophenyl)-1,3,4-oxadiazole (IIIe): Yield: 62%; Mp.156-157°C; R_f : 0.59 (toluene: ethylacetate: formic acid ; 5: 4: 1)FTIR (KBr, cm^{-1}) 3045 (C-H),1530 (C=N), 1550 (C=C), 1230 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.2-8.5 (m, 9H, Ar-H), 5.4 (s, 2H, OCH_2); MS: m/z 372(M^+), 373(M^++1) ; Anal. Calcd for $C_{18}H_{12}N_3O_2Cl_1$: C, 73.01; H, 6.32; N, 12.05. Found: C, 73.02; H, 6.34; N, 12.03.

2-(quinoline-8-yloxymethyl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazole (IIIf): Yield: 68%; Mp.195-197°C; R_f : 0.54 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3530 (O-H), 2925 (C-H),1638 (C=N),1454 (C=C), 1070 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.3-8.0 (m, 10H, Ar-H), 4.6(s, 1H, OH), 4.8 (s, 2H, OCH_2); MS: m/z 320 (M^+); Anal. Calcd for $C_{18}H_{14}N_3O_3$: C, 72.33; H, 8.01; N, 12.01. Found: C, 72.33; H, 8.01; N, 12.03.

2-(quinoline-8-yloxymethyl)-5-(3-chlorophenyl)-1,3,4-oxadiazole (IIIg): Yield: 60%; Mp.145-147°C; R_f : 0.58 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 2850 (C-H),1639 (C=N), 1458 (C=C), 1070 (C-O-C), 656 (C-Cl); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.0-8.2 (m, 10H, Ar-H), 5.1 (s, 1H, OH), 4.2 (s, 2H, OCH_2); MS: m/z 337(M^+), 338 (M^++1); Anal.Calcd for $C_{18}H_{13}N_3O_2Cl_1$: C, 74.01; H, 7.04; N, 9.33.Found: C, 74.02; H, 7.03; N, 9.32.

2-(quinoline-8-yloxymethyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (IIIh): Yield: 63%; Mp.155-156°C; R_f : 0.61 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3050 (C-H), 1539 (C=N), 1508 (C=C), 1090 (C-O-C), 650(C-Cl); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 6.9-8.4 (m, 10H, Ar-H), 4.6 (s, 2H, OCH_2); MS: m/z 338(M^+), 339(M^++1); Anal.Calcd for $C_{18}H_{13}N_3O_2Cl_1$: C, 73.01; H, 7.04; N, 8.33.Found: C, 73.02; H, 7.03; N, 8.32.

2-(quinoline-8-yloxymethyl)-5-(3-nitrophenyl)-1,3,4-oxadiazole (IIIi): Yield: 66%; Mp.145-147°C; R_f : 0.62 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3020 (C-H), 1630 (C=N), 1554(C=C), 1170 (C-O-C), 1150 (N-=O); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.2-8.5 (m, 10H, Ar-H), 4.6 (s, 2H, OCH_2); MS: m/z 349(M^+); Anal. Calcd for $C_{18}H_{13}N_4O_4$: C, 70.13; H, 6.04; N, 9.16. Found: C, 70.12; H, 6.02; N, 9.13.

2-(quinoline-8-yloxymethyl)-5-(2,4-dihydroxyphenyl)-1,3,4-oxadiazole (IIIj): Yield: 72%; Mp.185-186°C; R_f : 0.56 (toluene: ethylacetate: formic acid ; 5: 4: 1); FTIR (KBr, cm^{-1}) 3450 (O-H), 1530 (C=N),1510 (C=C), 1205 (C-O-C); ^{1}H-NMR (300 MHz, DMSO-d_6, TMS) δ: 7.0-8.1 (m, 9H, Ar-H), 5.5 (s, 2H, 2OH), 4.9 (s, 2H, OCH_2); MS: m/z 336(M^+); Anal. Calcd for $C_{18}H_{14}N_3O_4$: C, 71.13; H, 5.04; N, 9.16. Found: C, 71.12; H, 5.02; N, 9.13.

RESULTS AND DISCUSSION

Various 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives **(IIIa-j)** were synthesized and synthesized compounds were screened for their *in vitro* growth inhibiting activity against different strains of bacteria and fungi viz., *S. aureus, E. coli, P. aeruginosa, C. albicans, A. flavus,* and *A. fumigates* and the results were compared with the standard such as Ampicillin (50μg/ml) and Fluconazole (50μg/ml) using agar diffusion technique. Compounds **IIIc** and **IIIf** was found to be equipotent as ampicillin when tested against the strains of E. coli where as tested compounds **IIIc, IIIf** and **IIIi** showed good antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa* and *C. albicans*. Whereas remaining compounds have shown moderate antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa, A. flavus,* and *A. Fumigates* given in Table 1

Table 1: Antimicrobial activity of for 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives (IIIa-j)

Compd. no.	Zone of inhibition in mm					
	Antibacterial Activity			Antifungal Activity		
	SA	EC	PA	CA	AF	AFU
IIIa	15	14	12	10	20	18
IIIb	24	20	16	10	13	17
IIIc	15	10	17	20	15	18
IIId	17	20	23	22	20	12
IIIe	24	17	18	19	20	14
IIIf	23	11	10	16	13	23
IIIg	22	16	17	20	12	18
IIIh	17	15	18	20	18	10
IIIi	14	20	24	20	17	18
IIIj	19	20	24	10	16	15
Ampicillin	24	25	25	-	-	-
Fluconazole	-	-	-	17	16	17

Where SA-*S. aureus*, EC-*E. coli*, PA-*P. aeruginosa*, CA-*C. albicans*, AF-*A. flavus*, AFU-*A. fumigatus*

SCREENING FOR ANTIMICROBIAL ACTIVITY

The antimicrobial activity of all the newly synthesized compounds **(IIIa-j)** was determined by well plate method[21-22] in nutrient agar (Hi-Media) (antibacterial activity) and Sabouraud dextrose agar (SDA) (Hi- Media) (antifungal activity)[23-24]. The *in vitro* antimicrobial activity was carried out against 24h old cultures of bacterial and 72h old cultures of fungal strain. The bacterial and fungal strains for the study are listed in Table 1. The compounds were tested at a concentration of 100 µg/ml and solutions were prepared were prepared in dimethyl formamide (DMF). The petridishes used for antibacterial screening were incubated at 37±1° C for 24h, while those used for antifungal activity were incubated at 28°C for 48-72h. The results were compared to Ampicillin (50µg/ml) and Fluconazole (50µg/ml) for antibacterial and antifungal activity respectively by measuring zone of inhibition in mm. The antibacterial and antifungal screening results were presented in Table 1.

CONCLUSIONS

The entire study reveals that there is wide scope of modifications possible for 1,3,4-oxadiazole ring system. Oxadiazole ring system could be incorporated into many more ring systems which itself have their own activity and could lead to more potent and highly active compounds. Various 2-(quinoline-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole derivatives **(IIIa-j)** were synthesized and synthesized compounds were screened for their *in vitro* growth inhibiting activity against different strains of bacteria and fungi viz., *S. aureus, E. coli, P. aeruginosa, C. albicans, A. flavus,* and *A. fumigates* and the results were compared with the standard such as Ampicillin (50µg/ml) and Fluconazole (50µg/ml) using agar diffusion technique. Compounds **IIIc** and **IIIf** was found to be equipotent as ampicillin when tested against the strains of E. coli where as tested compounds **IIIc, IIIf** and **IIIi** showed good antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa* and *C. albicans*. Whereas remaining compounds have shown moderate antibacterial and antifungal activity when tested against the strains of *S. aureus, P. aeruginosa, A. flavus,* and *A. Fumigates* given in Table 1.

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HETEROCYCLIC SYNTHESIS USING NITRILIMINES PART 15: SYNTHESIS OF NEW 1,2,4,5-TETRAZINONE AND 1,2,4,5-TETRAZEPINONE DERIVATIVES

Hany M. M. Dalloul

Department of Chemistry, Faculty of Applied Science,
Al-Aqsa University of Gaza, P.O.Box 4051, Gaza 76888, Palestine.
E-mail: hmdalloul60@yahoo.com

ABSTRACT

*The reaction of C-aroyl-N-arylnitrilimines **II** with Girard-reagent P **III** led to the formation of the 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-ones **IVa-f** and 1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-ones **Va-f**, which underwent thermal oxidation to 1,6-dihydro-1,2,4,5-tetrazin-6-ones and 6,7-dihydro-1,2,4,5-tetrazepin-6-ones. The microanalysis and spectral data of the synthesized compounds are in full agreement with their molecular structure.*

KEYWORDS

Nitrilimines, Cyclization, 1,2,4,5-Tetrazinones, 1,2,4,5-Tetrazepinones.

RESUMO

*A reação de C-aroil-N-arilnitriliminas com o reagente de Girard P **III** levou a formação dos 1,2,3,4-tetrahidro-1,2,4,5-tetrazino-3-onas **IVa-f** e 1,2,6,7-tetrahidro-1,2,4,5-tetrazepino-6-onas **Va-f**. Com oxidação térmica formaram 1,6-dihidro-1,2,4,5-tetrazino-6-onas e 6,7-dihidro-1,2,4,5-tetrazepino-6-onas. A microanalise e os dados espectrais dos compostos sintetizados concordam plenamente com a estrutura molecular.*

PALAVRAS-CHAVE

Nitriliminas, Ciclização; 1,2,4,5-Tetrazinonas; 1,2,4,5-Tetrazepinonas.

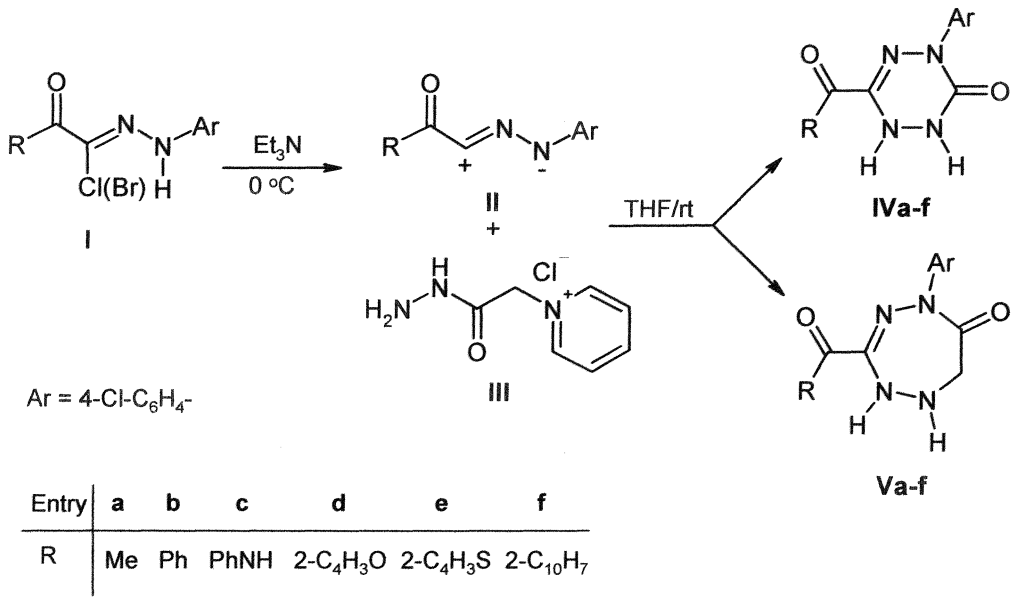
1. INTRODUCTION

Substituted 1,2,4,5-tetrazines represent significant class of heterocycles that find many useful pharmacological and medicinal applications [1-4]. Azolotetrazinones have been the focus of medicinal chemists in the past decades because of the outstanding antineoplastic activity exhibited by them [5]. Imidazole tetrazinone (Temozolomide: Temodal®) has shown promising antitumor activity against low and high-grade glioma [3-6], melanoma [7,8], and mycosis fungoides [8,9]. Furthermore, some pyridopyrrolotetrazine derivatives showed significant activity against leukemia, non-small lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast tumors cell lines. Different methods were used to synthesize 1,2,4,5-tetrazinone derivatives [6], some of which employed the cyclocondensation of nitrilimines, generated in situ from the corresponding hydrazonoyl halides by the action of a suitable base, with nucleophilic substrates incorporating suitably located electrophilic centers. Ottensooser [10] was first reported the synthesis of 1,2,4,6-tetrazepine derivative by the action of dilute potassium hydroxide solution on isobutyl chlorourea. Some derivatives of the fused tetrazepine ring system have been prepared by Sidhu *et al.* [11] by the treatment of 5-(2-aminophenyl)-4-5,6-dihydro-*4H*-1,2,4,6-tetrazepine with ferric chloride or sodium nitrite solution.

In continuation of our research line dealing with the construction of heterocyclic systems by means of nitrilimines cyclocondensation methodology [7-9], we investigated the reaction of C-substituted N-arylnitrilimines **II** with acetylhydrazide pyridinium chloride (Girard-reagent P) **III** in an attempt to synthesize new derivatives of 1,2,4,5-tetrazinones **IVa-f** and 1,2,4,5-tetrazepin-6-ones **Va-f** in anticipation of expected interesting biological activities.

2. RESULTS AND DISCUSSION

Recently we found that 1,1-dimethyl- and 1-methyl-1-phenylhydrazine react readily with nitrilimines, generated *in situ* from the action of triethylamine onto the hydrazonoyl halides, yielding the corresponding acyclic electrophilic addition products, which cyclized intramolecularly to the corresponding 1,2,3,4-tetrahydro-1,2,4,5-tetrazines under thermal conditions [12]. On the other hand, the reaction of the same nitrilimines **II** with acetylhydrazide pyridinium chloride **III** (Girard-reagent P) for 12-18 hours in 1,4-dioxane at room temperature gave a cyclocondensation products, 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-ones **IVa-f** and 1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-ones **Va-f** (Figure 1). The purity of the isolated compounds was checked by TLC in different solvents.



Entry	a	b	c	d	e	f
R	Me	Ph	PhNH	2-C_4H_3O	2-C_4H_3S	2-$C_{10}H_7$

Figure 1. Schematic diagram for the synthesis of compounds **IVa-f** and **Va-f**

The formation of compounds **IVa-f** and **Va-f** is assumed to involve unisolable nucleophilic addition adducts **VIII**, which undergo intramolecular cyclization in tow pathways as shown in Figure 2. The cyclization at the carbon of amide group (path a) followed with elimination of pyridine methochloride molecule [13] affording the 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one derivatives **IVa-f** and the cyclization at methylene carbon (path b) followed with loosing pyridine hydrochloride molecule yielding the unknown 1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one derivatives **Va-f** as a minor products.

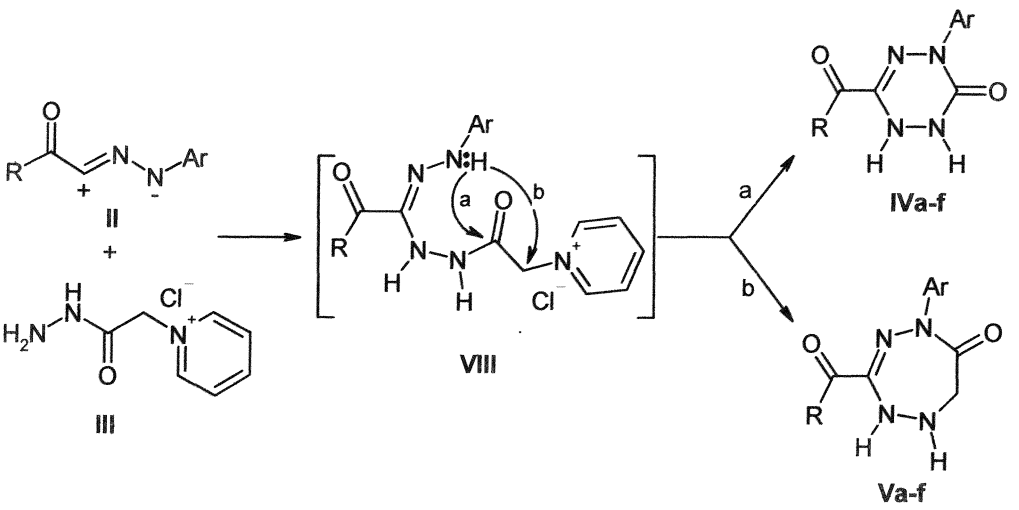
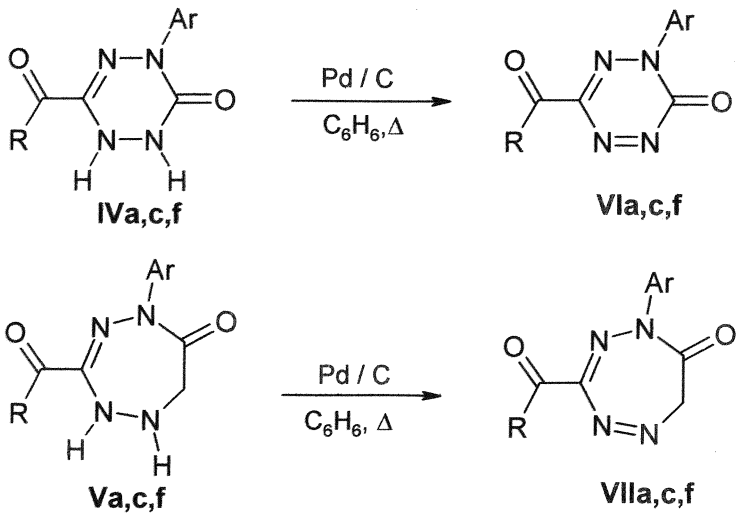


Figure 2. Suggested reaction mechanism

2.1. Spectroscopical Data

The structures of the titled compounds **IVa-f** and **Va-f** have been confirmed by elemental analysis and their spectral data (experimental part). Their IR spectra showed intense absorption bands within the 3435-3220 cm^{-1} range that were attributed to HN-NH and 1675-1670 cm^{-1} assigned to carbonyl of the ring. All these products gave two singlet signals at 6.6-6.4 ppm in their ^1H NMR spectra, attributed to the HN-NH protons. In compounds **Va-f**, the signal of CH_2 protons appeared as singlet at 4.3 ppm. The ^{13}C NMR spectra of the synthesized compounds **IVa-f** and **Va-f** showed all the signals of the proposed structures, specially carbonyl carbon of the ring were found to resonate at about 172 and 171 ppm and the signal at 43.8 ppm are assignable to methylene carbon of the ring in compounds **Va-f**.

The oxidation of compounds **IVa,c,f** and **Va,c,f** was carried out in refluxing benzene in presence of activated charcoal, afforded 1,6-dihydro-1,2,4,5-tetrazin-3-ones **VIa,c,f** and 6,7-dihydro-1,2,4,5-tetrazepin-6-ones **VIIa,c,f** respectively, (Figure 3). Both the analytical and spectral data (IR, ^1H NMR, ^{13}C NMR and mass spectra) of the title compounds **VIa,c,f** and **VIIa,c,f** were in full agreement with the proposed structures and depicted in experimental part. Their mass spectra displayed the correct molecular ion peaks (M^+) in accordance with the suggested structures. Their IR spectra indicating the disappearance of absorption band in the 3435-3220 cm^{-1} region due to the HN-NH function. In their ^1H NMR data, no signals for HN-NH (6.6-6.4 ppm) were observed. Their ^{13}C NMR spectra revealed all the signals of the proposed structures.



IVa,c,f **VIa,c,f**

Va,c,f **VIIa,c,f**

Figure 3. Thermal oxidation of compounds **IVa,c,f** and **Va,c,f**

3. EXPERIMENTAL SECTION

3.1. General Remarks

Melting points were determined on thermal melting point apparatus and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in DMSO-d_6 solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as δ values in parts per millions (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were performed at the Microanalytical Center of Cairo University, Egypt. Girard-reagent P, tetrahydrofuran (THF), benzene and triethylamine were purchased from Avocado Chemical Company, England. Hydrazonoyl halides **I** [14] were prepared according to the methods reported in the literature.

3.2. Synthesis of Compounds IVa-f and Va-f

To a mixture of the appropriate hydrazonoyl halide **I** (10 mmol) and acetylhydrazide pyridinium chloride **III** (10 mmol) in dry tetrahydrofuran or 1,4-dioxane (100 mL), triethylamine (3 ml, 20 mmol) was added at room temperature and the reaction mixture was controlled by TLC. The stirring continued until the starting substrates were completely consumed (12-18 h). The triethylammonium chloride salt was filtered off, the solvent was removed under reduced pressure and the residue was triturated with methanol. The solid thus obtained was filtered off and chromotographed using silica gel TLC, elution with benzene: ethyl acetate: petroleum ether (40-60 °C) 5:4:1 afforded the desired products **IVa-f**.
The following compounds were prepared using this method:

6-Acetyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (IVa): White solid; yield: 67%; Mp. 178-180 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ: 2.56 (s, 3H, CH_3), 6.51 (s, 1H, NH), 6.45 (s, 1H, NH), 7.10-7.68 (m, 4H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 192.4 (CH_3C=O), 171.8 (ring C=O), 146.8 (C=N), 141.6-125.1 (Ar-C), 26.5 (CH_3). IR (KBr disk, cm^{-1}): 3430, 3236 (NH), 1675 (ring C=O), 1690 (C=O), 1598 (C=N). MS, (*m/z*): 252/254 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{10}H_9ClN_4O_2$ (M_r = 252.66): C, 47.54; H, 3.59; N, 22.17%; Found: C, 47.60; H, 3.50 N, 22.10%.

6-Benzoyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (IVb): White solid, yield: 62%; Mp. 161-163 °C, ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ: 6.52 (s, 1H, NH), 6.47 (s, 1H, NH), 7.13-7.72 (m, 9H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 184.7 (PhC=O), 171.6 (ring C=O), 146.6 (C=N), 141.6-121.4 (Ar-C). IR (KBr disk, cm^{-1}): 3432, 3224 (NH), 1674 (ring C=O), 1660 (PhC=O), 1596 (C=N). MS, m/z: 314/316 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{15}H_{11}ClN_4O_2$ (M_r = 314.73): C, 57.24; H, 3.52; N, 17.80%; Found: C, 57.35; H, 3.45 N, 17.89%.

4-(4-Chlorophenyl)-6-phenylaminocarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (IVc): Off white solid, yield: 68%; Mp. 189-191 °C, ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ: 6.48 (s, 1H, NH), 6.44 (s, 1H, NH), 7.13-7.71 (m,

9H, Ar-H), 10.2 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 171.6 (ring C=O), 159.7 (PhNHC=O), 147.6 (C=N), 141.4-121.6 (Ar-C). IR (KBr disk, cm^{-1}): 3428, 3272, 3227 (NH), 1672 (ring C=O), 1655 (PhC=O), 1599 (C=N). MS, m/z: 329/331 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{15}H_{12}ClN_5O_2$ (M_r = 329.75): C, 54.64; H, 3.67; N, 21.24%; Found: C, 54.55; H, 3.75 N, 21.15%.

4-(4-Chlorophenyl)-6-(2-furoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (IVd): White solid, yield: 64%; Mp. 147-149 °C, ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ: 6.60 (s, 1H, NH), 6.56 (s, 1H, NH), 7.16-7.80 (m, 7H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 174.6 (C=O), 171.2 (ring C=O), 147.1 (C=N), 142.3-121.4 (Ar-C). IR (KBr disk, cm^{-1}): 3433, 3237 (NH), 1674 (ring C=O), 1665 (C=O), 1612 (C=N). MS, m/z: 304/306 $[M]^+$. Anal, Calcd for $C_{13}H_9ClN_4O_3$ (M_r = 304.69): C, 51.25; H, 2.98; N, 18.39%; Found: C, 51.35; H, 3.05 N, 18.30%.

4-(4-Chlorophenyl)-6-(2-thenoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (IVe): Yellow solid, yield: 65%; Mp. 195-197 °C, ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ: 6.58 (s, 1H, NH), 6.53 (s, 1H, NH), 7.12-7.82 (m, 7H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 175.4 (C=O), 171.4 (ring C=O), 146.9 (C=N), 142.6-121.7 (Ar-C). IR (KBr disk, cm^{-1}): 3431, 3228 (NH), 1675 (ring C=O), 1660 (C=O), 1610 (C=N). MS, m/z: 320/322 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{13}H_9ClN_4O_2S$ (M_r = 320.76): C, 48.68; H, 2.83; N, 17.47%; Found: C, 48.80; H, 2.90 N, 17.55%.

4-(4-Chlorophenyl)-6-(2-naphthoyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (IVf): Pale yellow solid, yield: 60%; Mp. 201-203 °C, ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ: 6.60 (s, 1H, NH), 6.54 (s, 1H, NH), 7.22-8.42 (m, 11H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 184.5 (C=O), 170.8 (ring C=O), 146.7 (C=N), 142.2-120.9 (Ar-C). IR (KBr disk, cm^{-1}): 3428, 3221 (NH), 1675 (ring C=O), 1650 (C=O), 1605 (C=N). MS, (*m/z*): 364/366 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{19}H_{13}ClN_4O_2$ (M_r = 364.79): C, 62.56 H, 3.59; N, 15.36%; Found: C, 62.45; H, 3.70 N, 15.30%.

3-Acetyl-5-(4-chlorophenyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Va): White solid, yield: 32%; Mp. 134-136 °C, ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ: 2.54 (s, 3H, CH_3), 4.34 (s, 2H, CH_2), 6.50 (s, 1H, NH), 6.41 (s, 1H, NH), 7.10-7.68 (m, 4H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 192.4 (CH_3C=O), 170.8 (ring C=O), 147.8 (C=N), 142.6-125.6 (Ar-C), 43.8 (CH_2), 26.6 (CH_3). IR (KBr disk, cm^{-1}): 3430, 3236 (NH), 1675 (ring C=O), 1687 (C=O), 1598 (C=N). MS, m/z: 266/268 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{11}H_{11}ClN_4O_2$ (M_r = 266.69): C, 49.54; H, 4.16; N, 21.01%; Found: C, 49.65; H, 4.05 N, 20.90%.

3-Benzoyl-5-(4-chlorophenyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Vb): White solid, yield: 31%; Mp. 154-156 °C, ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ: 4.33 (s, 2H, CH_2), 6.47 (s, 1H, NH), 6.43 (s, 1H, NH), 7.13-7.72 (m, 9H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 184.7 (PhC=O), 171.6 (ring C=O), 146.6 (C=N), 141.6-121.4 (Ar-C), 43.7 (CH_2). IR (KBr disk, cm^{-1}): 3430, 3236 (NH), 1674 (ring C=O), 1665 (PhC=O), 1596 (C=N). MS, m/z: 328/330 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{16}H_{13}ClN_4O_2$ (M_r = 328.76): C, 58.46; H, 3.99; N, 17.04%; Found: C, 58.36; H, 4.07 N, 16.95%.

5-(4-Chlorophenyl)-3-phenylaminocarbonyl-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Vc): White solid, yield: 30%; Mp. 179-181 °C, ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ: 4.32 (s, 2H, CH_2), 6.48 (s, 1H, NH), 6.42 (s, 1H, NH), 7.13-7.71 (m, 9H, Ar-H), 10.3 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ:

184.7 (PhC=O), 171.6 (ring C=O), 159.7 (PhNHC=O), 147.6 (C=N), 141.4-121.6 (Ar-C), 43.5 (CH_2). IR (KBr disk, cm^{-1}): 3430, 3275, 3236 (NH), 1672 (ring C=O), 1655 (PhC=O), 1599 (C=N). MS, m/z: 343/345 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{16}H_{14}ClN_5O_2$ (M_r = 343.78): C, 55.90; H, 4.10; N, 20.37%; Found: C, 55.88; H, 3.91 N, 20.25%.

5-(4-Chlorophenyl)-3-(2-furoyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Vd): White solid, yield: 33%; Mp. 149-151 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS) δ: 4.30 (s, 2H, CH_2), 6.52 (s, 1H, NH), 6.47 (s, 1H, NH), 7.16-7.80 (m, 7H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 174.6 (C=O), 171.2 (ring C=O), 147.1 (C=N), 142.3-121.4 (Ar-C), 43.6 (CH_2). IR (KBr disk, cm^{-1}): 1674 (ring C=O), 1665 (C=O), 1612 (C=N). MS, m/z: 318/320 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{14}H_{11}ClN_4O_3$ (M_r = 318.72): C, 52.76; H, 3.48; N, 17.58%; Found: C, 52.65; H, 3.40 N, 17.65%.

5-(4-Chlorophenyl)-3-(2-thenoyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Ve): White solid, yield: 31%; Mp. 171-173 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS) δ: 4.33 (s, 2H, CH_2), 6.50 (s, 1H, NH), 6.46 (s, 1H, NH), 7.12-7.82 (m, 7H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 175.4 (C=O), 171.4 (ring C=O), 146.9 (C=N), 142.6-121.7 (Ar-C), 43.5 (CH_2). IR (KBr disk, cm^{-1}): 3430, 3236 (NH), 1675 (ring C=O), 1660 (C=O), 1610 (C=N). MS, m/z: 334/336 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{14}H_{11}ClN_4O_2S$ (M_r = 334.79): C, 50.23; H, 3.31; N, 16.74%; Found: C, 50.30; H, 3.21 N, 16.65%.

5-(4-chlorophenyl)-3-(2-naphthoyl)-1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-one (Vf): White solid, yield: 28%; Mp. 162-164 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS) δ: 4.32 (s, 2H, CH_2), 6.45 (s, 1H, NH), 6.41 (s, 1H, NH), 7.22-8.42 (m, 11H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 184.5 (C=O), 170.8 (ring C=O), 146.7 (C=N), 142.2-120.9 (Ar-C), 43.7 (CH_2). IR (KBr disk, cm^{-1}): 3430, 3236 (NH), 1675 (ring C=O), 1650 (C=O), 1605 (C=N). MS, m/z: 378/380 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{20}H_{15}ClN_4O_2$ (M_r = 378.82): C, 63.41; H, 3.99; N, 14.79%; Found: C, 63.30; H, 4.10 N, 14.85%.

3.3. Thermal Oxidation of Compounds 4a,c,f and 5a,c,f

A compounds **4a,c,f** or **5a,c,f** (5 mmol) and Pd/charcoal in benzene (50 mL) were heated to reflux for 2-4 hours and monitored by TLC. The reaction mixture was cooled, then filtered and the solvent evaporated. The residual solid was collected and recrystallized from ethanol to give the desired compounds **4a,c,f and 5a,c,f**. The following compounds were prepared using this method:

3-Acetyl-5-(4-chlorophenyl)-1,6-dihydro-1,2,4,5-tetrazin-3-ones (VIa): White solid, yield: 77%; Mp. 230-232 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS) δ: 2.54 (s, 3H, CH_3), 7.10-7.68 (m, 4H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 192.8 (RC=O), 172.5 (ring C=O), 147.8 (C=N), 142.6-126.0 (Ar-C), 26.7 (CH_3). IR (KBr disk, cm^{-1}): 1690 (RC=O), 1675 (ring C=O), 1610 (C=N). MS, m/z: 250/252 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{10}H_7ClN_4O_2$ (M_r = 250.65): C, 47.92; H, 2.82; N, 22.35%; Found: C, 47.80; H, 2.90 N, 22.25%.

5-(4-Chlorophenyl)-3-phenylaminocarbonyl-1,6-dihydro-1,2,4,5-tetrazin-3-ones (VIc): White solid, yield: 54%; Mp. 230-232 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS) δ: 7.10-7.68 (m, 9H, Ar-H), 9.96 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 172.3 (ring C=O), 160.3 (PhNHC=O), 147.3 (C=N),

142.3-126.2 (Ar-C). IR (KBr disk, cm^{-1}): 3277 (NH), 1672 (ring C=O), 1660 (RC=O), 1615 (C=N). MS, m/z: 327/329 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{15}H_{10}ClN_5O_2$ (M_r = 327.73): C, 54.97; H, 3.08; N, 21.37%; Found: C, 55.10; H, 2.95 N, 21.25%.

5-(4-chlorophenyl)-3-(2-naphthoyl)-1,6-dihydro-1,2,4,5-tetrazin-3-ones (VIf): White solid, yield: 76%; Mp. 230-232 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS) δ: 7.10-7.68 (m, 11H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 185.2 (RC=O), 171.7 (ring C=O), 147.7 (C=N), 143.4-121.8 (Ar-C). IR (KBr disk, cm^{-1}): 1675 (ring C=O), 1650 (RC=O), 1610 (C=N). MS, m/z: 362/364 $[M]^+$. Anal, Calcd for $C_{19}H_{11}ClN_4O_2$ (M_r = 362.78): C, 62.91; H, 3.06; N, 15.44%; Found: C, 62.80; H, 2.95 N, 15.55%.

3-Acetyl-5-(4-chlorophenyl)-6,7-tetrahydro-1,2,4,5-tetra-zepin-6-one (VIIa): White solid, yield: 74%; Mp. 201-203 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS) δ: 4.44 (s, 2H, CH_2), 7.22-8.42 (m, 4H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 192.0 (C=O), 172.2 (ring C=O), 148.3 (C=N), 142.9-124.8 (Ar-C), 44.7 (CH_2), 26.7 (CH_3). IR (KBr disk, cm^{-1}): 1693 (C=O), 1675 (ring C=O), 1605 (C=N). MS, m/z: 264/266 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{11}H_9ClN_4O_2$ (M_r = 264.67): C, 49.92; H, 3.43; N, 21.17%; Found: C, 50.05; H, 3.50 N, 21.10%.

5-(4-Chlorophenyl)-3-phenylaminocarbonyl-6,7-tetrahydro-1,2,4,5-tetra-zepin-6-one (VIIc): White solid, yield: 71%; Mp. 201-203 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS) δ: 4.43 (s, 2H, CH_2), 7.22-8.42 (m, 9H, Ar-H), 9.98 (s, 1H, NH). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 172.8 (ring C=O), 160.5 (PhNHC=O), 147.7 (C=N), 143.2-124.9 (Ar-C), 44.2 (CH_2). IR (KBr disk, cm^{-1}): 3273 (NH), 1673 (ring C=O), 1655 (C=O), 1610 (C=N). MS, m/z: 341/343 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{16}H_{12}ClN_5O_2$ (M_r = 341.76): C, 53.23; H, 3.54; N, 20.49%; Found: C, 53.35; H, 3.60 N, 20.55%.

5-(4-chlorophenyl)-3-(2-naphthoyl)-6,7-tetrahydro-1,2,4,5-tetra-zepin-6-one (VIIf): White solid, yield: 70%; Mp. 201-203 °C, ^1H NMR (300 MHz, DMSO-d_6, TMS) δ: 4.46 (s, 2H, CH_2), 7.22-8.42 (m, 11H, Ar-H). ^{13}C NMR (300 MHz, DMSO-d_6, TMS) δ: 184.8 (C=O), 172.4 (ring C=O), 147.4 (C=N), 143.6-121.4 (Ar-C) 44.8 (CH_2). IR (KBr disk, cm^{-1}): 1675 (ring C=O), 1650 (C=O), 1600 (C=N). MS, m/z: 376/378 $[M]^+$ chlorine isotopes. Anal, Calcd for $C_{20}H_{13}ClN_4O_2$ (M_r = 376.81): C, 63.75; H, 5.48; N, 14.87%; Found: C, 63.80; H, 5.55 N, 14.95%.

4. CONCLUSION

In conclusion, the cyclocondensation of several nitrilimines with Girard-reagent P leads to formation of 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-ones **IVa-f** and 1,2,6,7-tetrahydro-1,2,4,5-tetrazepin-6-ones **Va-f**, which thermally oxidized in presence of activated charcoal to 1,6-dihydro-1,2,4,5-tetrazin-3-ones **VIa,c,f** and 6,7-dihydro-1,2,4,5-tetrazepin-6-ones **VIIa,c,f**.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME AMIDE DERIVATIVES

Asif Husain and Mohd Rashid

Department of Pharmaceutical Chemistry, Faculty of Pharmacy

Hamdard University, New Delhi-110062, INDIA

Email: *drasifhusain@yahoo.com*

ABSTRACT

*A series of amide derivatives has been synthesized through one-pot method by condensing appropriate 4-oxo-4-(4-substituted phenyl)butanoic acid moiety with isoniazid. The amides have been evaluated for their antimicrobial activity (Minimum Inhibitory Concentration - MIC) against Bacillus subtilis, Klebsiella pneumoniae and Candida albicans. One compound, **2b**, was found to have significant antimicrobial activity.*

RESUMO

Uma série de derivados de amidas foi sintetizada condensando o ácido 4-oxo-4-(4-fenil substituído) butanóico apropriado com isoniazida.. A atividade antimicrobial (Concentração Inibitória Mínima - CIM) foi avaliada com Bacillus subtilis, Klebsiella pneumoniae e Candida albicans. O composto 2b exibiu atividade antimicrobial significante.

INTRODUCTION

Over the past few decades the bacterial resistance to antibiotics has become one of the most important problems of infections treatment (1). Searching for new compounds, which would combine a non specific activity against a broad spectrum of bacteria and low toxicity seems to be a promising way to overcome that problem. Isoniazid is an important antibacterial drug and to increase its usefulness various derivatives have been synthesized with encouraging results (2).

On the other hand, the derivatives of 4-oxo-4-(substituted phenyl)butanoic acid also show potential antimicrobial activities (3, 4). In view of these points and in continuation of our work on novel amides (1-3), it was considered worthwhile to study various amide derivatives of isoniazid with 4-oxo-4-(substituted phenyl)butanoic acids with a view to obtain potential antimicrobial agents. Therefore, five different 4-oxo-4-(substituted phenyl)butanoic acids were condensed with isoniazid and their structures were established on the basis of elemental analysis, ^{1}H NMR and Mass spectral data. These compounds were evaluated for their antimicrobial activities against some selected microbes.

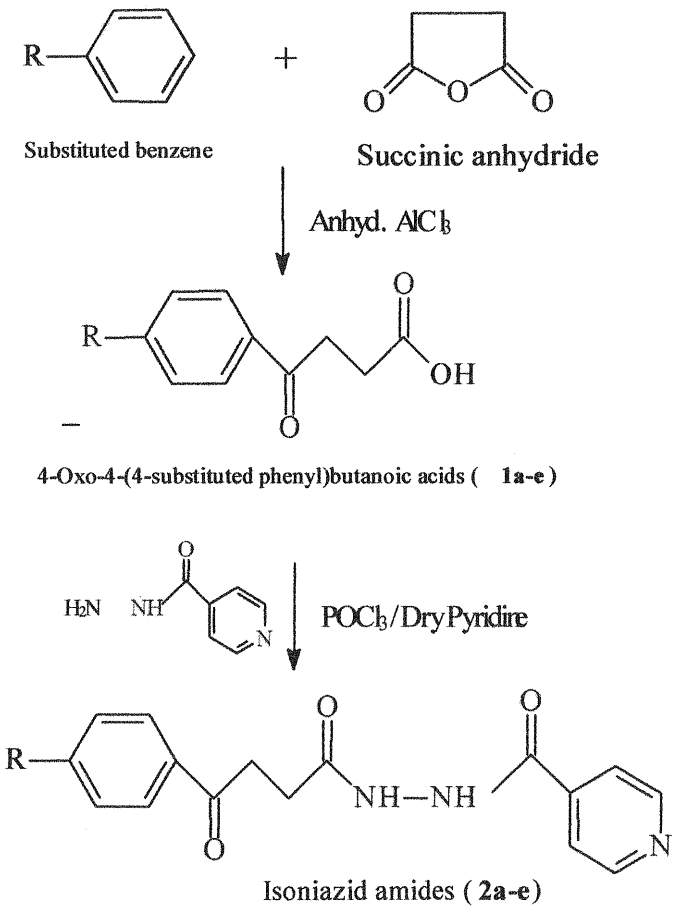
MATERIALS AND METHODS

Synthesis

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H-NMR spectra were recorded on DPX-300 NMR spectrometer. The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system at 70 eV. Microanalyses of the compounds were found within ±0.4% of the theoretical values. All solvents were distilled prior use. The progress of the reactions was monitored on silica gel G plates using iodine vapors as visualizing agent.

Synthesis of 4-oxo-4-(substituted phenyl)butanoic acid (1a-e)

These compounds were synthesized by following the method reported in literature (3).



Scheme 1. Protocol for synthesis of isoniazid amides (**2a-e**).

General procedure for the synthesis of Isoniazid amides (2a-e)

Amides were synthesized by dissolving 4-oxo-4-(substituted phenyl)butanoic acid (**1a-e**) (0.001 mol) and isoniazid (0.001 mol) in minimum quantity of dry pyridine separately. The two solutions were then mixed together and stirred magnetically followed by the addition of phosphorous oxychloride (0.9ml) drop wise while maintaining the temperature below 5°. The contents were stirred for another half-hour and left overnight. The reaction mixture was then poured into ice cold water and a solid mass, which separated out, was filtered, washed, dried and crystallized from ethanol to give **2a-e** (See Table 1).

Antimicrobial activity

All the newly synthesized compounds were screened for their antibacterial activity against *Bacillus subtilis*, *Klebsiella pneumoniaa* and *Candida albicans* at a concentration of 100 µg/ml by turbidity method (5). Compounds inhibiting growth of one or more of the above microorganisms were further tested for minimum inhibitory concentration (*MIC*). Solvent (DMF) and growth controls were kept. Minimum inhibitory concentrations (*MICs*) were determined by broth dilution technique. The nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls were inoculated with approximately $5x10^5$ c.f.u. of actively dividing bacteria cells. The cultures were incubated for 24 h at 37°C and the growth was monitored visually and spectrophotometrically. Ciprofloxacin and griseofulvin were used as standard drugs for comparison. The lowest concentration (highest dilution) required to arrest the growth of microbes was regarded as *MIC*.

RESULTS AND DISCUSSION

Synthesis

The synthesis of the title compounds was performed in a one-pot reaction method and is presented in Scheme 1. In the initial step, 4-oxo-4-(substituted phenyl)butanoic acid (**1a-e**) were prepared by condensing substituted benzenes with succinic anhydride in presence of anhydrous aluminium chloride following Friedel-Craft's acylation reaction conditions (3). The desired amides (**2a-e**) were synthesized by reacting 4-oxo-4-(substituted phenyl)butanoic acid (**1a-e**) with isoniazid in dry pyridine in presence of phosphorous oxychloride as condensing agent and obtained in appreciable yields (50-61%). The purity of the compounds was controlled by TLC in solvent system toluene:ethyl acetate:formic acid (5:4:1). Spectral data and microanalysis data were in agreement with the proposed structures. The physical and analytical data are recorded in **Table-1**.

The nuclear magnetic resonance spectra (^{1}H NMR; δ ppm) showed two triplets at around δ 2.8 & 3.3 (-CH_2-CH_2-); signals in the region δ 7.5-8.6 (aryl protons). The mass spectra showed molecular ion peaks in reasonable intensities supporting the structure. There was splitting of Ar-$COCH_2CH_2$-CON-bond resulting in formation of Ar-$COCH_2CH_2$-C≡O^+ (fragment-1) or [Ar-$COCH_2CH$=C=O]$^+$ (fragment-2) and/or C_5H_4N-C≡O^+. These fragments provided important clue for successful formation of the product. Fragment-1/2 further splitted to Ar-C≡O^+ and to Ar^+ and then to $C_6H_5^+$ (m/z=77).

Table 1. Physical and spectral data of the amide derivatives of isoniazid (**2a-e**).

Compd	R	M.p.; Yield (%)	Mol. formula; Mass spectral data (m/z)	^{1}H NMR spectral data (δ ppm)	Antimicrobial activity (*MIC*)		
					B. subtilis	*K. pneumoniae*	*C. albicans*
2a	H–	128-130 58	$C_{16}H_{15}N_3O_3$ 297 (M^+), 279, 160, 105, 78, 77	2.77 & 3.43 (t, each, 2x -CH_2), 7.56 (m, 3H, H-3,4,5, phenyl ring), 7.89 (m, 2H, H-2,6, phenyl ring), 8.25 & 8.73 (d, each, A_2B_2, 4H, 4-pyridyl ring), 9.16 & 9.83 (s, each, 2x -NH-).	>100	>100	50.0
2b	Cl–	172-174 55	$C_{16}H_{14}ClN_3O_3$ 331 (M^+), 332 (M^++1), 193, 139, 111, 53	2.78 & 3.31 (t, each, 2x -CH_2-CH_2-), 7.43 & 7.67 (d, each, A_2B_2, 4H, *p*-chloro phenyl ring), 8.06 & 8.77 (d, each, A_2B_2, 4H, 4-pyridyl ring), 9.28 & 9.65 (s, each, 2x -NH-).	12.5	25.0	12.5
2c	CH_3–	140-142 50	$C_{17}H_{17}N_3O_3$ 311 (M^+), 119, 91, 78, 77	2.39 (s, 3H, –CH_3), 2.63 & 3.26 (t, each, 2x -CH_2-), 7.28 & 7.88 (d, each, A_2B_2, 4H, *p*-tolyl ring), 7.81 & 8.79 (d, each, A_2B_2, 4H, 4-pyridyl ring), 9.11 & 9.36 (s, each, 2x -NH-).	25.0	50.0	25.0
2d	C_2H_5–	156-158 56	$C_{18}H_{19}N_3O_3$ 325 (M^+), 307, 133, 105, 91, 77	1.25 (t, 3H, –CH_3), 2.68 (q, 2H, –CH_2–), 2.73 & 3.34 (t, each, 2x -CH_2), 7.29 & 7.83 (d, each, A_2B_2, 4H, *p*-ethyl phenyl ring), 7.81 & 8.71 (d, each, A_2B_2, 4H, 4-pyridyl ring), 9.08 & 9.19 (s, each, 2x -NH-).	>100	>100	>100
2e	CH_3O–	148-150 61	$C_{17}H_{17}N_3O_4$ 327 (M^+), 191, 189, 135, 78	3.82 (s, 3H, –OCH_3), 2.78 & 3.30 (t, each, 2x -CH_2-), 6.96 & 7.56 (d, each, A_2B_2, 4H, *p*-methoxy phenyl ring), 7.91 & 8.83 (d, each, 4H, A_2B_2, 4-pyridyl ring), 9.23 & 10.11 (s, each, 2x -NH-).	50.0	>100	25.0
Standard-1†					6.25	6.25	nt
Standard-2†					nt	nt	6.25
Control					-	-	-

nt= not tested; †Standard-1 = Ciprofloxacin, Standard-2 = Griseofulvin; *MIC* = minimum inhibitory concentration

The fragment $C_5H_4N\text{-}C{\equiv}O^+$ further splitted to $C_5H_4N^+$. The fragmentation pattern is presented in **Chart 1**.

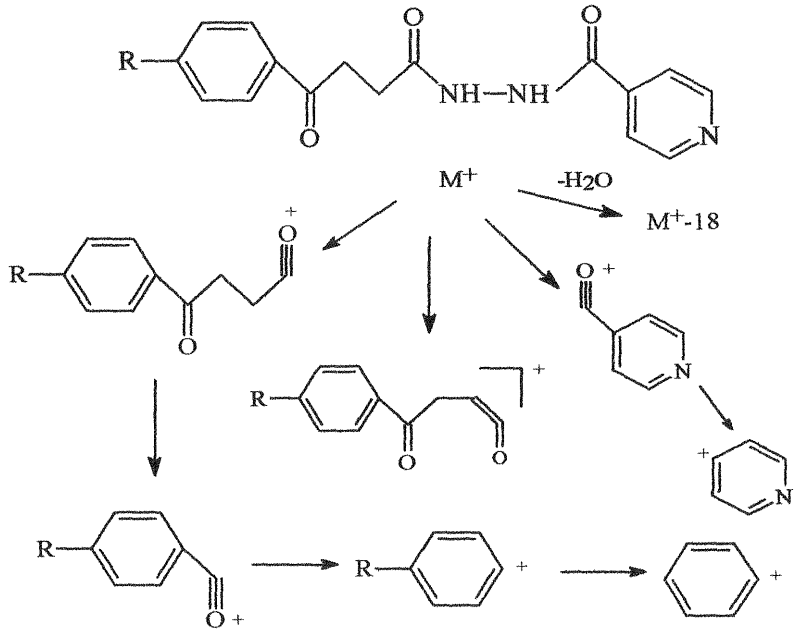


Chart 1. Proposed Mass fragmentation pattern of Amides

Antimicrobial activity

The antimicrobial activity (minimum inhibitory concentration - *MIC*) of the compounds was evaluated against *B. subtilis*, *K. pneumoniae* and *C. albicans*. Ciprofloxacin (*MIC*-6.25 μg/mL) and griseofulvin (*MIC*-6.25 μg/mL) were used as standard drugs for comparison. The compounds **2b** showed very good activity against *B. subtilis* and *C. albicans* with *MIC*-12.5 μg/mL and good activity against *K. pneumoniae* with *MIC*-25 μg/mL concentration. Another compound, compounds **2c**, showed significant activity against *B. subtilis* and *C. albicans* with *MIC*-25.0 μg/mL. Rest of the compounds were moderate in their action. From the antibacterial

results, it was observed that the compound having chloro function (**2b**) was most active among the tested compounds (**Table 1**).

CONCLUSION

In conclusion, five amide derivatives (**2a-e**) were successfully synthesized. Among these, one compound **2b** exhibited good activity against *B. subtilis* and *C. albicans* with *MIC*-12.5 μg/mL. These results showed the importance of exploring old drugs to obtain compounds of potential pharmaceutically interest.

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MINERALOGICAL ASPECTS OF RARE EARTH ELEMENTS

Paulo Cesar Pereira das Neves[a], Darcson Vieira de Freitas[a] and Lavinel G. Ionescu[b,c]

[a]Laboratório de Geologia e Mineralogia, Química Industrial
Universidade Luterana do Brasil, Canoas, BRASIL
[b]SCIENCO Scientific Consulting Services, Viamão, RS, BRASIL
[c]Sarmisegetusa Research Group, Santa Fe, New Mexico, USA

ABSTRACT

Rare earth elements or rare earth metals are a group elements including the fifteen lanthanides (Z=57 to Z=71). Scandium (Z=21) and yttrium (Z=39) are considered rare earths by IUPAC since they tend to occur in the same ore deposits as the lanthanides and have similar chemical properties. The present article describes mineralogical properties of yttrium and the lanthanides. A total of two hundred and seventy seven (277) minerals are known, the most common being monazites and bastnäzites. The rare earth metals have many important industrial applications.

KEY WORDS: Rare earth elements, lanthanides, yttrium, mineralogical aspects

RESUMO

Os elementos denominados de terras raras ou metais de terras raras consistem de um grupo de elementos incluindo os quinze lantanídeos (Z=57 a Z=71). O escândio (Z=21) e o ítrio (Z=39) são considerados terras raras pela IUPAC, já que ocorrem nos mesmos depósitos de minérios e possuem propriedades químicas semelhantes. O presente artigo trata das propriedades mineralógicas do ítrio e dos lantanídeos.
Um total de duzentos e setenta e sete (277) espécies minerais são conhecidas, sendo as mais importantes as monazitas e bastnäzitas. Os metais de terra raras têm muitas aplicações industriais importantes.

PALAVRAS CHAVE: Terras raras, lantanídeos, ítrio, aspectos mineralógicos

INTRODUCTION

This article represents a continuation o four work dealing with the mineralogy of the elements of the Periodic Table. We have already published a series of papers dealing with mineralogical aspects of Ag, Cu, Au, Pb, Pt, Li, H and U[1-7].

Rare earth elements or rare earth metals are defined by IUPAC as a collection of seventeen chemical elements in the Periodic Table, specifically, scandium (Z=21), yttrium (Z=39) and the fifteen lanthanides, Z=57 to Z=71, (La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu).

Scandium and yttrium are considered rare earths since they trend to occur in ore deposits with the lanthanides and have similar chemical properties. Geochemically speaking, scandium (Z=21) is not considered a member of this class[8] and we will not consider its mineralogy in this article.

The term "rare earth" comes from rare earth minerals. In old usage, the name was given to the mixture of oxide minerals was earth mixture. [9-12]

In 1787 Lt. Carl Axel Arrhenius discovered a black mineral in a quarry in the village of Ytterby in Sweden. The mineral was originally called ytterbite and was renamed gadolinite in 1800, after John Gadolin, a professor at Turku University in Finland. It was Gadolin that first isolated yttrium from the mineral.

A few years later, in 1803, Jacob Berzelius and Wilhelm Hisinger obtained cerium from bastnäzite, a mineral from Bastnäs near Riddarhyttan, Sweden. Eventually, a more careful separation and characterization of the earths from the mineral yielded Sc, Y, La and the fourteen lanthanide metals. [13,14,22-26]

Three of the rare earth elements (Tb, Er and Yb) derive their name from the village of Ytterby. The others are named for scientists who studied or discovered

them, Roman, Greek or Scandinavian mythology or places (Holmia is the Latin name of Stockholm, Lutetia for Paris).

The rare earth elements are not rare. Their absolute abundances in the lithosphere are relatively high. Cerium is the 25th most abundant element in the Earth's crust (~56ppm) and even the scarcest, thulium (~0.29ppm) is as common as bismuth (~$2x10^{-2}$ wt%) and more common than As, Cd, Hg and Se that are not considered rare. [13,14,22-26]

Significant deposits of rare earth minerals are located in Scandinavia, India, Russia, Brazil, South Africa, Australia, United States and China. At the present time, China is responsible for most of the world production of rare earth metals,

Promethium occurs in Nature only in trace amounts in uranium ores ($4x10^{-5}$ g/kg) as a spontaneous fission fragment of ^{238}U. Milligram quantities of $^{147}Pm^{+3}$ can be isolated by ion exchange techniques from fission products of nuclear reactors where ^{147}Pm (beta$^-$, 2.64y) is formed. [24]

Some properties of the rare earth elements are summarized in Table 1.[13,22-26]

The rare earth themselves, i.e., the minerals, are usually mixed oxides of the metals and are difficult to separate because of their chemical similarity. The rare earth metals never occur free in nature and have similar chemical properties because their atomic structures are similar. The most common valence is +3 and they all form stable oxides, carbides, borides and halides. They also form organic salts with chelates. [22-26]

These elements are important geochemical markers, are used to identify rocks and have high geochemical immobility. Even with prolonged geological times,

Table 1. Some Properties of the Rare Earth Elements. [13,14,22-26]

Properties	Y	La	Ce	Pr	Nd	Pm	Sm	Eu
Atomic mass (g/mol)	88,90585(2)	138,90547(7)	140,116(1)	140,90765(2)	144,242(3)	140,90765(2)	150,36(2)	151,964(1)
Electronic configuration	$[Kr]4d^15s^2$	$[Xe]5d^16s^2$	$[Xe]4f^26s^2$	$[Xe]4f^36s^2$	$[Xe]4f^46s^2$	$[Xe]4f^56s^2$	$[Xe]4f^66s^2$	$[Xe]4f^76s^2$
Density (g/cm^3)	4.47	6.15	6.77	6.77	7.01	7.3	7.52	5.24
Melting point (°C)	1526	920	798	931	1016	931	1072	822
Boiling poing (°C)	3338	3457	3426	3512	3068	3512	1791	1597
Heat of vaporization (kJ/mol)	363	414	414	296.8	273	-	166.4	143.5
Heat of fusion (kJ/mol)	11.4	6.2	5.46	6.89	7.14	86.7	8.63	9.21
Ionic Radius (Å)	0.9	1.061	1.034	1.013	0.995	0.979	0.964	0.947
Crystal structure	hexagonal	hexagonal	cubic face centered	hexagonal	hexagonal	Hexagonal	trigonal	cubic face centered
Discoverer	J.Gadolin	C. G.Mosander	W. von Hisinger and J.J.Berzelius	C.A. von Welsbach	C.A. von Welsbach	J.A. Marinky, L.E. Glendenin and C.D. Coryell	P.E.L. de Boisbaudran	E. A. Demarçay
Discovery year	1794	1839	1803	1885	1885	1945	1879	1901

Properties	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Atomic mass (g/mol)	157,25(3)	158,92535(2)	162,500(1)	164,93032(2)	167,259(3)	168,93421(2)	173,054(5)	174,9668(1)
Electronic configuration	$[Xe]4f^75d^16s2$	$[Xe]4f^96s2$	$[Xe]4f^{10}6s2$	$[Xe]4f^{11}6s2$	$[Xe]4f^{12}6s2$	$[Xe]4f^{13}6s2$	$[Xe]4f^{14}6s2$	$[Xe]4f^{14}5d^16s2$
Density (g/cm^3)	7.895	8.23	8.55	8.8	9.07	9.32	6.9	9.84
Melting point (°C)	1312	1357	1412	1470	1522	1545	824	1663
Boiling poing (°C)	3266	3023	2562	2695	2863	1947	1194	3395
Heat of vaporization (kJ/mol)	359.4	330.9	230	241	261	191	128.9	355.9
Heat of fusion (kJ/mol)	10.05	10.8	11.06	12.2	19.9	16.84	7.66	
Ionic Radius (Å)	0.938	0.923	0.912	0.901	0.881	0.869	0.858	0.848
Crystal structure	hexagonal	hexagonal	hexagonal	hexagonal	hexagonal	hexagonal	cubic face centered	hexagonal
Discoverer	J.C.G. de Marignac	C.G. Mosander	P.E.L. de Boisbaudran	M.Delafontaine and J.L. Soret	C.G. Mosander	P.T. Cleve	J.C.G. de Marignac	C.A. von Welsbach and G. Urbain

geochemical separation of the lanthanides was slow. There exists only a broad separation between light and heavy rare earths, commonly known as the cerium and yttrium earths. [9-12]

The more common minerals that contain yttrium and the heavier elements are gadolinite, euxenite, samarskite, xenotime, fergusonite, yttrotantalite, yttrotungstite, yttrofluorite, thalenite and yttrialite. Some of the heavy lanthanides are responsible for the typical yellow fluorescence of zircon.

Common minerals that contain cerium and the lighter lanthanides include monazite, bastnäzite, allanite, loparite, parasite, ancylite, cerite, chevkinite, lnthanite, stillwellite, fluorecite, britholite and cerianite. During the years, the principal ores of cerium and the lighter rare earths have been monazite from marine sands from Brazil, Egypt, India and Australia and rocks from South Africa, bastnäzite from California and China and loparite from Russia. 22-26

Among the anhydrous rare earth phosphates, the tetragonal mineral xenotime incorporates preferentially yttrium and yttrium earths, whereas monoclinic monazite incorporates cerium and the cerium earths. Because of their smaller size, yttrium and yttrium earths have a greater solubility in the rock forming mineral of the Earth's mantle and show less enrichment in the Earth's crust as compared to cerium and cerium earths, relative to chondritic abundance. Large orebodies of the cerium earths are known and are actively exploited around the world, while the yttrium orebodies are rarer, less concentrated and smaller. At the present most of the yttrium supply comes from the ion adsorption clay ores of Southern China.

Efficient separation techniques of the rare earth metals were developed mostly after 1960.They include ion exchange, solvent extraction, fractional crystallization and electrolytic reduction. Rare earth minerals are difficult to mine and the extraction of the metals is laborious because of their similar properties. For this reason, the rare earth metals are relatively expensive.

The rare earth elements exhibit complex spectra and the mixed oxides, when heated, produce an intensive white light similar to sun light. One application of this property are the cored carbon arcs.

Mixed rare earths are reduced to metals (misch metal) and the corresponding alloys are used in metallurgy. Alloys of cerium and mixed rare earths are used in lighter flints and rare earths have applications as catalysts in the petroleum industry. Garnets of yttrium and aluminum (YAG) have been employed as artificial diamonds in jewelry.

Rare earth ions are used in luminescent materials and optoelectronics, the most common being the Nd:YAG laser. Phosphors with rare earth dopants are common in cathode ray tube technology and television sets. Erbium doped fiber amplifiers are used in optical fiber communication systems. Batteries, magnets and superconductors contain rare earths. Samarium-cobalt and neodymium-iron-boron are examples of high flux rare earth magnets. Yttrium iron garnet (YIG) has been used as tunable microwave resonator and rare earth oxides are mixed with tungsten to improve high temperature welding. [22-26]

MINERALS CONTAINING RARE EARTH ELEMENTS

The International Mineralogical Association (IMA) had validated up to 2008 a total of two hundred and seventy two (272) species of minerals containing rare earth elements.[15] Five more species were validated by the IMA after 2008.

The mineralogical species with the corresponding rare earth element are listed as follows:

Abenakiite-(Ce); adamsite-(Y); aeschynite-(Ce); aeschynite-(Nd); aeschynite-(Y); agardite-(Ce); agardite-(La); agardite-(Y); allanite-(Ce); ancylite-(Ce); allanite-(Y); ancylite-(La); arsenoflorencite-(Ce); ashcroftine-(Y); astrocyanite-(Ce); bario-olgite; bastnäsite-(Ce); bastnäsite-(La); bastnäsite-(Y); belovite-(Ce); belovite-(La); bijvoetite-(Y); biraite-(Ce); bobtraillite; braitschite-(Ce); brannerite; britholite-(Ce); britholite-(Y); brockite; burbankite; byelorussite-(Ce); calcioancylite-(Ce); calcioancylite-(Nd); calcioburbankite; calciosamarskite; calkinsite-(Ce); cappelenite-(Y); carbocernaite; caysichite-(Y); cerianite-(Ce); ceriopyrochlore-(Ce); cerite-(Ce); cerite-(La); cervandonite-(Ce); chernovite-(Y); chevkinite-(Ce); chukhrovite-(Ce); chukhrovite-(Nd); chukhrovite-(Y); churchite-(Nd); churchite-(Y); ciprianiite; cordylite-(Ce); coskrenite-(Ce); crichtonite; daqingshanite-(Ce); darapiozite; davidite-(Ce); davidite-(La); davidite-(Y); decrespignyte-(Y); deloneite-(Ce); dessauite-(Y); dingdaohengite-(Ce); dissakisite-(Ce); dissakisite-(La); diversilite-(Ce); dollaseite-(Ce); donnayite-(Y); dusmatovite; euxenite-(Y); ewaldite; fergusonite-beta-(Ce); fergusonite-beta-(Nd); fergusonite-beta-(Y); fergusonite-(Ce); fergusonite-(Y); ferriallanite-(Ce); ferronordite-(Ce);

ferronordite-(La); fersmite; florencite-(Ce); florencite-(La); florencite-(Nd); fluocerite-(Ce); fluocerite-(La); fluorbritholite-(Ce); fluorcalciobritholite; fluorcaphite; flurthalénite-(Y); formanite-(Y); françoisite-(Ce); françoisite-(Nd); gadolinite-(Ce); gadolinite-(Y); gagarinite-(Y); galgenbergite-(Ce); gasparite-(Ce); gatelite-(Ce); georgbarsanovite; gerenite-(Y); goudeyite; gramaccioliite-(Y); gysinite-(Nd); häleniusite-(La); hellandite-(Ce); hellandite-(Y); hibonite; hingganite-(Ce); hingganite-(Y); hingganite-(Yb); hiortdahlite II; horváthite-(Y); huanghoite-(Ce); hundholmenite-(Y); hyalotekite; hydroxylbastnäesite-(Ce); hydroxylbastnäesite-(La); ikranite; iimoriite-(Y); ilmajokite; iraqite-(La); ishikawaite; isolueshite; iwashiroite-(Y); joaquinite-(Ce); johnsenite-(Ce); kainosite-(Y); kamotoite-(Y); kamphaugite-(Y); kapitsaite-(Y); karnasurtite-(Ce); keiviite-(Y); keiviite-(Yb); kentbrooksite; khanneshite; khristovite-(Ce); kimuraite-(Y); kobeite-(Y); kazoite-(La); kozoite-(Nd); kuannersuite-(Ce); kukharenkoite-(Ce); kukharenkoite-(La); kuliokite-(Y); landauite; lanthanite-(Ce); lanthanite-(La); lanthanite-(Nd); laplandite-(Ce); lepersonnite-(Gd); levinsonite-(Y); lokkaite-(Y); loparite-(Ce); loranskite-(Y); loveringite; lucasite-(Ce); lukechangite-(Ce); manganiandrosite-(Ce); manganiandrosite-(La); manganonordite-(Ce); maoniunpingite-(Ce); mckelveyte-(Y); melanocerite-(Ce); merrillite; michelelsenite; minasgeraisite-(Y); mineevite-(Y); miserite; monazite-(Ce); monazite-(La); monazite-(Nd); monazite-(Sm); monteregianite-(Y); mosandrite; moskvinite-(Y); mottanaite-(Ce); moydite-(Y); murataite-(Y); nacareniobsite-(Ce); nioboaeschynite-(Ce); nordite-(Ce); nordite-(La); okanoganite-(Y); olgite; orthojoaquinite-(Ce); orthojoaquinite-(La); paraniite-(Y);

paratooite-(La); parisite-(Ce); peprossiite-(Ce); percleveite-(Ce); perrierite-(Ce); petersenite-(Ce); petersite-(Y); phosinaite-(Ce); piergorite-(Ce); pisekite-(Y); plumboagardite; polyakovite-(Ce); polycrase-(Y); pyatenkoite-(Y); qaquarssukite-(Ce); reederite-(Y); remondite-(Ce); remondite-(La); retzian-(Ce); retzian-(La); rhabdophane-(Ce); rhabdophane-(La); rhabdophane-(Nd); rinkite; röntgenite-(Ce); rowlandite-(Y); sahamalite-(Ce); samarskite-(Y); samarskite-(Yb); saryarkite-(Y); sazhinite-(Ce); sazhinite-(La); sazykinaite-(Y); schuilingite-(Nd); seidite-(Ce); semenovite-(Ce); shabaite-(Nd); shomiokite-(Y); stavelotite-(La); steenstrupine-(Ce); stillwellite-(Ce); stornesite-(Y); strontiochevkinite; synchysite-(Ce); synchysite-(Nd); synchysite-(Y); tadzhikite-(Ce); tantalaeschynite-(Y); tanteuxenite-(Y); tengerite-(Y); thalénite-(Y); thomasclarkite-(Y); thobastnäsite; thorosteenstrupine; thortveitite; tienshanite; tombarthite-(Y); törnebohmite-(Ce); törnebohmite-(La); tritomite(Ce); tritomite(Y); tundrite-(Ce); tundrite-(Nd); vanadoandrosite-(Ce); västmanlandite-(Ce); vicanite-(Ce); vigezzite; vitusite-(Ce); vyuntspakhkite-(Y); wakefieldite-(Ce); wakefiedite-(Y); xenotime-(Y); xenotime-(Yb); yakovenchukite-(Y); yttrialite-(Y); yttrobetafite-(Y); yttrocrasite-(Y); yttropyrochlore-(Y); yttrotantalite-(Y); yttrotungstite-(Ce); yttrotungstite-(Y); zajacite-(Ce); zirsilite-(Ce) and zugshunstite-(Ce).

The following minerals containing rare earth elements, validated by the International Mineralogical Association (IMA) after 2008 are the following: nioboaeschynite-(Y)[16]; uedaite-(Ce)[17]; wakefieldite-(La)[18]; bussyite-(Ce)[19]; and stetindite[20].

Minerals such as aqualite contain rare earth elements in their empirical formula $(Fe_{0.23}Mn_{0.12}]\Sigma_{13.18}(Ca_{5.79}REE_{0.19})\Sigma_{5.98}(Zr_{2.92}Ti_{0.08})\Sigma_3(Si_{25.57}Ti_{0.21}Al_{0.19}Nb_{0.03})\Sigma_{26}[O_{66.46}(OH)_{5.54}]\Sigma_{72.0}[(OH)_{2.77}Cl_{1.23}]\Sigma_{4.0}$ on a basis of 29(Si, Zr, Ti, Al, N), but they are not present in the ideal formula $((H_3O)_8(Na,K,Sr)_5Ca_6Zr_3Si_{26}O_{66}(OH)_9Cl)^{21}$.

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THERMAL DISAPPEARANCE KINETICS OF RADICALS FORMED DURING RADIOLYSIS IN POLYCRYSTALLINE SOLID STATE OF SODIUM WOLFRAMATE DIHYDRATE

Mihail Contineanu[a], Adina-Elena Stanciu[b], Iulia Contineanu[c] and Ana Neacşu[c*]

[a]Faculty of Chemistry, University of Bucharest, 4-12 Regina Elisabeta Blvd., Bucharest, ROMANIA 030018
e-mail:mihconti@yahoo.com
[b]"Prof.Dr.Al.Trestioreanu" Institute of Oncology, Department of Carcinogenesis and Molecular Biology, Sos. Fundeni, Nr.252, Sector 2, Bucharest, ROMANIA 022328
e-mail: adinaelenastanciu@yahoo.com.
[c] Institute of Physical Chemistry "Ilie Murgulescu", 202 Spl. Independentei, Bucharest, ROMANIA 060021
e-mail: icontineanu@yahoo.com, anna_matache@yahoo.com

ABSTRACT

A kinetic study of the $WO_4^{\bullet -}$ radical, formed by gamma irradiation of polycrystalline $Na_2WO_4 \cdot 2H_2O$ UCB at room temperature has been performed using the EPR technique. A suitable mechanism for the formation of paramagnetic centers by irradiation and thermal annealing is proposed. The mechanism agrees well with the experimental kinetic data.

KEY WORDS: paramagnetic species, absorbed dose, thermal disappearance, radiolytical process, sodium wolframate.

RESUMO

Um estudo cinético do radical $WO_4^{\bullet -}$ formado pela irradiação gama de $Na_2WO_4 \cdot 2H_2O$ UCB policristalino foi efetuado a temperatura ambiente usando ressonância paramagnética eletrônica (RPE). Um mecanismo adequado foi proposto para a formação de centros paramagnéticos pela irradiação e para o cozimento térmico. O mecanismo proposto concorda com os resultados cinéticos experimentais.

PALAVRAS CHAVES: espécies paramagnéticas, processo radiolítico, dose absorvida, desaparecimento térmico, wolframato de sódio.

Corresponding e-mail: anna_matache@yahoo.com

1. INTRODUCTION

The oxygenated compounds such as wolframates and parawolframates, where W is in the VI valence state, are not paramagnetic. Irradiation generates radicals in the VII and V valence state, that are trapped in the lattice and can be studied by the EPR technique[1,2].

The results of the present kinetic study of the thermal recombination of the radicals formed on $Na_2WO_4 \cdot 2H_2O$ UCB (Union Chimique Belge, Brussels, Belgium) irradiation, are completely different from those obtained for $Na_2WO_4 \cdot 2H_2O$ supplied by Merck[3].

This difference in the thermal behavior of the same substance is due to the sample history: its mode of preparation, the absorbed impurities from the synthesis process and its degree of aging.

The influence of the preparation method on the thermal stability of the radicals formed upon irradiation of the same substance prepared in various ways, has been previously found with irradiation of the oxygenated compounds with selenium[4] and chromium[5].

The presence of the additions in the form of some ions foreign to the network having different ionic radius and polarizing properties from the principal ion, change both the number and chemical bonds strength and the stability of the radicals. The presence of some foreign cations in the crystalline network can lead either to the decrease, or increase of the stability of the radicals. The existence of the additives from the synthesis process influences the radical stability due to the formation of a supplementary number of cationic and anionic dislocations in the crystal, leading to the increasing or decreasing of the radiolytic stability[6].

The different thermal behavior of the same radical, formed in the same matrix, may be also due to the microcrystalline structure determined by the macro and micro imperfections from crystal biography[7,8]. Each type of imperfection exhibits a certain influence upon radiolytical stability.

There is no information concerning the $Na_2WO_4 \cdot 2H_2O$ UCB radiolysis in polycrystalline solid state.

Some information, regarding the process mechanism, has been obtained from the kinetic study of the thermal disappearance of the radicals formed by this substance.

2. EXPERIMENTAL

For irradiation were used polycrystalline samples of $Na_2WO_4 \cdot 2H_2O$ UCB. The irradiations were performed at room temperature by γ rays from a ^{137}Cs source with 800 Ci activity and 1.05 Gy h^{-1} dose rate.

EPR spectra of the irradiated samples were recorded with an ART 5 spectrograph (IFIN – Institutul de Fizica si Inginerie Nucleara, Turnu Magurele), operating in the X band with a 100 kHz high frequency modulation. In order to determine the g factor Mn^{2+} ion in CaO matrix was used as a standard.

3. RESULTS AND DISCUSSION

By γ irradiation at room temperature of $Na_2WO_4 \cdot 2H_2O$ UCB in polycrystalline solid state, wide singlet spectra (ΔH=1.57 mT) of small intensity are recorded. In the EPR spectrum shown in Figure 1 the existence of some hyperfine splittings (marked with "a") of four components having an intensity of about 12% of the singlet can be noted.

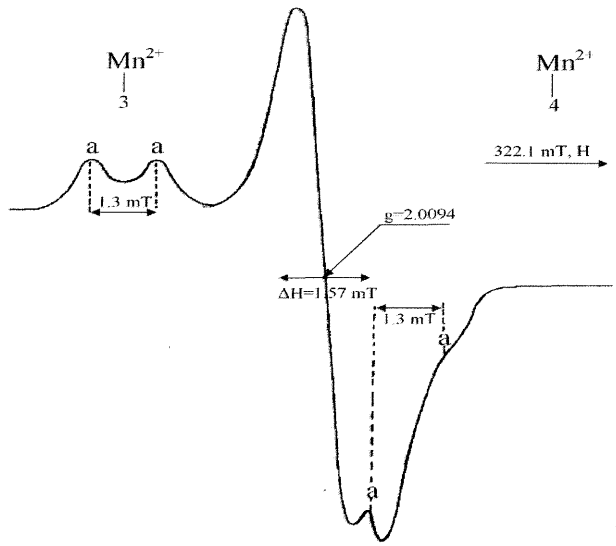


Figure 1.EPR spectrum of a $Na_2WO_4 \cdot 2H_2O$ UCB polycrystalline sample, γ irradiated at room temperature with a dose of $2 \cdot 10^4$ Gy.

For the spectrum interpretation it should be noted that W has many isotopes with different nuclear spin: the nuclei of $^{180,182,184,186}W$ isotopes, with 85.6% natural nuclear abundance have the nuclear spin equal with zero (I=0) and the ^{183}W isotope, with 14.6% of natural abundance has an unpaired nuclear spin (I=1/2).

It can be noticed that the 14,6% natural abundance of the ^{183}W isotope is close to the ratio between the hyperfine lines intensity and singlet intensity.

The signal from Figure 1 belongs to the $\dot{WO_4^-}$ radical, with W in VII valence state, similar to $\dot{CrO_4^-}$ obtained by CrO_4^{2-} irradiation[9].

Zelder and Livingston[10] proposed the hypothesis that the unpaired electron from the $\dot{WO_4^-}$ center is strongly delocalized, having the possibility to distribute on a WO_4^{2-} neighbor ion to form a center with two W atoms of the $\dot{WO_4^-}$ -WO_4^{2-} or $\left(\dot{W_2O_8}\right)^{3-}$ type.

The central singlet with high intensity comes from isotopes species with two nuclei I=0, which represent 85.6%.

The formation of the four symmetrical hyperfine splittings from the main line is a confirmation of the hypothesis that the odd electron from $\dot{WO_4^-}$ radical interacts with two ^{183}W (I=1/2) nonequivalent nuclei. Due to the strongly dipolar interaction that takes place between the radical species in the polycrystalline sample, the hyperfine structure is poorly resolved, leading to an uneven width of spectral lines[11].

In order to establish the influence of integral dose of irradiation upon $\left(\dot{W_2O_8}\right)^{3-}$ radical concentration, samples having equal amounts of wolframate have been irradiated at different times. The EPR spectra were recorded under the same conditions.

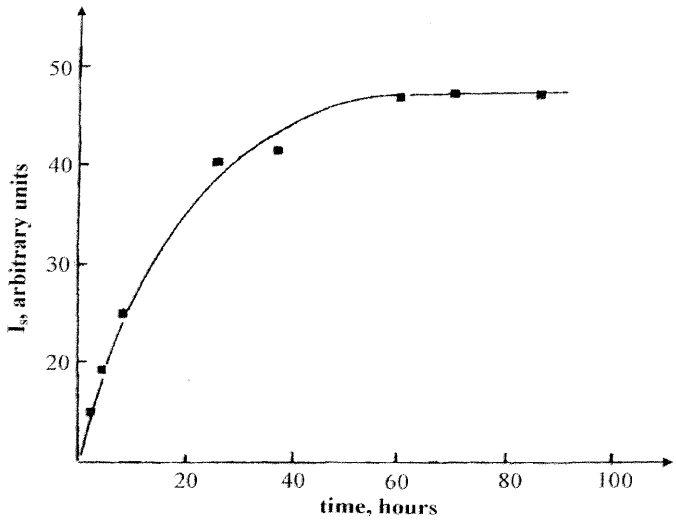


Figure 2. Variation of the relative intensity (Ir) of the EPR signal of $Na_2WO_4 \cdot 2H_2O$ UCB polycrystalline samples versus irradiation time (dose rate $1.05 \cdot 10^2$ Gyh^{-1}).

Figure 2 illustrates the variation of the EPR signal intensity versus irradiation time (dose rate $1.05 \cdot 10^2$ Gyh^{-1}).

First, it can be noticed that radical concentration increases proportionally with the integral dose up to $2.5 \cdot 10^3$Gy and then reaches a plateau.

It is important to explain the causes of the attainment of this stationary state. The migration of the radicals followed by their recombination was suggested[12]. However, this process can not be considered in the solid state at room temperature. More plausible are the following two explanations: the radicals, after their formation, absorb energy from the incident radiation resulting in their destruction. At high irradiation doses the radical concentration increases. Being arranged in

close positions, they interact among themselves producing recombinations. This last hypothesis is supported by the EPR spectral change at higher irradiation doses.

The stability of the $\left(W_2\dot{O}_8\right)^{3-}$ paramagnetic centers with temperature has been studied by means of reaction isochronous procedure. For this purpose, a γ irradiated sample was gradually heated for 5 minutes stepwise (each step=10°C) from room temperature up to the temperature of the complete radical disappearance. The variation of the EPR signal intensity versus temperature is shown in Figure 3.

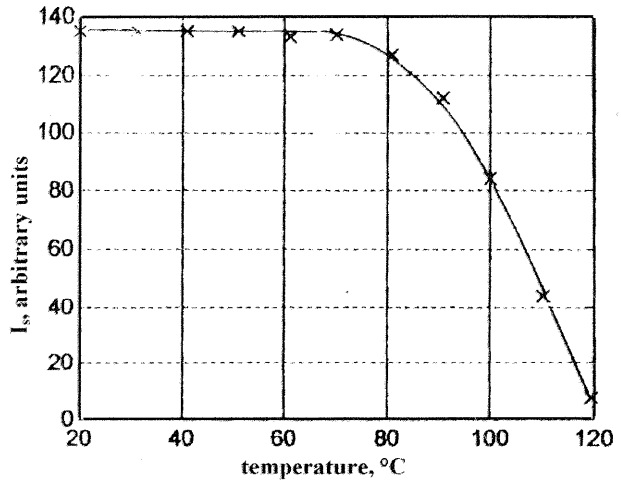


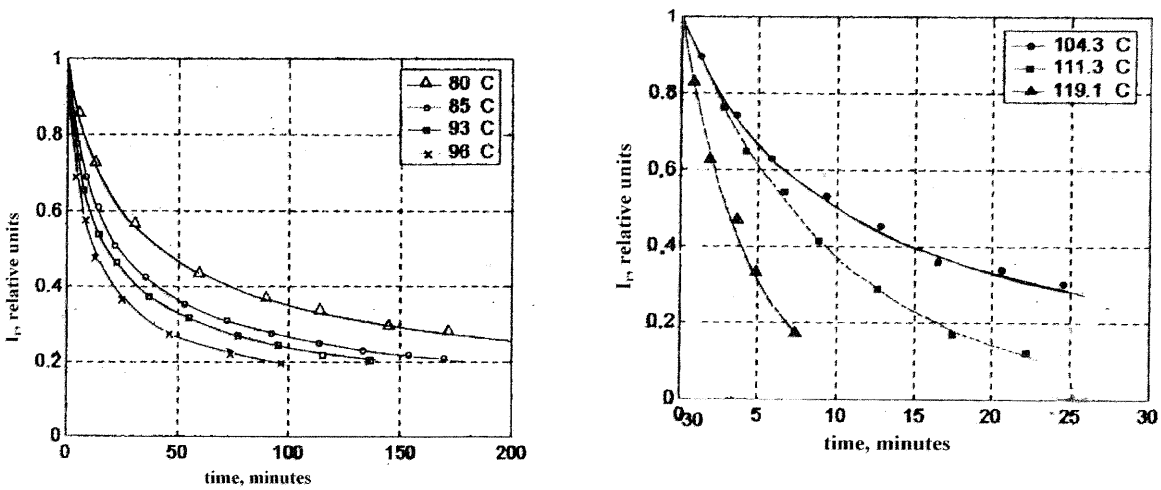
Figure 3. Isochronous variation of EPR signal intensity (arbitrary units) versus heating temperature for a γ irradiated $Na_2WO_4 \cdot 2H_2O$ UCB sample.

From Figure 3 it can be noted that the EPR signal intensity remains constant up to 70°C. Subsequently, it decreases linearly with increasing temperature. The complete disappearance occurs at 120°C.

The kinetic study performed by EPR for the thermal recombination process of the $\left(W_2\dot{O}_8\right)^{3-}$ radicals, formed on $Na_2WO_4 \cdot 2H_2O$ UCB radiolysis, involves the reaction isotherms procedure.

The temperature range, used to calculate the rate constants, has been chosen in order to fulfill two conditions: first, the reaction to occur in proportion to over 50% and second, the reaction to occur not too fast in order to reduce the experimental errors.

The kinetic study was performed on 80-120°C temperature range. The relative intensity ($I_r = I_t/I_0$, where I_t represents the intensity at the "t" moment and I_0 the initial intensity) with the time of isothermal heating is plotted in Figure 4.



a) b)

Figure 4. Variation of the EPR signal relative intensity of the irradiated samples and isothermally heated at the temperatures: a) 85-96°C b) 104-119°C.

From the reaction isotherms it can be seen that the radical thermal disappearance rate increases with increasing temperature. All the isotherms tend to a plateau evenly situated that decreases with higher temperature. The plateau appearance proves the fact that radicals have different thermal

stability. Trapped radicals remain in the crystalline lattice for all temperatures. For these radicals the energy received from exterior is lower than the binding energy.

For the calculation of the rate constants both integral and differential kinetic methods were used. In the integral method, the established equations from chemical kinetics were verified, for all whole and fractional reaction orders, with the specification that the radical concentration changed with the relative intensity of EPR signal (I_r).

The graph of each kinetic equation was done in linear form, corresponding for all reaction orders. The straight lines were plotted so that each slope had the least error related to the experimental points.

The experimental points gave the best line for the plot of the third order kinetic equation at 93°C temperature (Figure 5), indicating that the thermal disappearance of the radicals follows kinetics of third order.

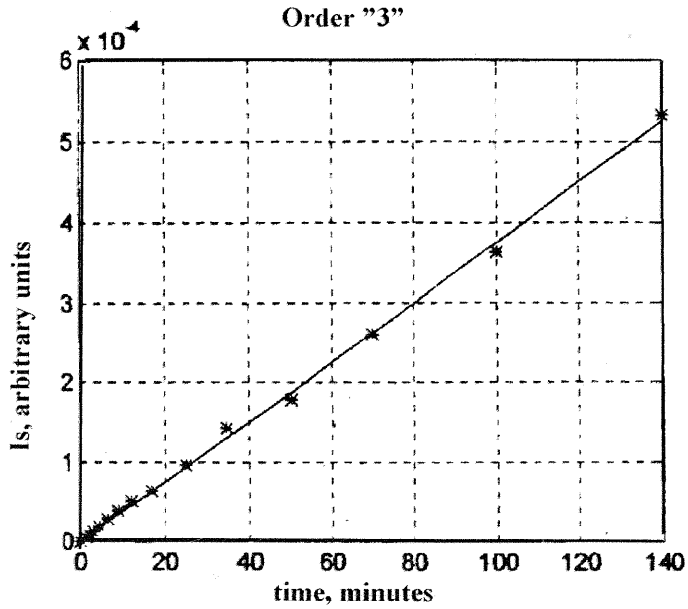


Figure 5. Plot of the kinetic equation corresponding toa reaction of third order, versus the time for isothermal heating at 93°C for a γ irradiated $Na_2WO_4 \cdot 2H_2O$ UCB sample.

Using the graphs corresponding to all reaction orders from 0 to 3, at 93°C, the rate constants have been calculated by the least squares method (Table 1).

To verify the reaction of third order, obtained from isotherms plotted for each reaction order, the ΔI_r deviation of each experimental point, related to the adequate point on the regression line, was determined (Table 1). The values obtained were related at the last point value on the regression line and in this way, errors in percent (ε_{max}) have been calculated.

Table 1. Kinetic parameters and maximum relative errors determined for $\left(W_2\dot{O}_8\right)^{3-}$ radical species disappearance at 93°C, formed on $Na_2WO_4 \cdot 2H_2O$ UCB γ irradiation.

Crt. No.	Reaction order "n"	k [s^{-1}] x 10^3	ΔI_r [u.r]	ε_{max} [%]
1	0	0.14	0.36	30.54
2	0,5	0.18	0.41	26.45
3	1	0.25	0.47	22.37
4	1,5	0.36	0.54	17.84
5	2	0.54	0.58	12.77
6	2,5	0.86	0.54	7.46
7	3	1.41	0.26	2.23
8	3,5	2.40	1.71	8.84
9	4	4.24	5.71	16.04

The maximum relative error (ε_{max}) versus reaction order, for 93°C isotherm is plotted in Figure 6.

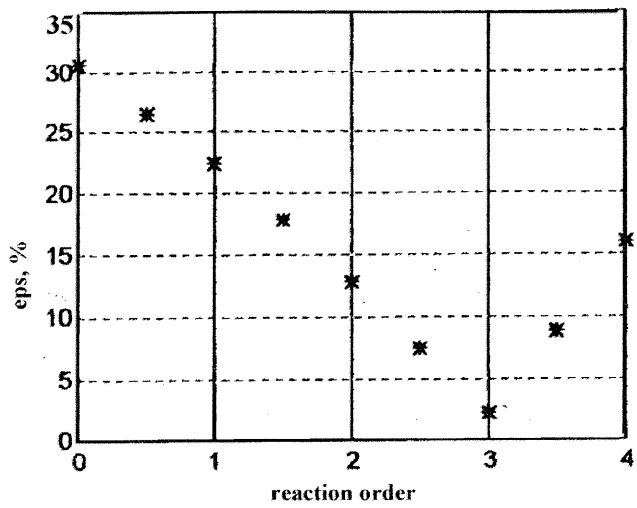


Figure 6. Variation of the maximum relative error in percent, versus the reaction order for the 93°C isotherm of a γ irradiated $Na_2WO_4 \cdot 2H_2O$ UCB sample.

It can be noted that the maximum relative error ε_{max} linear decreases with increase of reaction order, reaching a minimum value at order 3 and subsequently it increases linearly. The same behavior was observed for all isotherms as a function of reaction order.

The differential method was also used for the determination of reaction order and the calculation of rate constants corresponding to radical thermal disappearance.

The logarithm of the rate of radical disappearance ln(-dIr/dt) versus the logarithm of the relative intensity ln Ir of EPR signals at 93°C. is illustrated in Figure7.

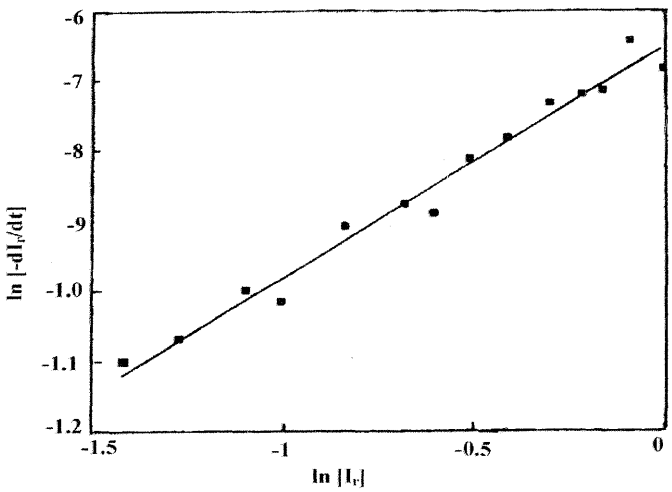


Figure 7.Variation of the logarithm rate of radical disappearance, versus the logarithm the relative intensity of EPR signals (I_r) at 93°C for a γ irradiated $Na_2WO_4 \cdot 2H_2O$ UCB sample.

Using the integral method, the reaction order determined was 3 and the rate constant $k=1.41 \cdot 10^{-3}\ s^{-1}$

By the differential method, the reaction order was 3.28 and the rate constant $k=1.47 \cdot 10^{-3}\ s^{-1}$. The agreement between the two methods is satisfactory.

The kinetic parameters corresponding to the radical thermal disappearance at different temperatures are presented in Table 2.

Table 2. The kinetic parameters for $\left(W_2\dot{O}_8\right)^{3-}$ radical species disappearance at different temperatures formed upon $Na_2WO_4 \cdot 2H_2O$ UCB radiolysis.

Reaction order "n"	t [°C]	T [K]	1/T [K^{-1}] x 10^3	k [s^{-1}] x 10^3	lgk + 3	A[s^{-1}]	Ea[kJ/mol]	ΔS^*, J/mol·K
3	80	353.15	2.8316	0.61	-0.21	$0.99 \cdot 10^8$	75.78	-117.6
	85	358.15	2.7921	1.11	0.046	$1.27 \cdot 10^8$		
	93	366.15	2.7311	1.41	0.15	$0.92 \cdot 10^8$		
	96	369.15	2.7089	2.19	0.34	$1.17 \cdot 10^8$		
2	104.7	377.85	2.6465	1.69	0.23	-		
1	111.3	384.45	2.6611	1.65	0.22	-		
	119.1	392.25	2.5493	3.95	0.60	-		

Analysing the results from Table 2 it can be noted that for the process studied for the recombination of radicals with an increasing temperature interval of 40°C, the reaction order decreased from 3 to 1.

Using the kinetic data corresponding to third order kinetics for radical disappearance, the Arrhenius plot was done. (Figure 8).

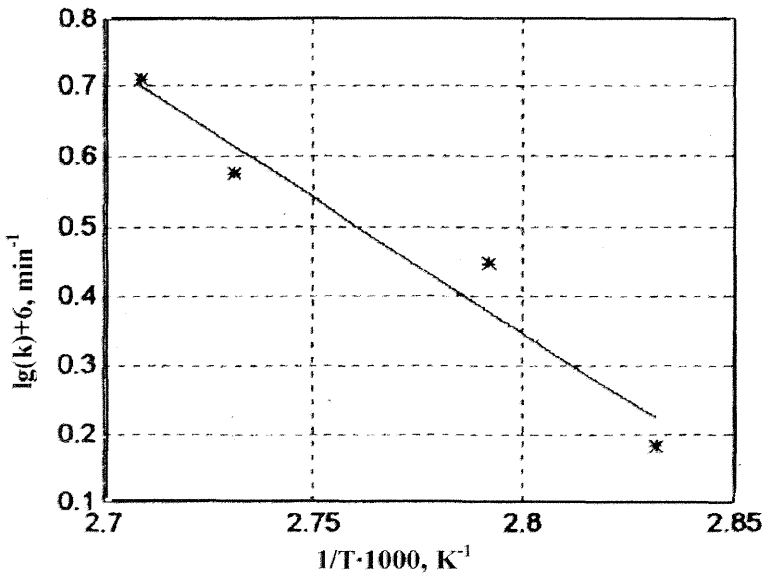


Figure 8. Arrhenius plot for the radical thermal disappearance in the temperature range 80-96°C for $Na_2WO_4 \cdot 2H_2O$ UCB γ irradiated sample.

From the slope of the straight line, presented in Figure 8, an activation energy Ea=75.78 kJ/mol and a pre-exponential factor $A=1.08\cdot10^{8}\ s^{-1}$ were calculated.

We mention that these values do not have the same meaning as those from the theory of the gas state collisions.

In this case, the reactant entities, the radicals respectively, do not move freely as gas molecules and the recombination process takes place only after the increase of the mobility of these species due to the temperature. Knowing the pre-exponential A factor, the activation entropy

ΔS^{*}=-117.6 J/mol·K , for the third order, using the formula: $\Delta S^{*}=R\left[\ln\frac{Ah}{k_B T}-m\right]$,

where, $h=6.625\cdot10^{-3}$ J·s, $k_B=1.38\cdot10^{-23}$ J/K, R=8.31 J/mol·K and m=3 was calculated.

The high and negative value of the activation entropy means that the activated complex has a more ordered structure than the reactants. The involvement of the three radicals in the reaction is accompanied by loss of the rotational and translational degrees of freedom.

The kinetics of third order indicates that the recombination process mechanism is a complicated one. The $\dot{W}O_4^-$ species disappear by a sequence of several possible reactions, so that the overall third order process is equal to that found experimentally.

$$\dot{W}O_4^- + \dot{W}O_4^- \begin{cases} \rightarrow 2WO_3 + O_2^{2-} \\ \rightarrow WO_4^{2-} + WO_3 + O \end{cases} \qquad (1)$$

$$\dot{W}O_4^- + WO_4^{2-} \rightarrow WO_3 + WO_2 + O_2^{2-} + \dot{O}^- \qquad (2)$$

The decrease of reaction order from 3 to 1, with increasing temperature indicates that some of the reactions become dominant in a temperature range, determining the overall order.

The first order reaction consists of $W\dot{O}_4^-$ species decomposition, with oxygen ejection and tungsten oxides formation:

$$W\dot{O}_4^- \longrightarrow \begin{cases} \rightarrow WO_3 + \dot{O}^- \\ \rightarrow WO_2 + \dot{O}_2^- \end{cases} \qquad (3)$$

The electrons trapped in the crystalline lattice become mobile by heating and they could be trapped by the $W\dot{O}_4^-$ species to remake the initial ion.

$$W\dot{O}_4^- + \bar{e} \rightarrow WO_4^{2-} \qquad (4)$$

4. CONCLUSIONS

The radiolysis at room temperature in polycrystalline solid state of $Na_2WO_4 \cdot 2H_2O$ UCB was studied.

The EPR spectra recorded for the irradiated samples belong to the $\left(W_2\dot{O}_8\right)^{3-}$ radical that is stable at room temperature. From the kinetic study with increasing temperature, a decrease of the reaction order from 3 to 1 for the radical thermal annealing process was observed. The mechanism proposed for the radiolytic formation of radicals and radical thermal recombination is in agreement with the kinetic results.

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WALTER LWOWSKI, NEW MEXICO'S GREAT ORGANIC CHEMIST

Lavinel G. Ionescu
Scienco Scientific Consulting Services
Viamão, RS, BRASIL
and
Sarmisegetusa Research Group
Santa Fe, NM, USA

ABSTRACT

Walter Lwowski was born in 1928 in Garmisch, Bavaria, Germany and passed away in Las Cruces, New Mexico, USA in 2010. He received a doctorate in organic chemistry (Dr. Rer. Nat.) from the University of Heidelberg in 1955. He held faculty positions at Yale University and New Mexico State University. His main research activities dealt with nitrene chemistry and nitrogen heterocyclic chemistry. His wide and important contributions gained him national and international recognition and he may be rightfully considered New Mexico's greatest and most illustrious organic chemist.
KEYWORDS: History of Chemistry, Organic Chemistry, Nitrenes, Nitrogen Heterocyclic Chemistry, Chemistry in New Mexico

RESUMO

Walter Lwowski nasceu em Garmisch, Bavaria, Alemanha em 1928 e faleceu em Las Cruces, Novo México, Estados Unidos em 2010 . Ele recebeu o título de Doutor em Química Orgânica (Doctor Rerum Naturae) da Universidade de Heidelberg em 1955. Ocupou cargos de professor em Yale University e New Mexico State University. As suas atividades de pesquisa trataram da química do nitreno e da química dos compostos heterocíclicos do nitrogênio, As suas contribuições amplas e importantes levaram a seu reconhecimento nacional e internacional e ele pode ser considerado o químico orgânico mais ilustre do Estado do Novo México.
PALAVRAS CHAVE: História da Química, Química Orgânica, Nitrenos, Compostos Heterocíclicos do Nitrogênio, Química no Novo México

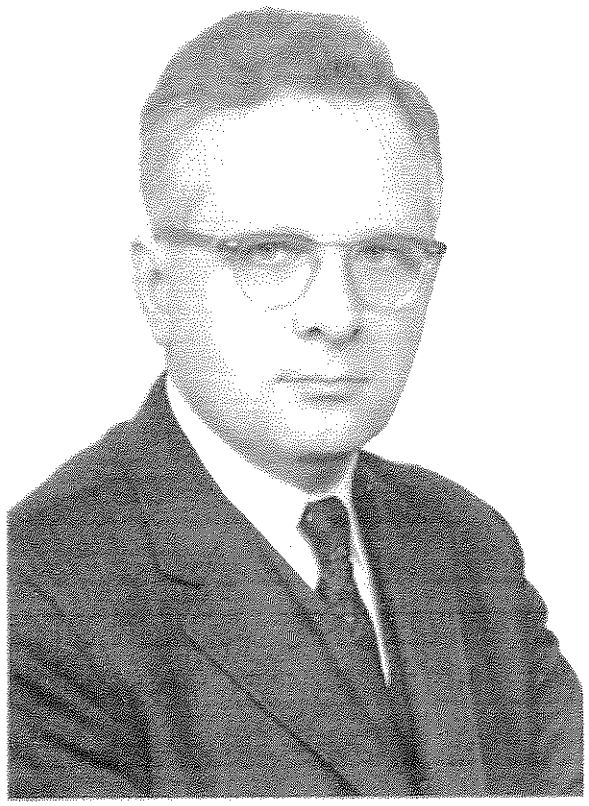
Walter Lwowski was born in Garmisch, Bavaria, Germany on December 28, 1928 and passed away in Las Cruces, New Mexico, USA on April 19, 2010. Garmisch is a beautiful town in the Bavarian Alps and is also the birth place of Richard Strauss and Karl Popper.

He received the degree of Diplom Chemiker from the University of Heidelberg in 1954 and the Doctorate in Organic Chemistry (*Doctor Rerum Naturae*) also from Heidelberg in 1955. During the same year he immigrated to the United States. Many promising young scientists from throughout the world were attracted to America during this period, very much alike to what happened during the golden age of the Roman Empire when the world's best scientists went to Rome.

Walter Lwowski did postdoctoral work with Donald J. Cram (Nobel Prize in Chemistry in 1987) from 1955 to 1957 and with Robert B. Woodward at Harvard University from 1957 to 1960. At Harvard , he was part of a team that worked on the total synthesis of chlorophyll, a research for which R.B. Woodward received the Nobel Prize in Chemistry in 1965.

From 1960 to 1966 he was a faculty member of the Chemistry Department of Yale University .

In 1966 Walter Lwowski joined New Mexico State University



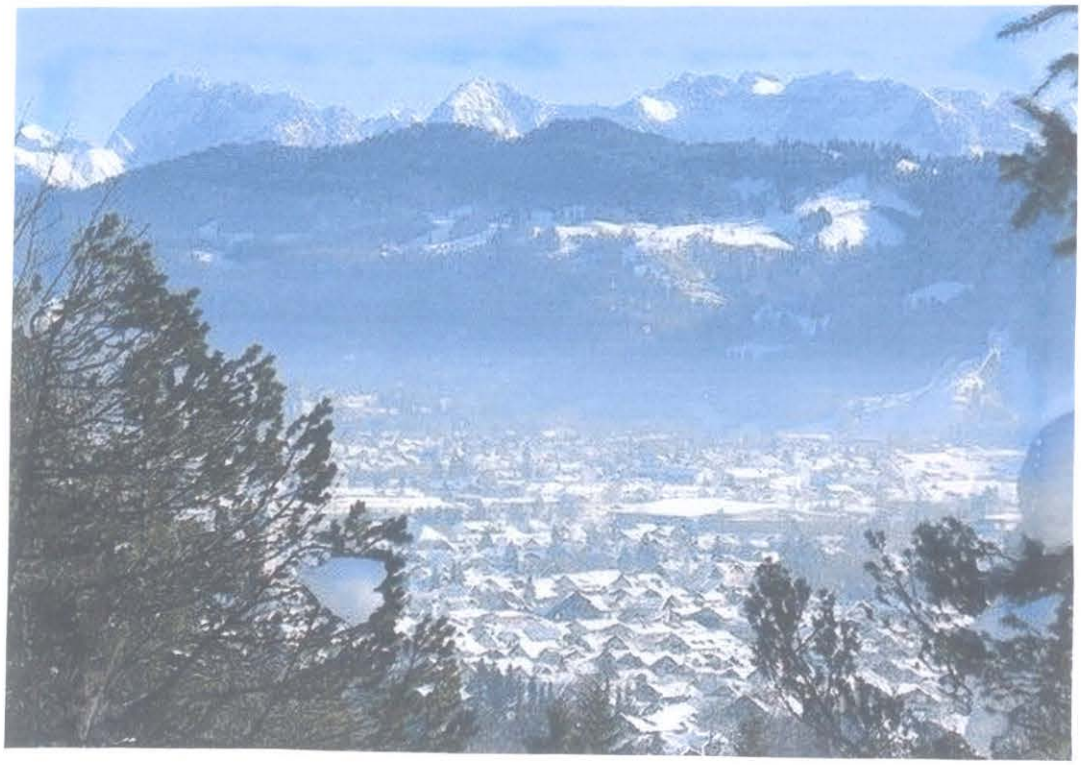
PROF. Dr. WALTER LWOWSKI (1928-2010)

as *Research Professor of Chemistry*, a position that he held until his formal retirement in 1991. His help and effort was instrumental in the development of the Graduate Program in Chemistry that began at NMSU in 1964. After formal retirement, Dr. W. Lwowski stayed as Emeritus Research Professor, retained an office and laboratory in the Chemistry Department and remained active until his death. In addition to research, he helped maintain research instruments and helped develop chemistry demonstration equipment for undergraduate instruction.

His research interest dealt mainly with nitrene and nitrogen heterocyclic chemistry. Specifically, it treated electron deficient species, especially nitrenes and their generation, reaction mechanisms and synthetic applications. The construction of nitrenes with various reactivities, insertion into C-H bonds, reaction with unshared electron pairs on sulfur and modification of nucleosides by reaction with nitrenes received special attention.

Other topics of research involved the migration of heteroatoms such as N and O, aminimides containing adjacent N+ and N- in five-membered rings, mesoionic heterocycles and large heterocycles.

Garmisch, Bavaria, Germany, Birthplace of Prof. W. Lwowski.



Garmisch in the Bavarian Alps is also the Birthplace of Richard Strauss and Karl Popper.

Prof. Dr. Walter Lwowski trained large number of master and doctoral students and postdoctoral fellows. His research was supported by substantial grants, especially from the National Institutes of Health and the National Science Foundation.
A list of representative publications is given at the end of this article.

Prof. Dr. Walter Lwowski was a widely respected person at New State University. He came to Las Cruces in 1966 after leaving the Chemistry Department of Yale University and accepting the position of *Research Professor of Chemistry* at NMSU.

At the time, New Mexico State University had a special and somewhat unique way of promoting high quality research and propagating the name of the University in the highest scholarly circles.

This was the Research Center. It had its own building with first class laboratories and auxiliary facilities and with special attention from the administration.

The first *Research Professor* was Clyde W. Tombaugh, discoverer of Pluto, our illustrious teacher and world famous astronomer. He discovered Pluto in 1930 at the age of 24. This explains in part why

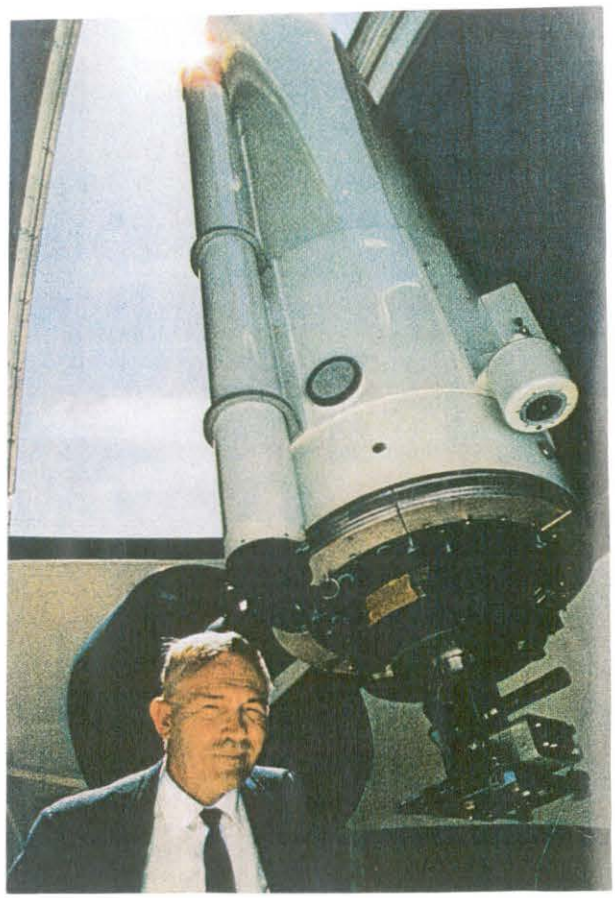
the Department of Astronomy was one of the best at New Mexico State University. In the 1960's there were also Research Professors in Mathematics and Biology.

Clyde W. Tombaugh (1906-1997) was a great, friendly, humble and very knowledgeable person. He was always present at the of meetings of the Astronomical Society of Las Cruces, where he was often the main attraction and the center of attention. His comments and reflections about extra-terrestrial life, space travel, astronomy and life on Earth were always full of insight, deep perception and wisdom. In Mesilla Park, where he used to live, he was the most distinguished and widely respected member of the community.

His office at the Research Center was always open to students and we still remember when we visited him in the 1960's and he gave us reprints of some articles about the discovery of Pluto and voyage to the planets.

Clyde W. Tombaugh and Walter Lwowski eventually became good friends and they used to go to lunch together very often. Later, the two of them and other researchers formed and almost formal "lunch group". Frank Harary, of Department of Computer Science at New Mexico State University, gave a detailed description of the highly

scholarly lunch group in an article published in *Solstice, Vol. 8, No.1, Summer 1997* ("To the Memory of Clyde Tombaugh, 1906-1997").



Prof. Clyde W. Tombaugh, Discoverer of Pluto, W. Lwowski's Friend and Our Illustrious Teacher of Astronomy.

General view of New Mexico State University. Picture taken from Mesilla Park, New Mexico in the 1960's.

Organ Mountains near Las Cruces, New Mexico .

Prof. Dr. Walter Lwowski was a very formal person, a "*Hern Professor* "of the Old School. He was almost always using a suit and tie. His daily rounds in the laboratory, where he verified the progress in the work of the graduate students and postdoctoral fellows were twice a day, about nine o'clock in the morning and early in the afternoon. Most of his collaborators tried to be at their posts at their laboratory benches during these visits.

Among his many graduate students, we remember two that were very different. One of them was Richard Moore, now deceased, who completed his Ph. D. Degree in the early 1970's. He was the biggest and probably the strongest person on the NMSU campus. The other was a Chinese student who completed the M.S. Degree and whose name we shall not mention. He was often absent at Prof. Lwowski's daily rounds and caused him some preoccupation. This fellow spent a lot of time, especially at the beginning of each month at the horse track or the dog races in Ciudad Juarez, Chihuahua, Mexico. Both of them gave Prof. Lwowski some extra work and worries.

Among his postdoctoral fellows we remember two, mainly because they worked very hard and were very serious and responsible. One was Dr. Siegfried Linke from Germany. The other was Dr. Walter Judd from New Zealand.

All chemistry students at New Mexico State University had high reespect and admiration for Professor Lwowski and in some way he represented the image of a great chemist, the important scientist that they wanted and dreamed to be some day.

The graduate students made a point of greeting him when they met in the hallways of the Chemistry Building saying loudly *"Good morning* " or "*Good afternoon Dr. Lwowski*". At times he would answer the greetings. Other times, it appeared that he did not notice the person or persons that just passed by him and simply ignored them. He might have been distracted, involved in deep thoughts or reflections or in a stern mood. What was really happening is still a mystery.

One day, two of his collaborators (S.M. Abdul Hai, a doctoral st udent from Pakistan and Dr. Walter Judd, a postdoctoral fellow from New Zealand) successfully completed a synthesis that was very difficult. They decided to celebrate and invited me to lunch. The three of us went to Len's, at the time on of the best restaurants in Las Cruces. It had a unique setting and decoration with a stairway descending into a cavern with an artificial stream and fish.

As we stood in line, waiting to be seated, Walter Lwowski and Clyde W. Tombaugh passed by us. They had special and preferential treatment. The three of us, including his two collaborators, greeted them. Prof. Lwowski passed by us and seemed not to have noticed or heard anything. After they were a few steps away, Prof. Clyde W. Tombaugh stopped, returned and came in our direction. He gave me a tap on the shoulder and said *"Hi Lavinel, how are you doing?"*. Walter Lwowski looked amazed and very surprised, but continued on his way. Of course, I knew Prof. Clyde W. Tombaugh very well from the meetings of the Astronomical Society of Las Cruces, the Department of Astronomy at NMSU and from Mesilla Park, where we both used to live.

One of the excellent events at New Mexico State University was the Chemistry Seminars Program.

Unlike many institutions throughout the world, at NMSU the guest speakers were encouraged to interact and speak to as many faculty members and students as possible. The seminars were attended by all faculty and all graduate students and usually included the serving of refreshments.

Unfortunately, we remember many institutions in three continents

where the guest speaker was literally hidden or shown off by his host and was kept away from the students, considered second class citizens. Some were rushed to the airport as soon as they finished the lecture. Attendance at seminars was not compulsory and at times the audience was very small since the topic was physical chemistry or was too specialized.

In the 1960's at New Mexico State University, all the faculty members and graduate students were strongly encouraged to attend all seminars. We still remember guest speakers such as Fred Basolo, Stanley L. Miller and Harry B. Gray.

All visitors received special, "vip" treatment. They usually landed at the International Airport in El Paso, Texas and dined at the best restaurants in El Paso, Ciudad Juarez or the Las Cruces area. We remember places like the Camino Real in Cd. Juarez and La Hacienda in Mesilla , where the Wells Fargo Coaches used to stop one and a half centuries ago. During his stay in Las Cruces, the guest speaker had some time reserved to go to lunch with a small group of graduate students.

During Harry B. Gray's visit to Las Cruces, Prof. Lwowski was one of his hosts. The story goes that they went to dinner at La Hacienda,

an excellent restaurant in La Mesilla, with beautiful settings, gardens and wild birds. Walter Lwowski was a good connoisseur of wines. When the wine list came, Harry Gray gave it to Lwowski to choose the wine. After much selection and no decision, the guest became a a little impatient and said: "*The hell Walter, let's take a gallon of Gallo* !". At the time, Gallo was one of the cheapest wines produced and sold in California.

The next day, Harry Gray asked some graduate students to take him to lunch to the cheapest restaurant in Las Cruces. They accompanied him to La Casita, where a sopaipilla and a coke costed 25 cents. He liked it and enjoyed the lunch and the company of the graduate students very much.

As far as we know, Prof. Dr. Walter Lwowski never married. His main devotion in life was chemistry. He liked very much chemical instruments, especially NMR spectrometers. One of his hobbies was to repair instruments and cars. When the Chemistry Department at the University of Texas at El Paso (UTEP) acquired the first NMR instrument, the workers managed to drop it and damaged it while unloading. Prof. Dr. Walter Lwowski went to El Paso and got it working in perfect conditions in a few hours.

Tetrahedron
Volume 46, Issue 22, 1990, Pages 7599-7659

The total synthesis of chlorophyll *a*

Robert Burns Woodward[1], William A. Ayer, John M. Beaton, Friedrich Bickelhaupt, Raymond Bonnett, Paul Buchschacher, Gerhard L. Closs, Hans Dutler, John Hannah, Fred P. Hauck, Shô Itô, Albert Langemann, Eugene Le Goff, Willy Leimgruber[2], Walter Lwowski, Jürgen Sauer, Zdenek Valenta and Heinrich Volz

Converse Memorial Laboratory, Harvard University, Cambridge, Massachusetts 02138 U.S.A.

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The author in front of the Old Chemistry Building at New Mexico State University in the mid 1960's.

Being from the Bavarian Alps, Walter Lwowski liked mountain climbing. He hiked the Organ Mountains near Las Cruces from one end to the other.

Having been born the same city as Richard Strauss, Prof. Walter Lwowski liked classical music and was a patron of the Las Cruces and El Paso Symphony Orchestras.

Prof. Dr. Walter Lwowski bequeathed a major portion of his estate to New Mexico State University to create an endowment for the maintenance, repair and purchase of chemical research instruments for the Department of Chemistry and Biochemistry.

Prof. Dr. Walter Lwowski was a member of the Editorial Board of several journals including the *Journal of Organic Chemistry* and the *Journal of Heterocyclic Chemistry.*
He was also a member of the Editorial Board of the *Southern Brazilian Journal of Chemistry* since its founding and gave us special assistance, especially during the early stages.

Prof. Dr. Walter Lwowski made fundamental and important contributions to chemistry and earned widespread national and international recognition. He may be rightfully considered New Mexico's greatest and most illustrious organic chemist.

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