

SYNTHESIS AND CHARACTERIZATION OF NEW 2, 5-DISUBSTITUTED-1, 3, 4- THIADIAZOLE DERIVATIVES

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ABSTRACT

In this study, a new 1, 3, 4-Thiadiazole derivatives have been synthesized by many cyclization reactions. Starting from (2, 5 – dimercapto -1, 3, 4-Thiadiazole) a variety of compounds have been synthesized. Derivative (1) was synthesized by the reaction of hydrazine hydrate with carbon disulphide. The derivative (1) was reacted with 1, 2-dibromoethane in presence of alkali ethanol to give the derivative (2). The derivative (3) was obtained from the reaction of derivative (2) with hydrazine hydrate. Schiff base (4) was formation by reacting of derivative(3) with p-Hydroxybenzaldehyde. From phenolic Schiff base (4), Methylolic derivative (5) has been prepared. Etheric derivative (6) was synthesized by the reaction of Methylolic derivative with saturated alcohol. Derivative (7) was synthesized by the reaction of Etheric derivative (6) with Epichlorohydrine. The last step of this study was the preparation of a derivative (8) by reacting of derivative(7) with morpholine via ring opening. All these derivatives were verified by using (FT-IR, UV) spectra photometer, ¹H-NMR spectra and elemental analysis (C.H.N.S).

KEYWORDS: Synthesis, New, 2, 5-Disubstituted--1, 3, 4-Thiadiazol Derivatives

INTRODUCTION

Thiadiazole is a five membered ring system containing sulphur and two nitrogen atoms. It's occurring in four isomeric forms ⁽¹⁾. All references, molecular compositions and spectroscopic, show that most compounds are for derivative 1, 3, 4-thiadiazole. Thiadiazole is one of the most important biochemical materials and it is one of the most popular isomers in the industrial and the pharmaceutical fields compared to other species. The first 1, 3, 4-Thiadiazole was described by Fischer in 1882 but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh. They found when a substitution occur in locations (2, 5) of the thiadiazole compound with two groups of thiol (SH) this will give a more power to the compound with a wide range of applications. 2, 5-disubstituted-1, 3,4-thiadiazole derivatives have been found to possess biological activities including antifungal,⁽²⁾ antibacterial,⁽³⁾ and anticancer⁽⁴⁾. Schiff bases contain an imine group(-N=CH-) within their composition, they are formed by condensation reaction between a carbonyl compounds (ketones or aldehydes) and primary amines ⁽⁵⁾. Schiff bases are used in a wide range of uses, in medicinal and biological fields⁽⁶⁾. The methylolic Schiff bases derivatives are used in the production of industrial polymers, such as PVA⁽⁷⁾. Epoxy derivatives are poly ethers contain on one or more of the epoxy groups at the end of the chain, known as (Alkylene oxide or oxiranes) ⁽⁸⁾. These derivatives are used in coatings and adhesives ⁽⁹⁾. Epoxy derivatives undergoes to the polymerization process through its ring opening and its participation in a process known industrially as "curing", using "curing agent" such as the amine compounds⁽¹⁰⁾.

EXPERIMENTAL

FT-IR spectra were recorded using solid KBr disc by testing Shimadzu (FT-IR 8300). Ultra violet spectra were recorded using Shimadzu (UV-Visible) within range (200 -900) nm, ¹H-NMR spectra were carried out in Al –al Bayt University (Jordan) operating at 300 MHz in DMSO-d₆ as solvent with the TMS as internal standard and the elements analysis of compounds (C.H.N.S) by using a Perkin-Elmer, RE2400, measurement was made at College of Education for Pure Science (Ibn Al- Haitham), Baghdad University. All the chemical materials and solvents were purchased from (Merck and BDH) companies.

Preparation of Derivative [1] (2, 5- Disubstituted-1, 3,4-Thiadiazole)⁽¹¹⁾

A mixture of hydrazine hydrate (80%) (0.10 mole, 4.81 ml) with (0.20 mole, 12ml) carbon disulfide in (30 mL) absolute ethanol was synthesized. The mixture was refluxed for (5 hrs.). Then cooled, filtered and recrystallized in distilled water.

Preparation of derivative [2]

[2, 2- Disubstituted-bis-(1, 3, 4-Thiadiazole)-5-Disulfide Alkyl]⁽¹²⁾:

In absolute ethanol (0.71g) from Sodium hydroxide was dissolved with stirring for 1hr. (0.012 mole, 1.71g,) of the compound [1] was dissolved in absolute ethanol (7.3ml). Then the first prepared solution was added to the second solution, the mixture was stirred for 15 minutes. Then (0.006 mole, 0.51 ml) from 1, 2-dibromoethane was added. The mixture was refluxed for (5 hrs). at (210) C⁰, then the mixture was cooled, filtered and recrystallized in absolute ethanol.

Preparation of Derivative [3]⁽¹³⁾: [2, 2-dihydrazino-bis -1, 3, 4-Thiadiazole-5-Disulfide- Alkyl]

(0.011 mole, 3.21 g) of compound [2] was dissolved in absolute ethanol (25.5 ml) then (0.03 mole, 0.97ml) of hydrazine hydrate (99%) were added. The mixture was refluxed for (5 hrs). At (105-115) C⁰, then the mixture was cooled, filtered, recrystallized from absolute ethanol.

Preparation of Phenolic Schiff base (Compound [4])⁽¹⁴⁾:

(1mole) of compound [2, 2- dihydrazino-bis-1, 3, 4-thiadiazole -5-disulfide ethane] with (2mole) of the compound (p-Hydroxybenzaldehyde) were mixed in absolute ethanol (40 mL), refluxed for (8 hrs). then cooled, filtered, recrystallized in absolute ethanol.

Preparation of Derivative [5] (Methyloic Schiff Base Compound)⁽¹⁵⁾:

(5.4g, 0.02mole) phenolic Schiff Base [4] and (1.21g, 0.041mole) of formaldehyde were mixed in THF (75ml), the reactants were mixed gently with 10% of alcoholic Sodium hydroxide solution to keep the acidity of the solution at PH (9-10). The mixture was refluxed in oil bath at (50-60) C⁰ for (4 hrs). The mixture then neutralized with 10% of alcoholic phosphoric acid, then filtered and recrystallized in tetra hydro furan (THF).

Preparation of Saturated Etheric Compound [6]⁽¹⁶⁾

(0.81mol) of saturated alcohol (Butanol) with (1ml) of sulphuric acid were mixed at (10) C⁰, then (0.21mole) of a Methyloic Schiff base compound [5] was added gradually with stirring at room temperature for (2) hr. with the rise of the temperature to the boiling point of the alcohol used. The mixture was refluxed for (24 hrs). Then cooled, the mixture was

neutralized with sodium hydroxide. The compound was extracted using chloroform, recrystallized from chloroform, then dried.

Preparation of Epoxy Schiff Base Compound [7] ⁽¹⁷⁾

(24.51 ml, 0.32 mole) of Epichlorohydrin was mixed with (7.21 ml, 0.13 mole) of saturated alcohol (Butanol) and (0.011 mole) of an etheric Schiff base compound [6], for 20 mins at (55) C⁰, then gently added (4.2g, 0.12 mole) of sodium hydroxide in two stages with a maintained temperature below (60) C⁰. The mixing continues for three hrs. after the first addition the aqueous layer was separated from the organic layer, then a second batch of sodium hydroxide added and mixed for (1hr). the aqueous layer was separated while the organic layer dried and recrystallized from (THF).

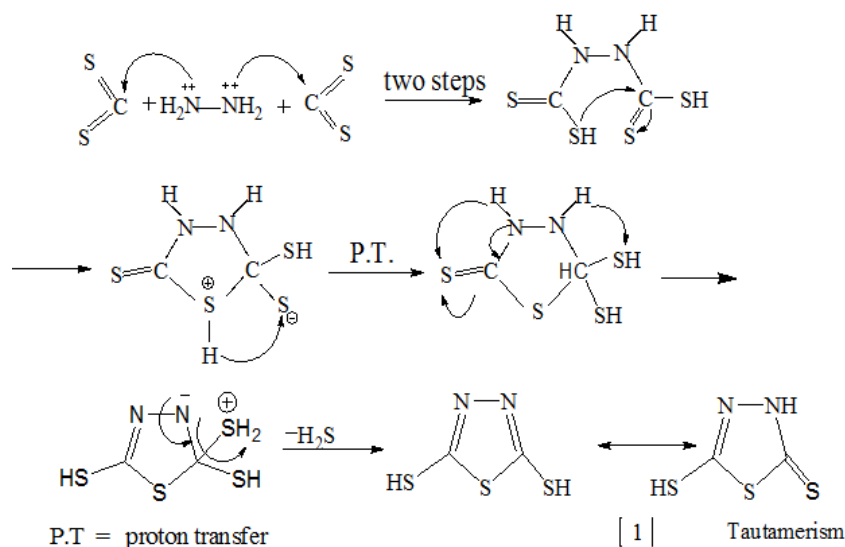
Preparation of Compound [8] with Opening of the Ring ⁽¹⁸⁾

(0.011 mol) of the epoxy Schiff base compound [7] was mixed with (15 ml) of methanol at (10) C⁰, then (1.75 ml, 0.021 mole) of morpholine was added, refluxed for (72 hrs). at (110-120) C⁰, then cooled, filtered, recrystallized from methanol.

RESULTS & DISCUSSIONS

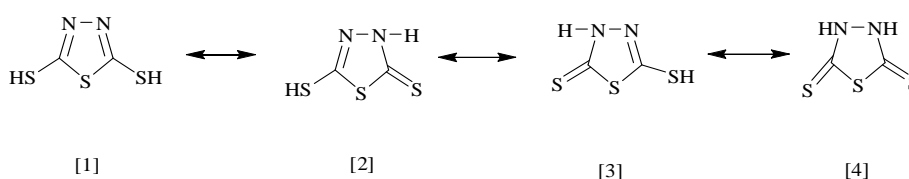
2, 5-disubstituted-1, 3, 4-thiadiazole [1] was prepared as shown in Scheme (1). Some physical properties for this compound were listed in Table (1).

The suggested mechanism for this reaction is shown in the Scheme (1)



Scheme (1)

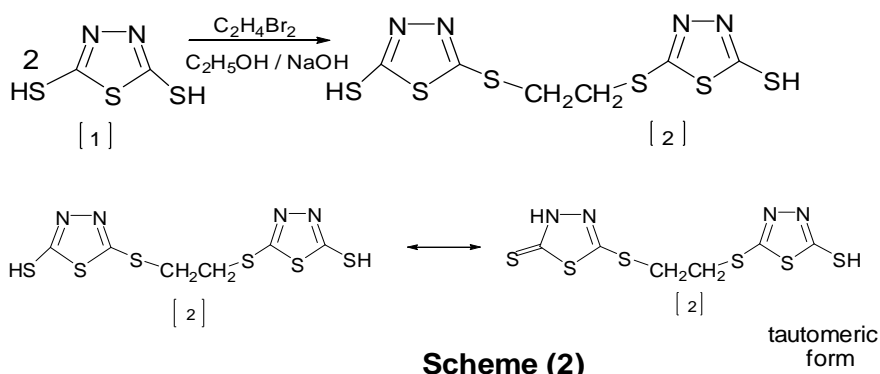
Derivative [1] has four tautomeric forms ⁽¹⁹⁾



Derivative[1] was characterized by its melting point and by (FT-IR, UV) spectrum. Melting point was recorded (160- 162)C°.The FT-IR spectrum of derivative (1)Fig (1), showed a medium intensity band at 1620 cm^{-1} was due to $\nu(\text{C}=\text{N})$. 1273 cm^{-1} due to $\nu(\text{C}=\text{S})$ and showed the stretching vibration(2719-2580) cm^{-1} due to $\nu(\text{S}-\text{H}$ thiol) and showed the absorption band at (3251) cm^{-1} , due to $\nu(\text{NH}$, thion form). That means derivative[1] can exist in the thiol and thion form⁽²⁰⁾.

The (UV) spectrum of compound [1], Fig (6), showed the absorption band at 331nm for $(n-\pi^*)$ resulting from a nonbonding electronic transitions of atoms heterogeneous(S, N) to thiadiazole ring and at 236nm for $(\pi-\pi^*)$ belonging to the imine group $(-\text{N}=\text{CH}-)$.

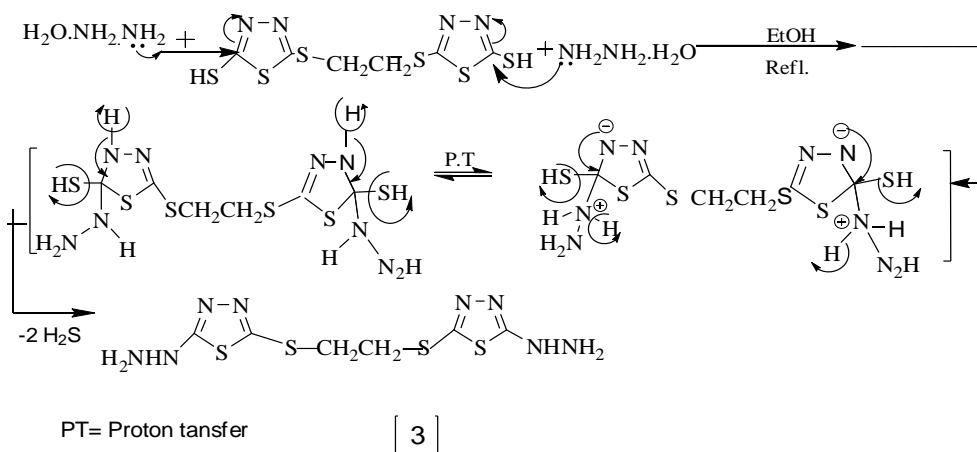
Compound [2] was prepared as shown in Scheme (2).Some physical properties for this compound were listed in the Table (1).



Compound [2] was characterized by FT-IR spectroscopy; FT-IR spectrum of compound (2), shows the absorption bands at (3205- 3275) cm^{-1} , due to $\nu(\text{NH}$, thion form) and $\nu(\text{S}-\text{H}$ thiol) showed weak absorption at (2769) cm^{-1} , that mean compound [2] can exist in the thiol and thion form. Bands at (2962-2924) cm^{-1} were due to $\nu(\text{CH}_2)$ group. Band absorption at (1639) cm^{-1} was due to $\nu(\text{C}=\text{N}$, imine group). Absorption at (1141) cm^{-1} was due to $\nu(\text{C}=\text{S})$ stretching vibration band.

Compound [3] was prepared as shown in Scheme (3).Some physical properties for this compound were listed in the Table (1).

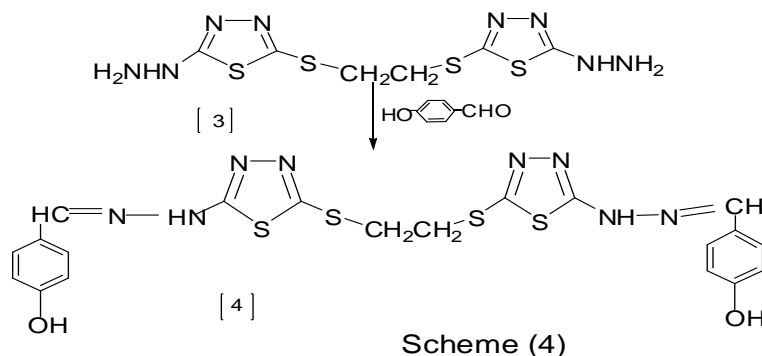
The suggested mechanism for this reaction is shown in the Scheme (3)



Scheme (3)

Compound [3] was characterized by FT-IR spectroscopy; The FT-IR spectrum of derivative (3) Fig (2), shows the absorption band at $(3209) \text{ cm}^{-1}$, due to $\nu(\text{NH})$ and $\nu(\text{NH}_2)$ bands showed at $(3227-3305) \text{ cm}^{-1}$, bands at $(2962-2824) \text{ cm}^{-1}$, due to aliphatic $\nu(\text{CH}_2)$ group. Band absorption at $(1643) \text{ cm}^{-1}$ was due to $(\text{C}=\text{N})$ stretching vibration.

Compound [4] was prepared as shown in Scheme (4). Some physical properties for this compound were listed in the Table (1).



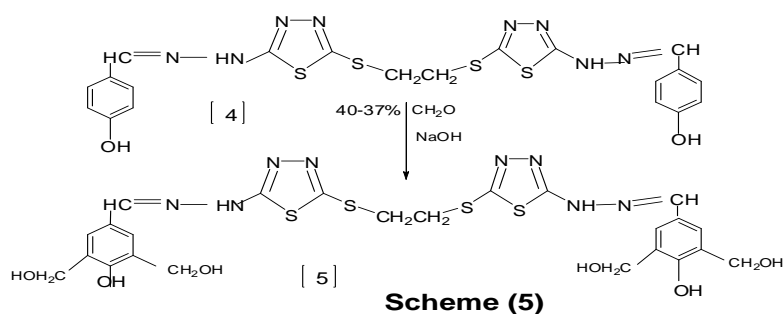
Compound [4] was characterized by (FT-IR, UV) spectrum; The FT-IR spectrum of compound (4), showed the bands at $(3498-3444) \text{ cm}^{-1}$, due to $\nu(\text{O-H})$ and bands showed at $(3286-3387) \text{ cm}^{-1}$ due to $\nu(\text{NH})$, bands at $(2969-2808) \text{ cm}^{-1}$, due to aliphatic $\nu(\text{CH}_2)$ group. Bands absorption at $(1670-1600) \text{ cm}^{-1}$ was due to $\nu(\text{C}=\text{N})$ stretching and $(1273-1249) \text{ cm}^{-1}$ absorption bands for phenolic group $\nu(\text{C-O})$.

The (UV) spectrum of compound [4], showed the absorption band at (315 nm) for electronic transitions $(n-\pi^*)$ and at (226 nm) for transitions $(\pi-\pi^*)$.

$^1\text{H-NMR}$ spectrum of compound (4), Fig.(7), showed characteristic signals at $\delta=(9.4-10.1) \text{ ppm}$ for $(s, 2\text{H}, (2\text{OH}))$, $(6.78-8.190) \text{ ppm}$ belong to $(m, 10\text{H}, 2(-\text{CHC}_6\text{H}_4\text{OH}))$ singlet signal at $\delta=(4.49-5.17) \text{ ppm}$ due to $(s, 2\text{H}, (2\text{NH}))$ and at 2.50 ppm was due to the solvent DMSO-d_6 . $\delta=(0.9-1.6) \text{ ppm}$ due to $(t, 4\text{H}, (2\text{CH}_2))$.

Elemental analysis for compound (4) $\text{C}_{20}\text{H}_{18}\text{N}_8\text{S}_4\text{O}_2$: [H, 3.341(4.251); C, 45.28(45.589); N, 21.13(21.634); S, 24.15 (24.634)]

Compound [5] was prepared as shown in Scheme (5). Some physical properties for this compound was listed in Table (1).



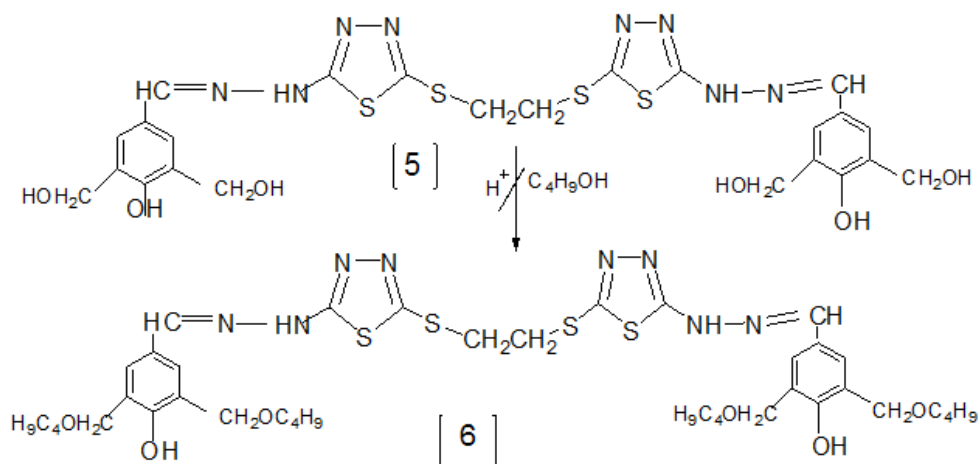
Compound [5] was characterized by (FT-IR) spectrum; The FT-IR spectrum of compound (5), showed the bands

at (3271-3236) cm^{-1} , due to ν (NH) and ν (O-H) band showed at (3363) cm^{-1} , bands at (1678-1604) cm^{-1} was due to ν (C=N). Bands absorption at (2943-2931) cm^{-1} , due to ν (CH_2) group and aromatic (CH) group showed a frequency at (3155) cm^{-1} . Also appeared other absorption band at (1512) cm^{-1} , was due to aromatic group ν (C=C) ⁽²⁰⁾.

Elemental analysis for compound (5) $\text{C}_{24}\text{H}_{26}\text{N}_8\text{S}_4\text{O}_6$: [H, 4.0(4.951), C, 44.3(44.5);

N, 17.2(17.8); S, 19.2 (19.5)].

Compound [6] was prepared as shown in Scheme (6). Some physical properties for this compound were listed in Table (1).



Scheme (6)

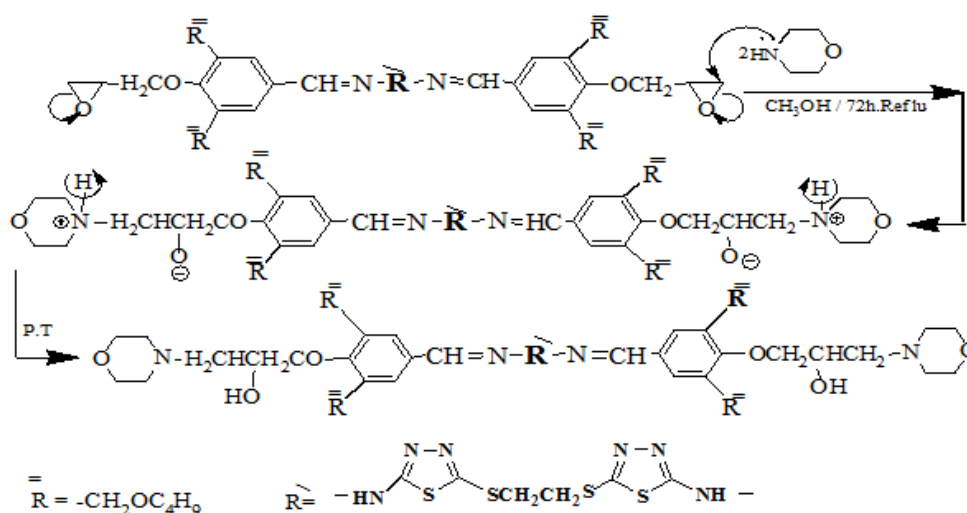
Compound [6] was characterized by (FT-IR) spectrum; The FT-IR spectrum of compound (6) Fig. (3), the appearance of new absorption bands at (1111 -1184) cm^{-1} , due to ν (C-O-C) stretching vibration. Showed the absorption band of the phenolic ν (OH) group at (3460) cm^{-1} . ν (CH_2) bands showed at (2954-2912) cm^{-1} . Showed characteristic FT-IR bands at (1540-1604) cm^{-1} , due to ν (C=N) for each of the Schiff bases and aromatic ring ⁽²⁰⁾.

The $^1\text{H-NMR}$ spectrum of derivative (6), Fig. (8), showed characteristic signals at δ =(9.9-10.1) ppm belong (s, 2H, (2OH)), (6.7-8.55) ppm due to (m, 6H, 2(-CH-C₆H₂OH)), δ =(4.1-5.1) ppm belong to (s, 2H, (2NH)), Singlet signal at δ =(3.68- 3.7) ppm due to (s, 8H, 4(-CH₂O)), (t, 4H, (2CH₂)) at δ =(1.1-1.5) ppm, (0.6 -1.0) ppm due to (m, 36H, (4C₄H₉)) and at 2.50 ppm was due to the solvent DMSO-d₆.

Compound [7] was characterized by (FT-IR) spectrum; The FT-IR spectrum of compound (7), Fig. (4), the appearance of new absorption bands at (1161-1222) cm^{-1} , due to ν (C-O-C) and strong bands (2954-2924) cm^{-1} for ν (CH_2). Showed characteristic FT-IR bands at (972 -948) cm^{-1} , due to epoxy group, known as (Alkylene oxide).

Some physical properties for this compound (7) were listed in Table (1).

Compound [8] was prepared as shown in Scheme (8). Some physical properties for this compound were listed in Table (1). The suggested mechanism for this reaction is shown in the Scheme (8)

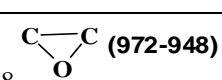
**Scheme (8)**

Compound [8] was characterized by (FT-IR) spectrum; The FT-IR spectrum of compound (8), Fig. (5), showed the absorption bands at $(1111-1224)\text{cm}^{-1}$, due to $\nu(\text{C-O-C})$, $\nu(\text{C=N})$ at $(1654-1604)\text{cm}^{-1}$ and $\nu(\text{CH}_2)$ bands showed at $(2958-2827)\text{cm}^{-1}$. Also absorption band appear at $(3410)\text{cm}^{-1}$, due to $\nu(\text{OH})$ group.

Table 1: Shows the Physical Properties of Compounds (1-8) with Formula

N0	Molecular Formula	M.P C ⁰	Colour	Yield %	N0	Molecular Formula	M.P C ⁰	Colour	Yield %
1	C ₂ H ₂ N ₂ S ₃	160-162	Light yellow	60	6	C ₄₀ H ₅₈ N ₈ S ₄ O ₆	Oily	Brown	52
2	C ₆ H ₆ N ₄ S ₆	204-206	White	55	7	C ₄₆ H ₆₆ N ₈ S ₄ O ₈	Oily	Brown-yellow	45
3	C ₆ H ₁₀ N ₈ S ₄	235-237	Grey	75	8	C ₅₄ H ₆₈ N ₈ S ₄ O ₁₀	Oily	Brown	55
4	C ₂₀ H ₁₈ N ₈ S ₄ O ₂	158-160	Yellow	72					
5	C ₂₄ H ₂₆ N ₈ S ₄ O ₆	Oily	Dark red	50					

Table 2: (FT-IR) Spectrum Data of Compounds (1-8)

Comp. No.	ν OH	ν CH ₂	ν C=N	ν C-O-C	Others
[1]	-	-	1620	-	ν SH (2719), ν C=S(1273) ν NH(3251), ν C-S-C(698)
[2]	-	2962- 2924	1639	-	ν C=S(1141-1014), ν C-S-C(597)
[3]	-	2962-2927	1643	-	ν NH NH ₂ (3209-3448), ν C-N (1284), ν N-N (1531)
[4]	3498 3444	2989-2808	1670-1600	-	ν C=C (1550), ν C-O(1280) ν C-H aromatic (3159), ν NH (3387-3286)
[5]	3363	2943-2931	1678-1604	-	ν C=C (1512), ν C-O(1273) ν C-H aromatic (3155)
[6]	3460	2954-2912	1604-1540	1165-1122	ν C-H aromatic (3120) ν C-O (1249)
[7]	-	2954-2924	1604-1689	1161-1222	 (972-948) ν C-Haromatic (3078)

[8]	3410	2958-2927	1654-1604	1111-1068	ν C-H out of plane (732), ν C-Aromatic (3078), ν N-H (3251) , ν C-O (1249)
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Table 3: Shows the Elemental Analysis (C.H.N.S) of the Derivatives ([4], [5])

N O	Structure Formula	(C.H.N.S) Analysis % calculated (Found)			
		% H	% C	% N	% S
[4]		3.341 (4.151)	45.28 (45.589)	21.13 (21.624)	24.15 (24.654)
[5]		4.0 (4.751)	44.3 (44.4)	17.2(17.7)	19.2 (19.52)

Table 4: Signal of Absorption (¹H-NMR) for Compounds Measured ([4], [6])

Comp. No.	Molecular Formula	Chemical Shift	Group
[4]	C ₂₀ H ₁₈ N ₈ S ₄ O ₂	δ =(9.4-10.1) ppm δ = (6.78-8.190) ppm δ =(4.49- 5.17)ppm δ = (0.9 -1.6) ppm	(s,2H, 2OH) (m,10H,2 (-CHC ₆ H ₄ OH)) (s,2H, (2NH)) (t,4H, (2CH ₂))
[6]	C ₄₀ H ₅₈ N ₈ S ₄ O ₆	δ =(9.9-10.1) ppm δ = (6.7-8.55) ppm δ = (4.1-5.1) ppm δ = (3.68- 3.7) ppm δ = (1.1-1.5) ppm δ = (0.6 -1.0) ppm	(s,2H, (2OH)) (m,6H, 2(-CH-C ₆ H ₂ OH)) (s,2H, (2NH)) (s,8H, 4(-CH ₂ O)) (t,4H, (2CH ₂)) (m, 36H, (4C ₄ H ₉))

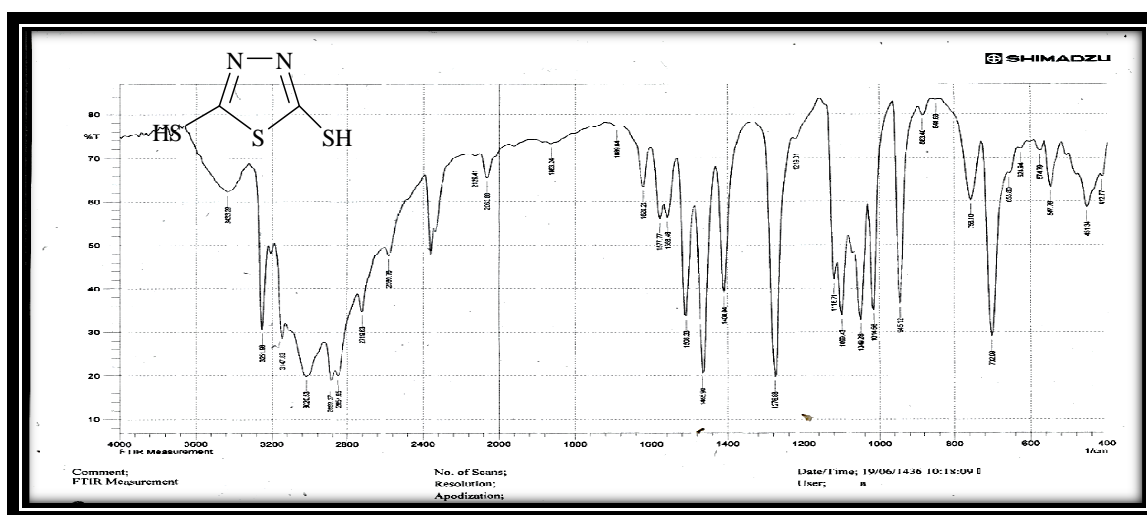


Figure 1: FT-IR Spectrum of Compound (1)

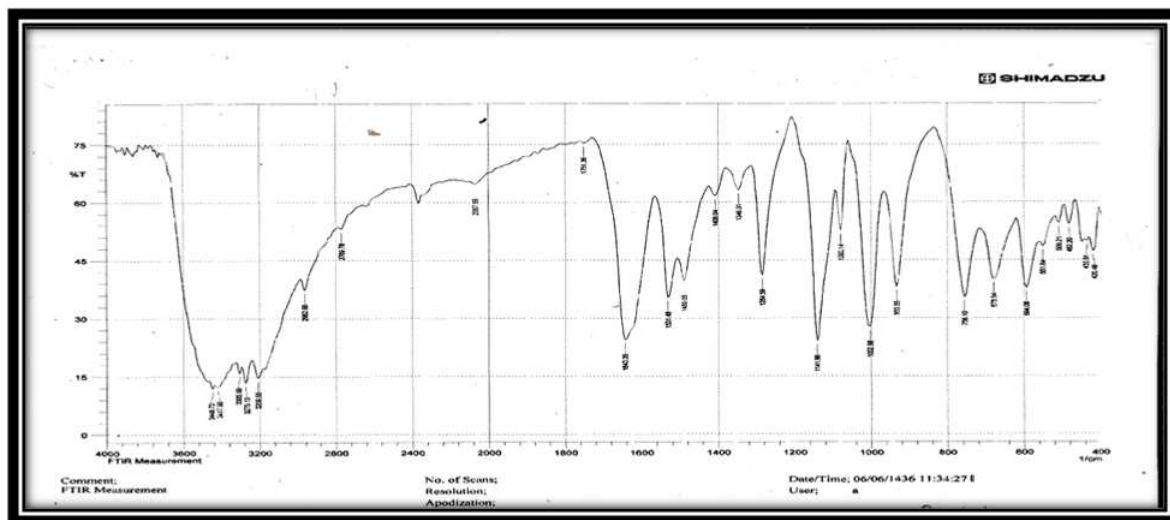
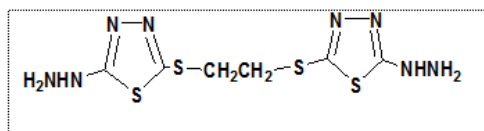


Figure 2: FT-IR Spectrum of Compound (3)

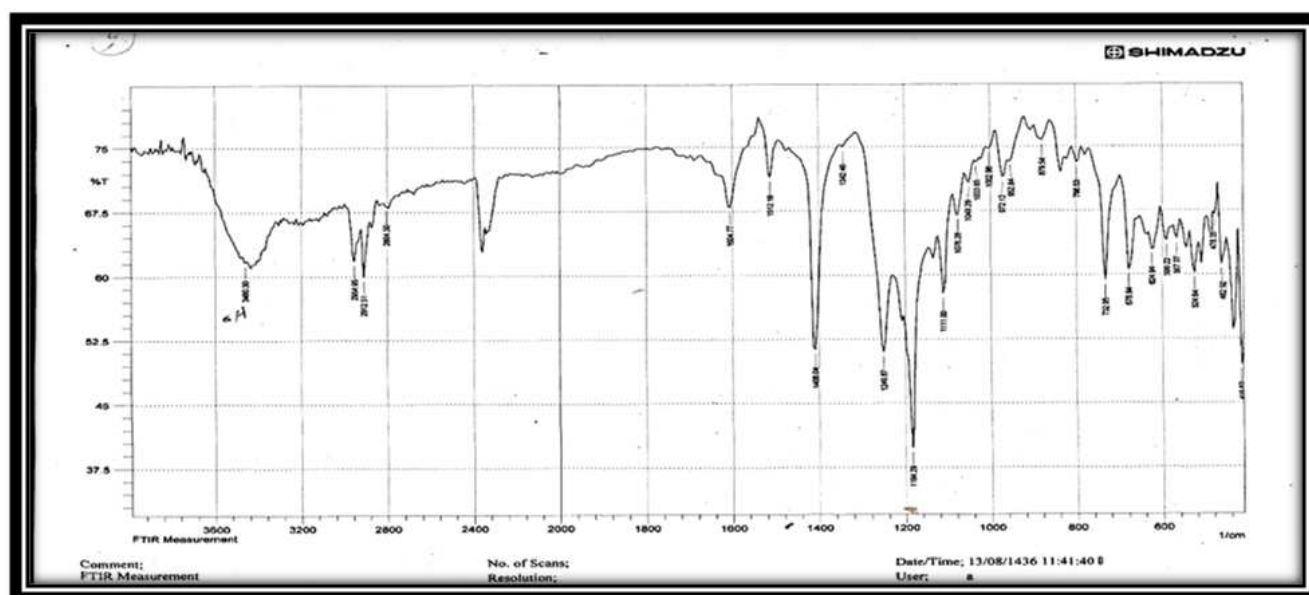
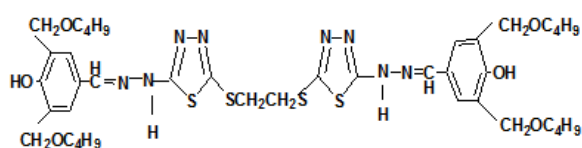


Figure 3: FT-IR Spectrum of Compound (6)

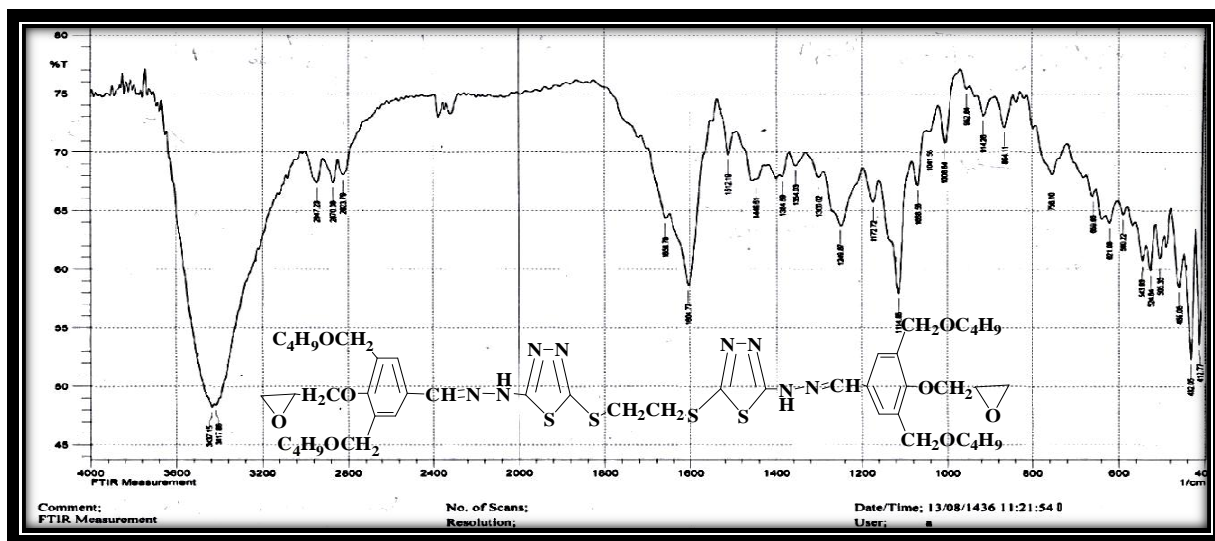


Figure 4: FT-IR Spectrum of Compound (7)

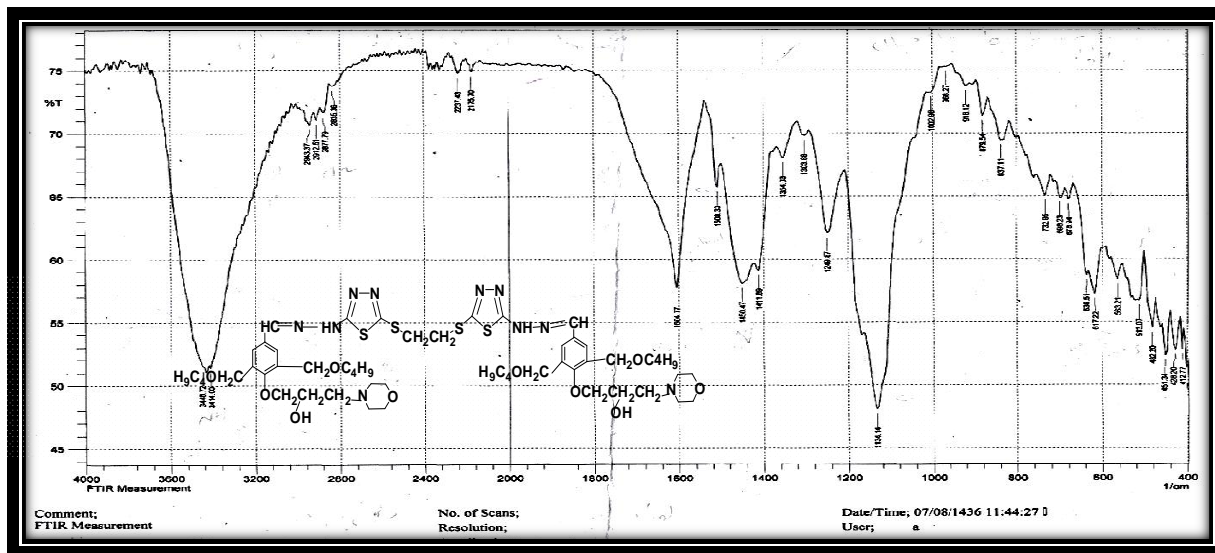


Figure 5: FT-IR Spectrum of Compound (8)

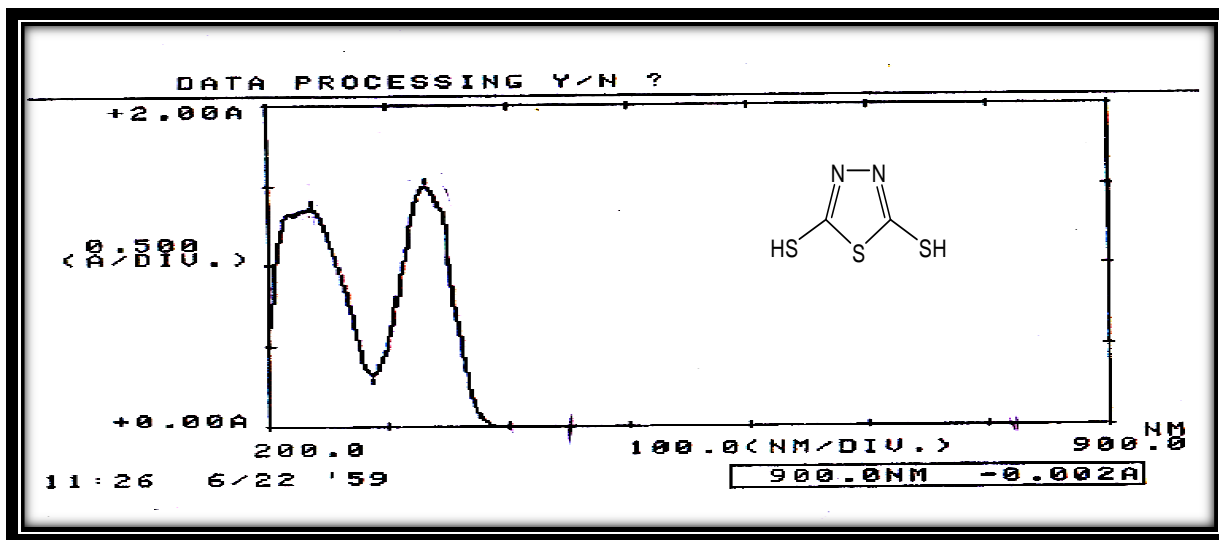


Figure 6: UV Spectrum of Compound (1)

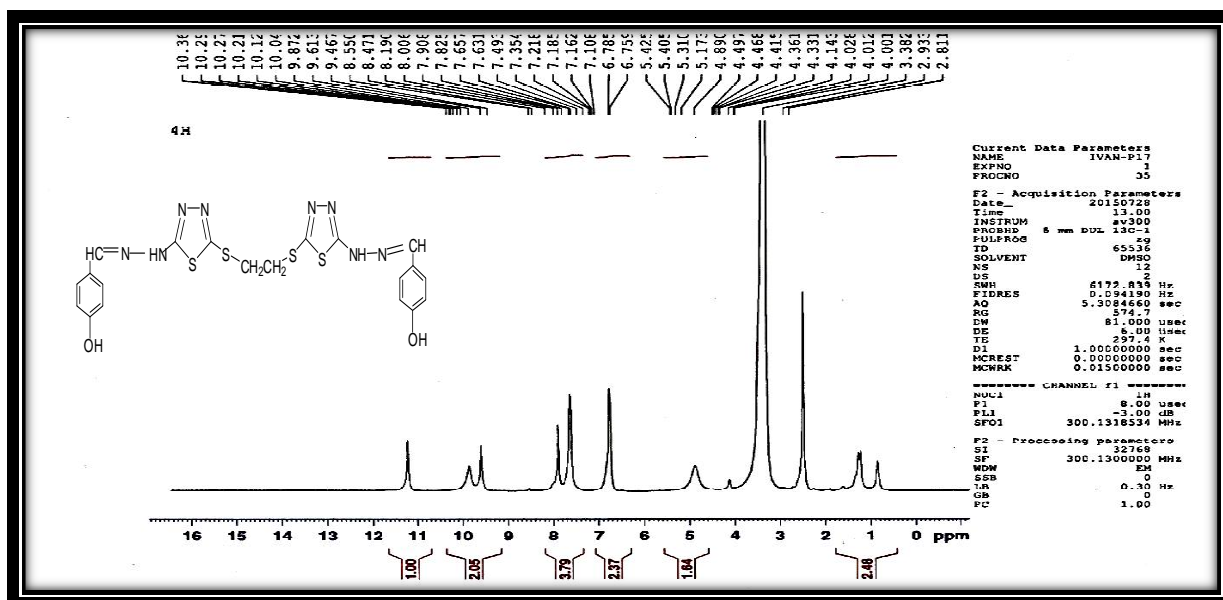
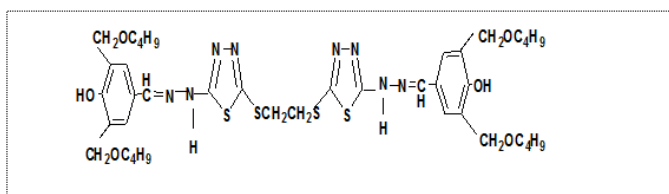


Figure 7: ¹H-NMR Spectrum of Compound (4)



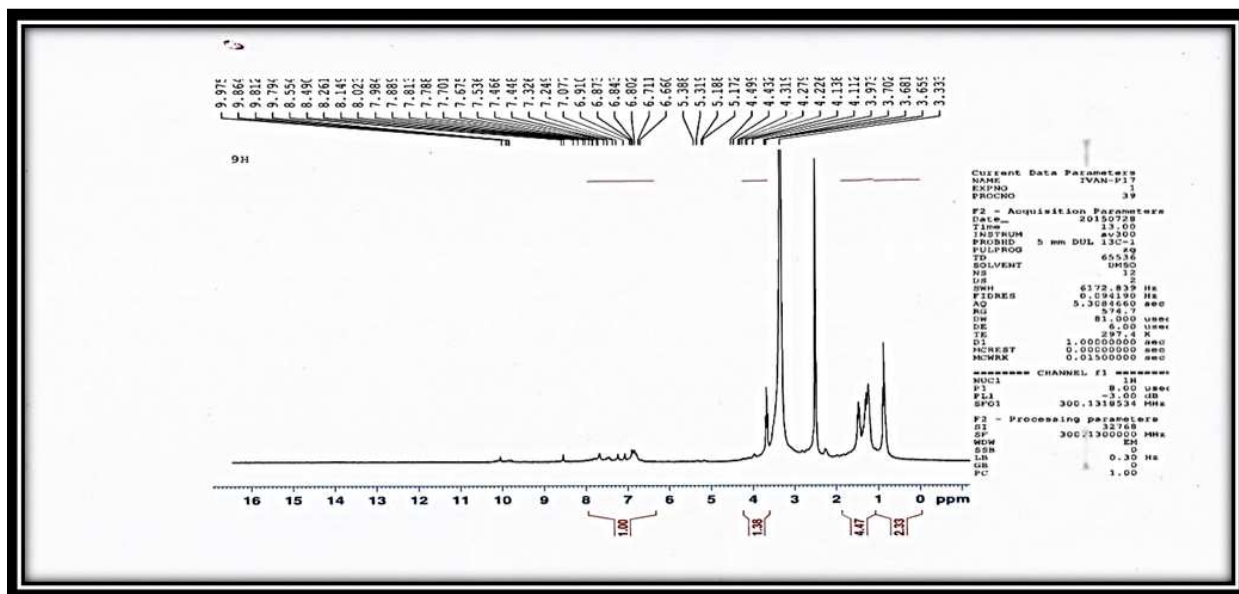


Figure 8: $^1\text{H-NMR}$ Spectrum of Compound (6)

CONCLUSIONS

During the preparation of the new derivatives from the basic component, (2, 5-disubstituted-1, 3,4-thiadiazole) the Epoxy Schiff base and methylol derivatives have been prepared, and these derivatives have great importance because they are used in industrial applications widely, especially coatings and adhesives.

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