

**SYNTHESIS OF SOME NEW THIADIAZINE-1,
1-DIOXIDE DERIVATIVES**

BY

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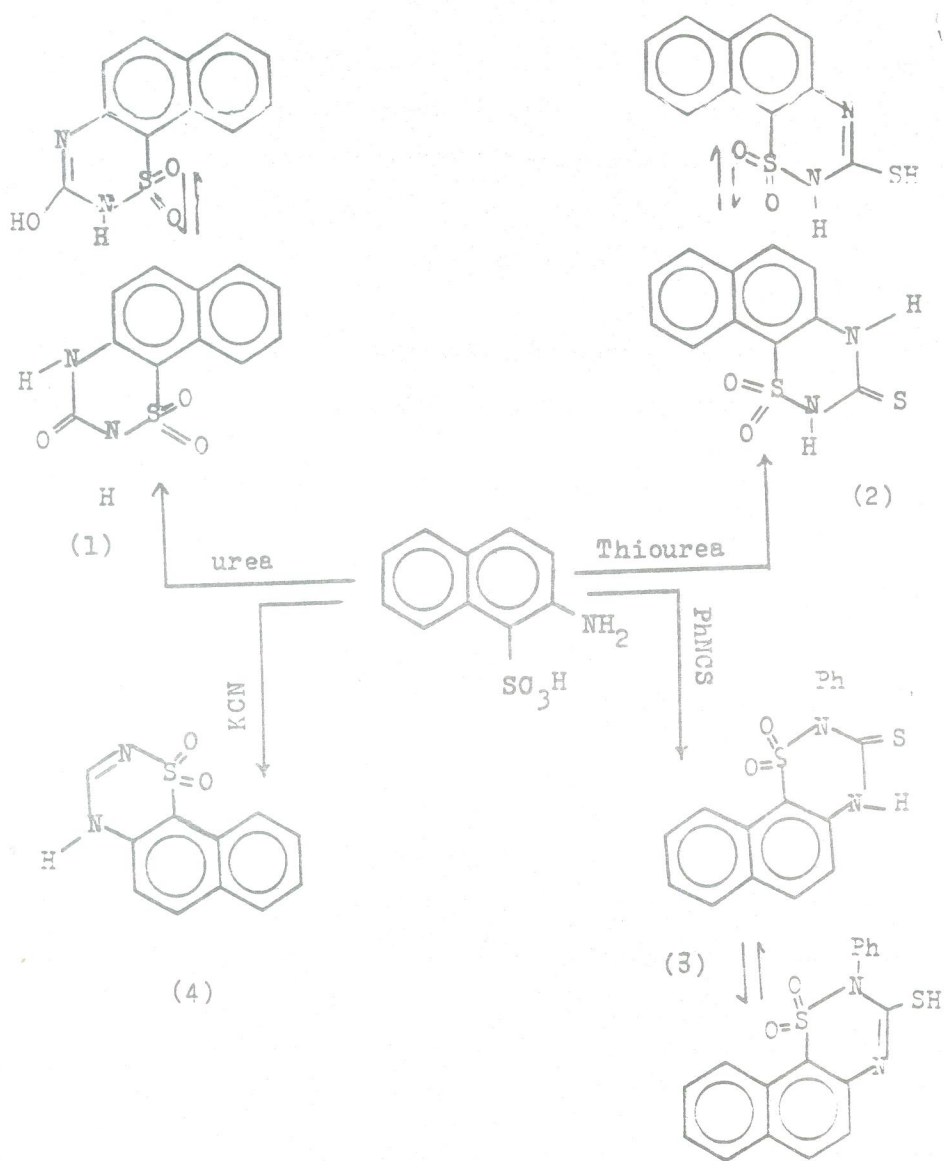
ABSTRACT

Synthesis of naphtho (2,1-e)-3-oxo and 3-thio-2-substituted- 1,2,4-perhydrothiadiazine-1,1-dioxide has been developed beginning with a 2-aminonaphthalene sulphonic acid and urea. thiourea, phenyl isothiocyanate and sodium or potassium cyanide in alkaline media also, the naphtho (2,1-e)-3-substituted-1,2,4-2(H)-thiadiazine 1,1-dioxide was prepared from the reaction of 2- aminonaphthalene sulphoic acid and acetamide, benzamide and salicylamide in alkaline media. The structure of each compound was ascertained with IR. ¹H NMR spectra and microanalyses. The antibacterial activity of the prepared compounds was examined.

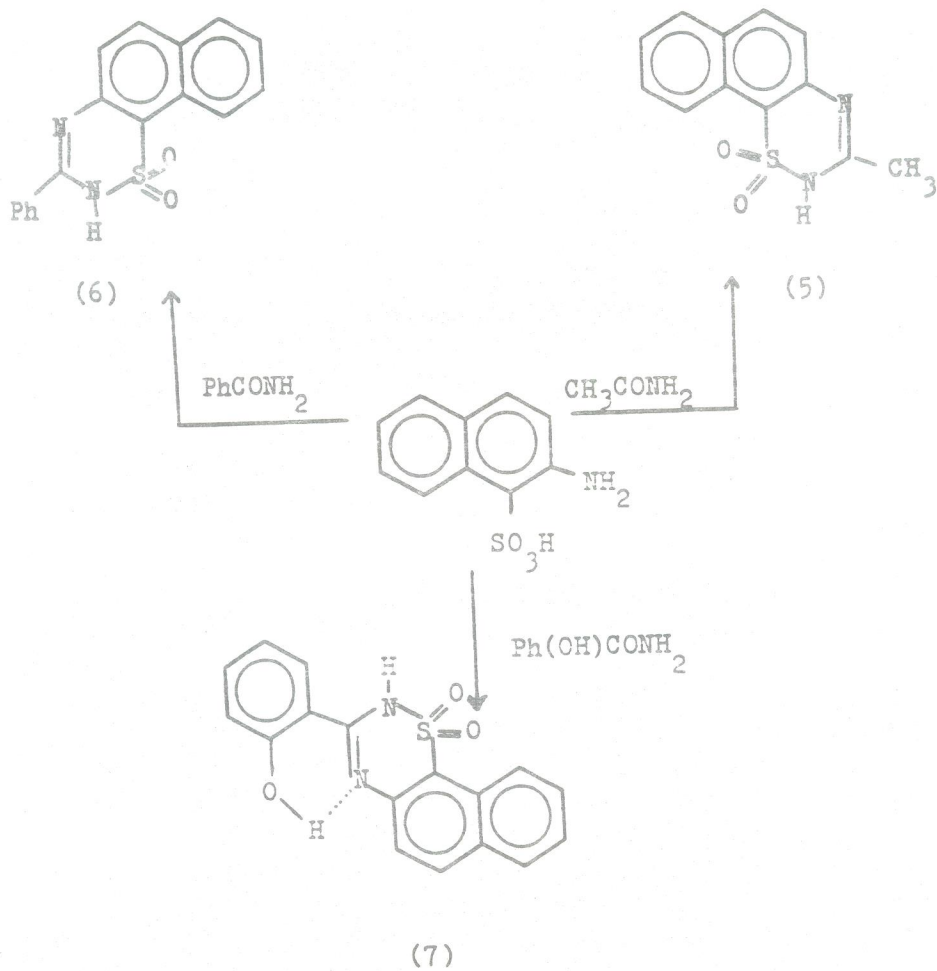
INTRODUCTION

A Literature survey has revealed that, the thiadiazine derivatives are reported to exhibit broad spectrum of biological activity such as tuberculostic (4) antimicrobial (7) insecticidal (2) and fungicidal (8) activities. Further, the many useful biological properties has been observed for sulfamide containing compounds e.g. anticonvulsant hypoglycemic histamin H₂-receptor antagonist and herbicidal (1,3,5,9)activities.

In this paper, we describe the general route for the preparation of naphtho (2, 1-e)-3-oxo and 3-thio-1,2,4-perhydrothiadiazine -1,1-dioxide(1,2)as well as 3-thio-2-substituted analogues (3). Also, the synthesis of naphtho (2,1-e)-3-substituted -



Scheme 1



Scheme (2)

تشييد بعض مشتقات الثياداي أزين - ١, ١ - داي أوكسيد الجديد

نبوية شرف الدين

قسم الكيمياء الصيدلية - كلية الصيدلية - جامعة طنطا

من تفاعل ٢-امينو - حامض النفثالين سلفونيك مع كل من اليوريا، الثيويوريا، الفينيل ايزوسينات وسياتيد الصوديوم تم تشييد النفثو (١, ٢ - ١) - ٣ - اوكسو وثيو - ٢ - مستبدلات - ١, ٢, ٤ - بير هيدروثيا داي أزين - ١, ١ - داي أوكسيد في الوسط القاعدى .

وكذلك تم تحضير المركب نفثو (١, ٢ - ١) - ٣ - مستبدلات - ١, ٢, ٤ - ٢ (يد) - ثياداي أزين - ١, ١ - داي أوكسيد من تفاعل ٢-امينو - حامض النفثالين سلفونيك مع كل من الأستيا أميد ، البنز أميد ، الساليسيل أميد في الوسط القاعدى .

وقد أثبتت التركيبات البنائية للمركبات المشيدة بواسطة القياسات الطيفية والتحليل الدقيقة وتم ايضا دراسة تأثير هذه المركبات على البكتيريا المختلفة.

تشبيد بعض مشتقات الثياداي أزين - ١, ١ - داي أوكسيد الجديد

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من تفاعل ٢-امينو - حامض النفثالين سلفونيك مع كل من اليوريا، الثيوبوريا، الفينيل ابزوسينات وسياتيد الصوديوم تم تشبيد النفثو (١, ٢ - إ) - ٣ - أوكسو وثيو - ٢ - مستبدلات - ١, ٢, ٤ - بير هيدروثيا داي أزين - ١, ١ - داي أوكسيد في الوسط القاعدي .

وكذلك تم تحضير المركب نفثو (١, ٢ - إ) - ٣ - مستبدلات - ١, ٢, ٤ - (يد) - ثياداي أزين - ١, ١ - داي أوكسيد من تفاعل ٢-امينو - حامض النفثالين سلفونيك مع كل من الأسيتا أميد، البنزأמיד، الساليسيل أميد في الوسط القاعدي .

وقد أثبتت التركيبات البنائية للمركبات المشيدة بواسطة القياسات الطيفية والتحليل الدقيقة وتم أيضا دراسة تأثير هذه المركبات على البكتيريا المختلفة.

1,2,4,2(H)-thiadiazine-1,1-dioxide(5-7) was explained. Further, the antibacterial activity of the prepared compounds was studied.

RESULTS AND DISCUSSION

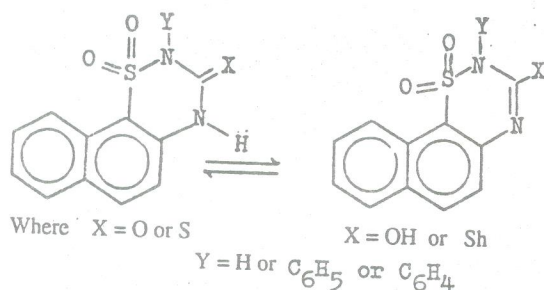
An alkine solution of 2-amino naphthalene sulphonic acid and urea or thiourea in water was heated at 80 °C to generate the corresponding 3-oxo- or 3-thio-compounds (1 and 2). Also, the compound (3) was produced from the reaction of alkaline solution of 2-amino naphthalene sulphonic acid with phenyl isothiocyanate in alcohol water mixture at 80 °C.

Furthermore, 2-amino naphthalene sulphonic acid in KOH solution reacted with sodium or potassium cyanide at 80 °C give compounds (4) (Scheme 1).

On the other hand, the compounds 5,6 and 7 were prepared from the reaction of 2-amino naphthalene sulphonic acid with acetamide, benzamide and salicylamide respectively in ethanol water mixture at 80 °C (Scheme 2).

The key spectroscopic properties for 1-7 compounds exhibited the characteristic absorption bands in IR spectra at 1110-1170 cm^{-1} and 1340-1390 cm^{-1} for the sulfonyl group(6), while the corresponding C=N band was observed at 1471-1689 cm^{-1} (C=N of thiazine)[6] for all compounds.

In the ^1H NMR spectra the N-H moiety appeared as two exchangeable separated signals at 8.7,8.9;8.86 and 8.66,8.9ppm for compounds 1,2 and 3 respectively due to NH and/or OH groups. This gives an evidence that these compounds exhibit a tautomeric structure as shown below. As well as, the compounds 1 and 2 have N-H moiety which appeared at 8.33 and 8.2ppm respectively. (C.F. scheme 1 and 2).



On the other hand, the prepared compounds were tested for their antimicrobial activities against *E. coli*, staphelococcus, aureus, & *Bacillus subtilis* using agar diffusion method. The experiment revealed that the compounds showed a moderate activity against the tested organisms.

EXPERIMENTAL

M.ps are uncorrected, IR spectra (KBr) wafer technique were carried out on Elmer 710B spectrophotometer. 1H NMR spectra ($DMSO-d_6$) using TMS as internal standard were recorded on HNM-PMX 60 NMR spectrometer. Microanalyses were performed at the Microanalytical unit, Cairo University.

PREPARATION OF NAPHTHO-(2-1-e)-3-OXO-(1) AND-3-THIO-1,2,4-PERHYDROTHIADIAZINE-1,1-DIOXIDE(2)

Dissolve 4.46 gm (0.02 mol) of 2-aminonaphthalene sulphonic acid in 2% aq. KOH. A. 0.02 mol of urea or thiourea was added to the previous solution. The mixture was heated at $80^\circ C$ for 4hr. The solution was left for 30 hr at room temperature and then left in refrigerator over night to give crystalline product which recrystallized from aqueous alcohol. The products were chromatographically homogeneous when developed with iodine solution and gave positive reaction with ninhydrin. The

synthesized compounds were soluble in acetic solution and insoluble in alkaline solution and ethanol.

Yield 65% m.p 258-259 C in the case of urea

IR spectra ($\text{cm}^{-1}\nu$): 1625 (C=N), 1170, 1365 (SO)

^1H NMR (σ ppm): 7-8 (m,Ar), 8.33 (s,NH), 8.7,9.9 (s, NH and /or OH)

Analysis ($\text{C}_{11}\text{H}_8\text{N}_2\text{O}_3\text{S}$, %): Found:C:53.5,H:3.5,N:11.0S:13.2

Calc :C:53.2,H:3.2N:11.3,S:12.9

Yield 68% m.p 250-251 C in the case of thiourea

IR spectra ($\text{cm}^{-1}\nu$): 1620 (C=N), 1160, 1350 (SO₂)

^1H NMR (σ ppm): 6.5-7.6(m.Ar) (s,NH), 8.6,8.86(s,NH and/or OH)

Analysis ($\text{C}_{11}\text{H}_8\text{N}_2\text{O}_2\text{S}_2$ %): Found:C:50.4, H:2.8N:10.4,S:24.0

Calcd:C:50.0, H:3.0, N:10.6,S:24.2.

PREPARATION OF NAPHTHO 9,10-3-THIO-2-PHENYL- 1,2,4-PERHYDROTHIADIAZINE-1,1-DIOXIDE(3)

A solution of 4.46 gm (0.02 mol) of 2-aminonaphthalene sulphonic acid in 50 ml of 2% aq. KOH was added to 0.02 mol of phenylisothiocyanate in 50 ml alcohol. The reaction mixture was heated at 80 °C for 4hr. The solution was left over night at room temperature, a pale gray shiny crystalline product was collected and recrystallized from acetone ether mixture.

Yield 72% m.p. 250-251 °C

IR spectra ($\text{cm}^{-1}\nu$): 1620 (C=N), 1150, 1360 (SO₂)

^1H NMR- (DMSO- d_6 , σ ppm), 6.7-7.05(m,Ar), 8.66,8.86
(s,NH and/or SH)

Analysis ($\text{C}_{17}\text{H}_{12}\text{N}_2\text{S}_2$, %): Found:C:59.5,H:3.8,N:7.9,S:18.4

Calcd: C: 60.0, H:3.5, N:8.2, S:18.8

PREPARATION OF NAPHTHO (2,1-e)-1,2,4-4(H)- THIADIAZINE-1,1-DIOXIDE(4)

To a solution of 4.46 gm (0.02 mol) of 2-aminophthalene sulphonic acid in 50 ml of 2% aq. KOH, add 0.03 mol of NaCN or KCN. The mixture was heated at 80° C for 4 hr then left at room temperature for 24hr. The solution was neutralized with cold 1N HCl to give crystalline product. The product recrystallized from alcohol

Yield 70% m.p. 280 °C

IR spectra ($\text{cm}^{-1}\nu$): 1620 (C=N), 1170, 1360 (SO₂)

¹H NMR (DMSO-d, σ ppm): 6.5-7.5(m.Ar), 8.3 (s.NH)

Analysis (C₁₁H₇N₂S, %): Found :C:57.5,H:3.3,N:12.4,S:14.0

Calcd: C:57.1,H:3.0,N:12.1,S:13.8

GENERAL PROCEDURE FOR PREPARATION OF ANPHTHO (2, 1-e)-3-SUBSTITUTED 1,2,4-2(H)- THIADIAZINE-1,1-DIOXIDE:(5,6 and 7)

A solution of 4.46 gm (0.02 mol) of 2- aminonaphthalene sulphonic acid in 50 ml of 2% aq. KOH was added to solution of the corresponding amide (0.02 mol) in 50 ml ethanol. The mixture was heated at 80 °C for 5 hr then left at room temperature over night. The obtained product was neutralized with cold 1N HC to give crystalline product which recrystallized from aqueous alcohol. The products were soluble in acidic solution and insoluble in aq. sod. carbonate and ethanol. Also, the synthesized compounds were chromatographically homogeneous when developed with iodine solution and gave positive reaction with ninhydrin. The compound (7) gave violet colour with ferric chloride solution.

THE COMPOUND(5)

Yield 75 %, m.p. 290-291° C

IR spectrum (cm^{-1}): 1625 (C=N), 1160, 1350 (SO₂)

¹H NMR (DMSO-d₆- σ ppm) : 7.5-8.03(m,Ar)8.6(s,NH)

Analysis: C₁₂H₁₀N₂SO₂, (%):

Found :C: 55.4,H:30.5,N:10.4

Calc'd : C: 54.96,H:3.8,N:10.7

THE COMPOUND (6)

Yield 72 % m.p. 298-299° C

IR spectrum (cm^{-1}): 1625 (C = N), 1160, 1350 (SO₂)

¹H NMR (DMSO-d₆- σ - ppm): 7.4-8.2 (m,Ar), 8.2 (s,NH).

Analysis (C₁₇H₁₂N₂SO₂, %):

Found :C:66.5,H:4.2,N:8.7

Calc'd :C:66.2,H:3.9,N:9.1

THE COMPOUND(7)

Yield 70 % m.p. 295-296° C

IR spectrum (cm^{-1}):1620 (C=N), 1150, 1360 (SO₂)

¹H NMR (DMSO-d₆, σ -ppm):7.5 - 8.1 (m,Ar)

8.2 (s,NH),8.7(s, OH)

Analysis (C₁₇H₁₂N₂SO₂ %):

Found: C: 62.5,H: 40.0,N:9.0

Calc'd. :C: 62.96,H: 3.7,N: 8.6

ANTIBACTERIALACTIVITY:

The Compounds were examined for their antibacterial activities against *Staphelococcus aureus* & *Bacillus subtilis* using agar diffusion method of 5 mg/ml aqueous alcohol. The compounds showed moderate activity against the used organisms. The results were tabulated in Table 1.

Table 1 : Antibacterial activities of prepared compounds

Compounds	Zone of inhibition (mm)		
	E.coli	B.subtilis	S.aureus
1			
2	-	9	-
3	13	-	-
4	8	9	9
5	-	10	-
6	-	-	-
7	-	-	9
Rifampicin	18	21	22

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