# Synthesis of New N-Substituted Phenothiazine Derivatives

Suaad.M.Al.Araji., Mohammad.R.Ahamad and Luma S.Ahamed.
Dept of Chemistery, College of Science University of Baghdad.

**الخلاصة**

يتضمن البحث تحضير مشتقات جديدة من الفينوثايازين وهي مشتقات معوضة على ذرة النتروجين.
وقد اعتبرت المادة الاولية وهي الفينوثايازين (١) لتحضير هذه المشتقات والتي تم الحصول عليها من تسخين داي فنيل امين مع الكبريت بدرجة $^{O}$C 270 وبوجود اليود كعامل مساعد .

عند معاملة الفينوثايزين (١) مع كلورو استيل كلورايد ليعطي $N_{10}$ استيل فينوثايزين (٢) الذي بدوره يتفاعل مع الهيدرازين المائي تحول الى مشتق الهايدرازين (٣) والاخير يستعمل لتحضير نوعين من مشتقات الحلقات غير المتجانسة :
أ) المركب 4,2,1 ترايازين – 4- فنيل – 3- ثايول فينوثايازين( ٥)
ب) المركب 4,2,1 ترايازين – 4- فنيل – 3- هيدروكسيل فينوثايازين( ١١)
تحضير المشتق 4,2,1 – 4- فنيل – 3- ثايول( ٥) من الغلق في محيط قاعدي للثايوسيميكاربازايد (٤)
تحضير المشتق 4,2,1 – 4- فنيل – 3 - هيدروكسيل( ١١) فقد حضر بنفس الطريقة اعلاه ولكن باستعمال مشتق السيميكار بازايد(١٠) بدل المشتق الثايوسيميكاربازايد
ج) الكله المركب 4,2,1 ترايزين–4- فنيل–3- ثايول فينوثايزين(٥) باستعمال هاليدات الكيل مختلفة وهي ( كلوروبروبان – كلوروبيوتان – برومو بنتان، بنزيل كلورايد )
د) الكله المركب 4,2,1 ترايزين–4- فنيل– 3- هيدروكسيل فينوثايازين ( 11) باستعمال هاليدات الكيل مختلفة وهي ( كلوروبروبان – كلوروبيوتان – برومو بنتان، بنزيل كلورايد )

## ABSTRACT

The aim of the present work is synthesis of new phenothiazine derivatives containing N-substituted phenothiazine.

To obtain these derivatives, the diphenyl amine was chosen as the starting material, which was heated for 6hrs with sulfur. In the presence of iodine at 270 C°, it gave the phenothiazine (1)
Treatment of phenothiazine (1) with (chloroacetyl chloride) gave the $N_{10}$ acetyl phenothiazine (2), which was treated with hydrazine hydrate to give the hydrazine (3). The hydrazine (3) was used for synthesis of two types of heterocyclic derivatives: -
(a) $N_{10}$ (4-phenyl – 1, 2, 4 - triazine – 3 – thiol) phenothiazine (5).
(b) $N_{10}$ (4-phenyl – 1,2,4- triazine – 3 – o1) phenothiazine (11).

Compound (5) was synthesized by the intermolecular cyclization of thiosemicarbazide derivative (4), which was obtained from the reaction of the hydrazide (3) and phenyl isothiocynate.

Compound (11) was synthesized in similar manner that used for the preparation of (5), by using semicarbazide derivative instead of thiosemicarbazide derivative.

(c) Alkylation of $N_{10}$ (4-phenyl–1,2,4-triazine–3–thio) phenothiazine (5) using different alkyl halides (chloro propane, bromo butane, chloro pentane, benzyl chloride) .
(d) Alkylation of $N_{10}$ (4- phenyl – 1, 2, 4-triazine-3-ol) phenothiazine (11) using different alkylhalides (chloro propane, bromo butane, chloro pentane, benzyl chloride) in basic condition.

## INTRODUCTION

During the past period phenothiazine and a number of its derivatives have been reported to posses various biological activities. So the importance of phenothiazine compounds as drugs have long been recognized (1). The pharmacological activities of phenothiazine have been attributed to the basic nitrogen of the ring, which donates electrons to the biological receptors, by a chargetransfer mechanism (2).

Phenothiazines are an important group of neuroleptics used in treatment of moderate and severe mental and emotional conditions (3). Another types of its derivatives have been reported as antiseptic, insecticides .In additional to the biological activities phenothiazine and its derivatives have found numerous application in other fields, complexes such as methylene blue are well-known as dyes, bacteriological stains, or redox indicators, to mention a few of their many applications. They have also been successfully employed as antioxidants in industrial applications (4). Finally more than 100 compounds are derived from the fundamental phenothiazine skeleton have been synthesized and pharmacologically tested in the past four decades (5). Therefore, the present work was directed toward synthesis of new derivatives of N-substituted phenothiazine derivatives, which expected to have possible biological activity.

## MATERIALS AND METHODS

Melting points were recorded using Gallen Kamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP3-300, and on (FT-IR) infrared spectrophotometer as KBr disc by AL- Nahrain University. Chemistry Dept. and by Baghdad Univ., College of Science, Chemistry Dept. Thin layer chromatography (T.L.C) was performed on aluminum sheets precoated with silica gel F254.The biological activity were performed by the genetic engineering and biotechnology for post graduate institute Baghdad university .

### General Experimental For The synthesis of New Compounds

### Experimental:

### 1.Stnthesis of Phenothiazine (1).(6)

A mixture of diphenylamine (1.69g, 0.01 mole) , sulfur (0.64g ,0.02mole) and 0.01gm of iodine was heated in a sand bath maintained at 250 -260 $^{o}$C for 6 hrs. The reaction mixture was cooled and dissolved in hot ethanol; the mixture was added to water. The formed yellow precipitate was filtered and recrystallized from ethanol m.p (181-182 $^{o}$C) yield 70% purity of phenothiazine was checked by T.L.C using chloroform: ethanol (8:2) as eluent .

### 2. Stnthesis of $N_{10}$ ( Chloro acetyl ) phenothiazine (2) .

To a solution of phenothiazine (5.8 g, 0.029 mole) in dry benzene 35 mL. containing triethyl amine (10 drops ) chloro acetyl chloride was gradually added with continuous stirring . The mixture was refluxed on water bath for 7hrs. T.L.C showed that the reaction was complete. The solvent was distilled, to give a residue which was washed with water to remove the acidic impurities .Then the solid was dissolved in hot ethanol, and was added to water, then the solid product was filtered. Finally the resulted solid was recrystallized from ethanol m.p. (111-113$^{o}$C) yield 62% .

**3. Stnthesis of $N_{10}$ ( Acetyl phenothiazine ) Hydrazine (3)(7)**

To a solution of (chloro acetyl) 10H phenothiazine (2,7 g, 0.01 mole) in ethanol (50 mL.) hydrazine hydrate (0.32g, 0.01 mole) was added and the resulting mixture was refluxed on water –bath for 5hrs. The formed precipitate was filtered and recrystallized from ethanol to give the hydrazine derivative (10) m.p. (170-173$^{o}$C) yield 73%.

**4. Stnthesis of $N_{10}$ ( Acetylphenothiazine ) Thiosemicarbazide (4)(8)**

To a solution of N10- acetyl phenothiazine hydrazine (0,281g, 0.001mole) in absolute ethanol (20 mL.) phenyl isothiocynate (0.135g , 0.001mole)was added with continuous stirring and the mixture was refluxed for 3- 4 hrs . The reaction mixture was cooled and the formed solid was recrystallized from benzene m.p. 160-162$^{O}$C yield 55%.

**5. Stnthesis of $N_{10}$ ( 4- phenyl – 1,2,4 triazine – 3 –thiol ) phenothiazine (5)(9)**

$N_{10}$ (acetyl phenothiazine) thiosemicarbazide (1g, 0,002 mole) was refluxed with 10% aqueous sodium hydroxide solution (25mL) for 3-4 hrs. the reaction mixture was filtered , cooled and neutralized by gradual addition with stirring of 10% acetic acid solution . The formed precipitate was filtered and recrystallized from ethanol , m.p. ( 215-217 $^{o}$C) yield 52%.

**6. Stnthesis of $N_{10}$(4–phenyl-1,2,5, triazine-3 alkyl thioether phenothiazine(6–9)(10)**

To a stirred solution of $N_{10}$ ( 4- phenyl-1,2,4, -triazine - 3 - thiol ) phenothiazine (0.388g , 0 . 001 mole ) in absolute ethanol ( 5 m L. ) was added during 20 min KOH( 0,056gm) with stirring , then (0.001 mole) of chloropropane / chlorobutane / Bromopentane / benzoylchloride was added drop wise and the reaction mixture was refluxed for 4hrs. T.L.C. (benzene: methanol 9:1) showed that the reaction was complete. The reaction mixture was filtered, cooled and filtrates were poured on to cold water then the resulting aqueous layer was extracted with chloroform (3 ×10 ml.). The combined chloroform layer was evaporated to give the desired compound. See table (1)

**7. Stnthesis of $N_{10}$( Acetyl phenothiazine) semicarbazid (10)**

Compound (10) was synthesis by the same method described for the synthesized of thiosemicarbazide using phenyl isocynate (1ml) . m.p (200- 202$^{o}$C) yield 55%

**8. Stnthesis of $N_{10}$ ( 4- phenyl -1,2,4,triazine- 3-ol ) phenothiozine (11)**

Using the same method which was described for the synthesized of 4 - phenyl -1,2,4, triazine-3- thiol phenothiazine, the derivative 3- hydroxy triazine was obtained m. p. (212- 214$^{o}$C) yield 46%.

**9. Stnthesis of $N_{10}$( 4- phenyl -alkyl -1,2,4- triazine –3-on) phenothiazine (12-15).**

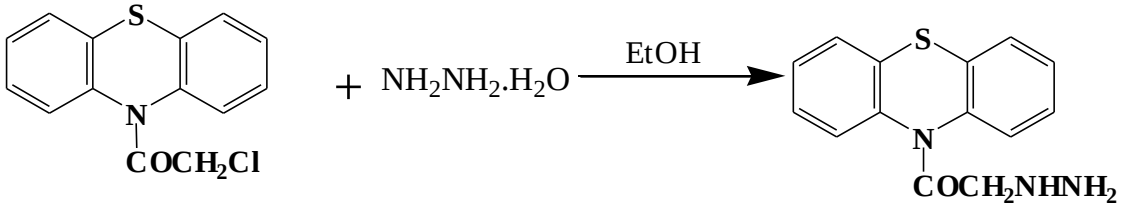
Using the same method for the preparation of $N_{10}$ (4–phenyl 1,2,4- triazine – 3–alkyl thioether) phenothiazine using compound (11) with alkyl halide see table (4).

## RESULTS AND DISCUSSION

**N-substituted phenothiazine:**

Literature survey showed that N-substituted phenothiazine is associated with range of biological and pharmacological properties.

chloro acetyl chloride in dry benzene was refluxed with 10H-phenothiazine it gave the corresponding $N_{10}$-chloro acetyl phenothiazine (2), IR spectrum showed strong stretching bands at 1690 and 1670cm$^{-1}$ due to (C=O) .To prepare heterocyclic compound (triazine), the hydrazine (3) was seen suitable chosen for this synthetic approach. When the $N_{10}$-chloro acetyl phenothiazine was refluxed with 98% hydrazine hydrate, it gave the expected hydrazine (3)

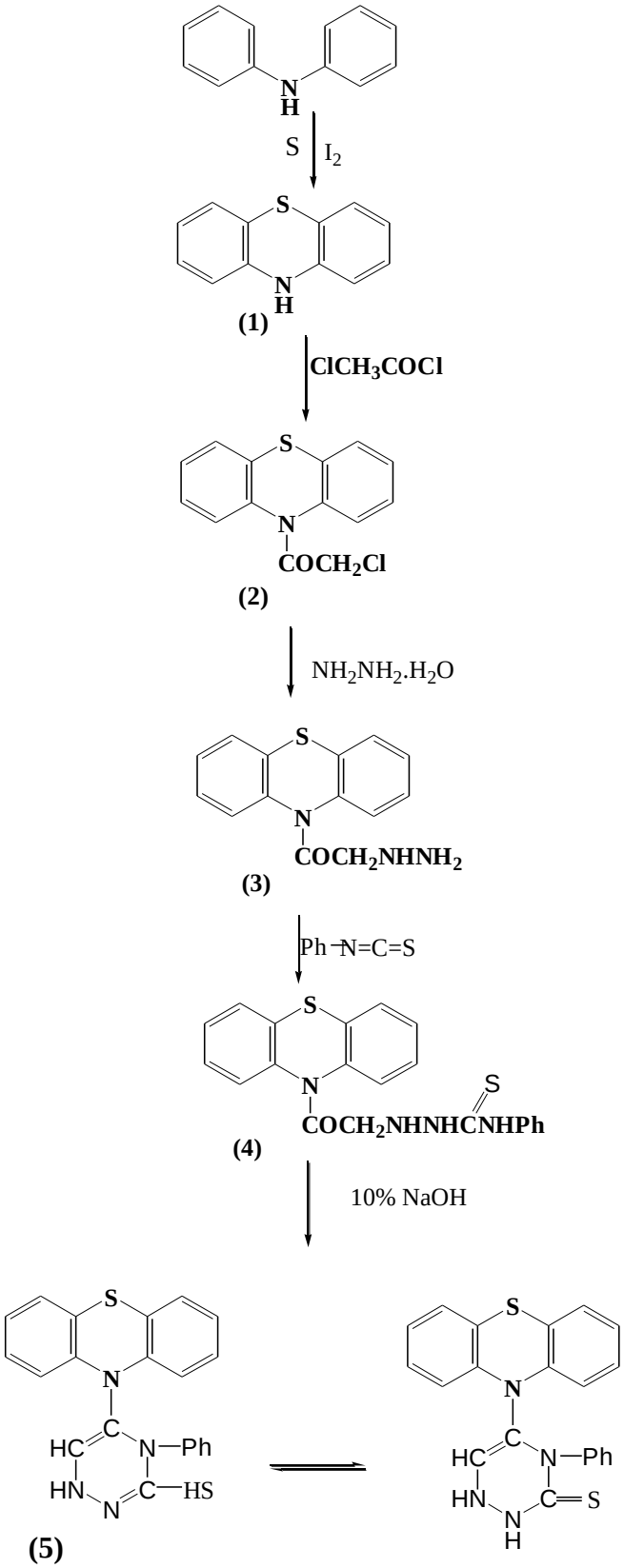



**(2)** **(3)**

Structure of compound (3) was confirmed by IR spectroscopy. IR spectrum showed a split broad at 3336 and 3200 cm$^{-1}$ which was assigned to the asymmetric and symmetric stretching bands of $NH_2$ and NH groups, and anther band at 1670 cm$^{-1}$ due to (C=O). The IR spectrum also showed a characteristics aromatic band at 3057cm$^{-1}$(C-H) , 1600 cm$^{-1}$ (C=C)aromatic and two bands at 1590-1560 cm$^{-1}$ characteristics of the phenothiazine nuclues .

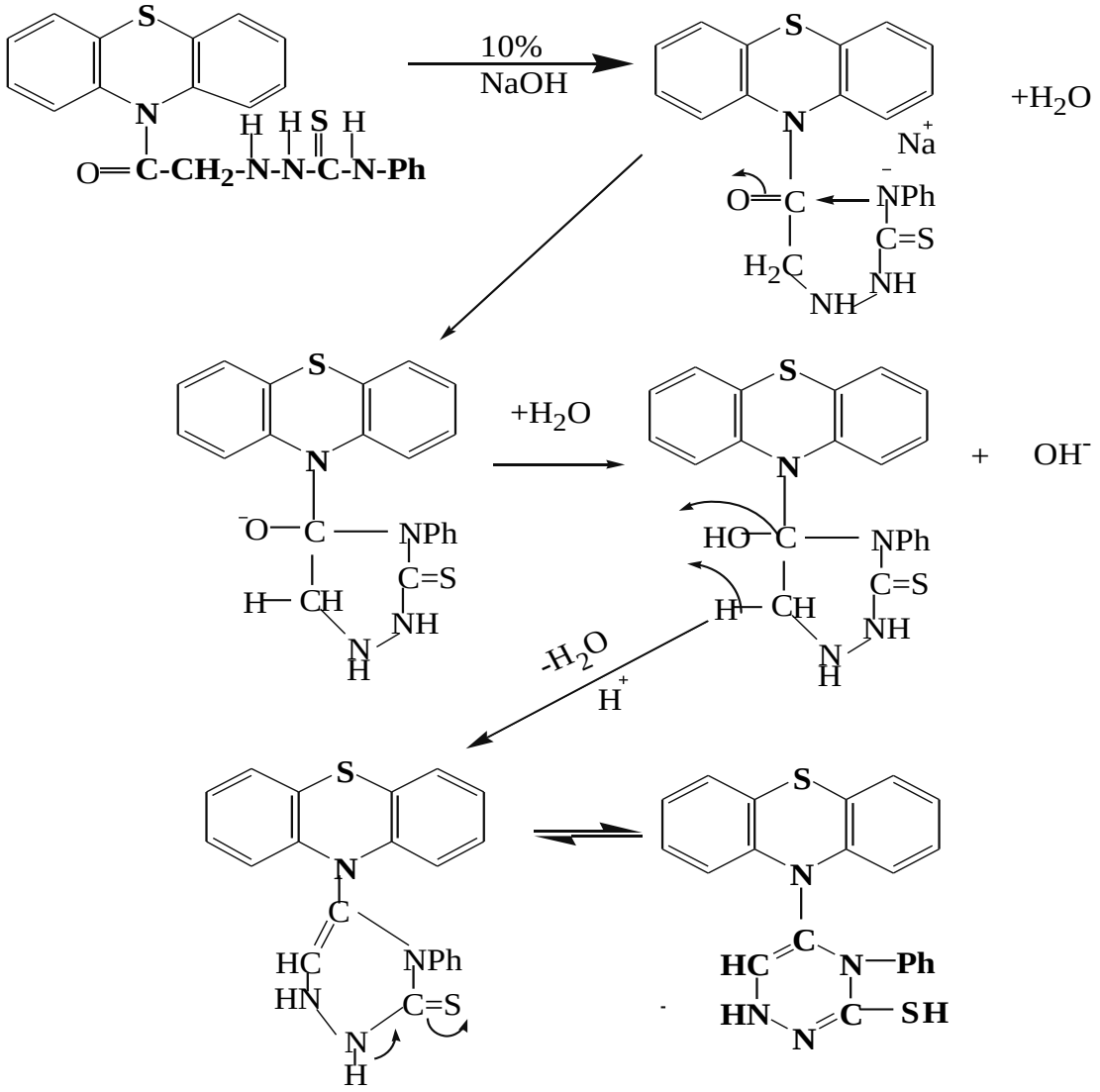
Refluxing of hydrazide (3) with phenyl isothiocynate in ethanol gave the thiosemicarbazide (4). IR spectrum showed stretching band at 3211 cm$^{-1}$ due to (NH) and 3111 cm$^{-1}$ (amide NH group), 1630 cm$^{-1}$ for (C=O) , 1600 cm$^{-1}$ for (C=C) aromatic. IR spectrum also showed absorption bands at 1546(C=N), 1250 cm$^{-1}$ (C=S) and 1506cm$^{-1}$ corresponding to thioamide II and I for ( $-\overset{S}{\overset{\parallel}{C}}-NH-$ ) .

The titled compound (5) was synthesized according to reaction scheme (1).


S
I2
(1)
ClCH3COCl
COCH2Cl
(2)
NH2NH2.H2O
COCH2NHNH2
(3)
Ph–N=C=S
COCH2NHNHCNHPh
(4)
10% NaOH
(5)

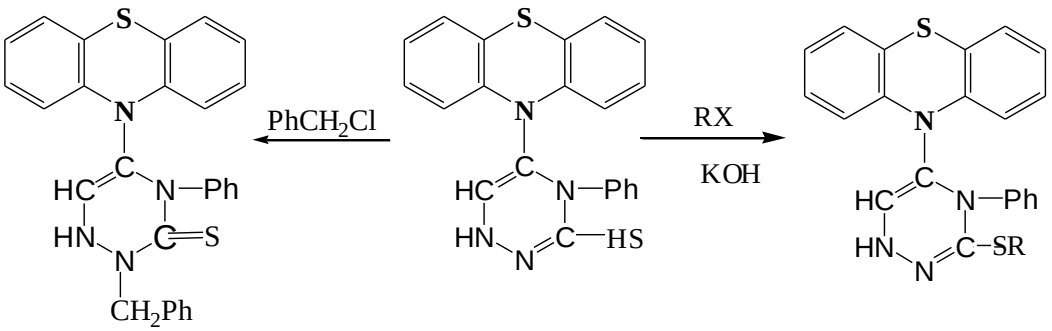
**Scheme 1**

The reaction of thiosemicarbazide (4) with 10% NaOH under refluxing condition affected intramolecular cyclization through the loss of $H_2O$ giving the desired thio-triazine derivative (5), the formation of (5) may be visualized by the following mechanism:-




Structure of thiotriazine derivative (5) was confirmed by IR. IR spectrum showed bands at 3301 $cm^{-1,}$and 3132 $cm^{-1}$ (NH) and 1606$cm^{-1}$ (C=N) also at 1323$cm^{-1}$ (C=S) and at 1450 $cm^{-1}$ corresponding to thioamide I and II **(** $-\overset{\overset{S}{\|}}{C}-NH-$ **).**

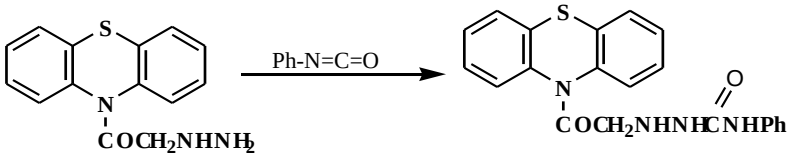
The refluxing of thiotriazine derivative**(5)** with alkyl halides in the presence of KOH in ethanol gave thioalkyl**(6-9)**the alkyl halides were used chloropropane, chloro butane ,bromo pentane ,benzyl chloride. Compounds (6-9) were obtained respectively according to the steps out lined in scheme (1). Alkylation of thiotriazine (5) under basic condition using different alkyl halides gave the thio ether derivatives (6-8) and N-benzyl derivative (9).




**(9)** **(5)** **(6-8)**

The thio-ether derivatives (6-8) showed the same IR spectral features .The only difference from compound (5) was the disappearance (NH) and(C=S) at (3301cm$^{-1}$ and1323 cm$^{-1}$) respectively with appearance of 1400cm$^{-1}$ for the Alkyl derivative (6-8) also appearance (C-H) aliphatic at 2900-2990 cm$^{-1}$,and ~1600 cm$^{-1}$ for (C=N) see table3 , and appearance (C-H) aromatic at 3050 cm.$^{-1}$

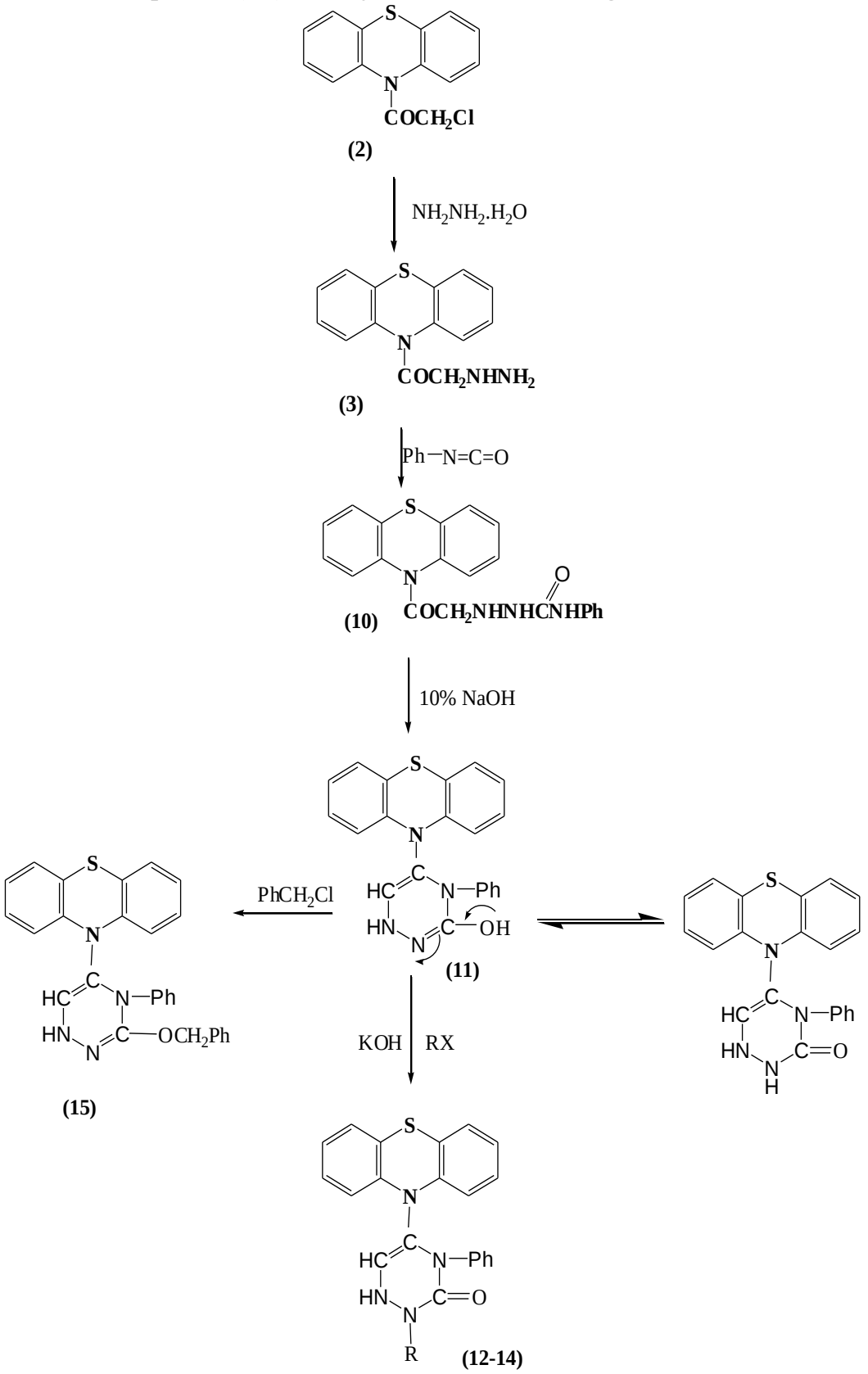
Refluxing of hydrazide (3) with phenyl isocynate in ethanol gave the semicarbazide derivative (10).




**(3)** **(10)**

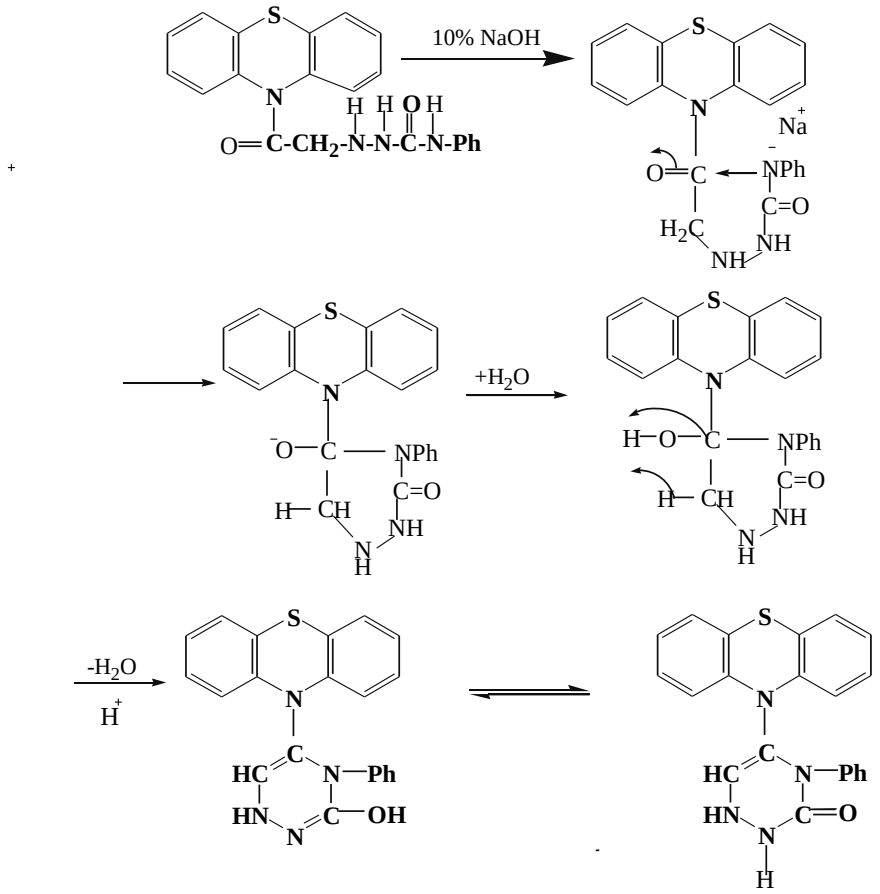
This compound was characterized by IR spectral data. IR spectrum showed stretching bands at 3290 and 3210 cm$^{-1}$ (amide NH) groups.Abroad band at 1670 cm$^{-1}$ was appeared and other band at 1620 cm$^{-1}$ which were attributed to amide I and amide II bands. The IR spectrum also showed characteristic aromatic band at 3020 cm$^{-1}$ and1600 cm$^{-1}$ (C=C).

The titled compound (11) was synthesized according to reaction scheme[2]




**Scheme 2**

The reaction of semicarbazide (10) with 10% NaOH under refluxing condition effected intramoleculare cyclization through the loss of $H_2O$ giving the desired hydroxyl-triazine derivatives. The formation of (11) may be visualized by the following mechanism.




The structure of hydroxytriazine derivative (11) was confirmed by IR spectra.

IR spectrum showed stretching bands at 3288 $cm^{-1}$(N-H). A broad band at 3436 $cm^{-1}$ for (O-H) band and other bands at 1645 and 1700 $cm^{-1}$ which were, attributed to amide I and amide II bands and 1566$cm^{-1}$ (C=N)

Alkylation of hydroxyl triazine(11)with different alkyl halides under basic condition gave two different alkylated products (12-15)and the hydroxyl triazine (11) is considered as nucleophile under $SN^2$ mechanism, the alkyl halides(propane chloride, butane chloride ,pentane bromide )are attacked by the better nucleophile ,i.e.nitrogen atom to give the N-alkyl derivative while under $SN^1$ mechanism benzyl chloride is attacked by the more electronegative atom, i.e., oxygen to give ether derivative (15) .The N-alkyl derivative (15) showed the same general IR spectral features figs. the only difference from(11)was disappearance of (C=O) band.

Table -1: Physical properties of compounds (2-9)

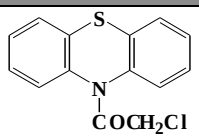
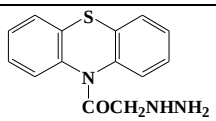
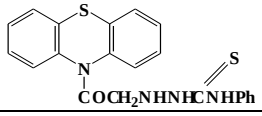
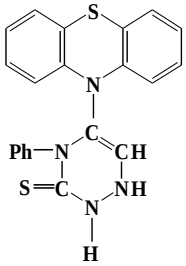
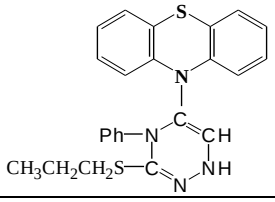
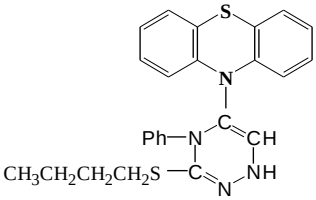
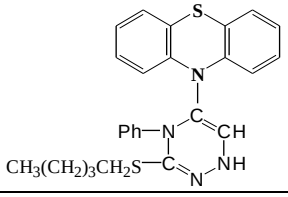
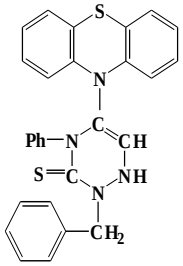
| Compd. No. | Structure | Chemical formula MWt | M. P.C$^{o}$ | % Yield | Colour of Cryst. |
|---|---|---|---|---|---|
| 2 |  | $C_{14}H_{10}N$ SOCl (275) | 111-113 | 62 | White |
| 3 |  | $C_{14}H_{13}N_3$ SO (271) | 170-173 | 73 | yellow |
| 4 |  | $C_{21}H_{18}N_4$ S $_2$O (406) | 160 | 55 | yellow |
| 5 |  | $C_{21}H_{16}N_4S_2$ (388) | 215-217 | 52 | White |
| 6 |  | $C_{24}H_{22}N_4S_2$ (430) | 186-188 | 75.3 | White |
| 7 |  | $C_{25}H_{24}N_4S_2$ (444) | 168-170 | 73 | White |
| 8 |  | $C_{26}H_{26}N_4S_2$ (458) | 118-120 | 73 | White |
| 9 |  | $C_{28}H_{22}N_4S_2$ (478) | 113 | 65 | Gray |

Table - 2: Infrared data of compounds (2-5)

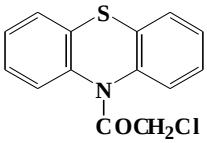
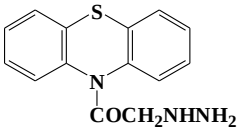
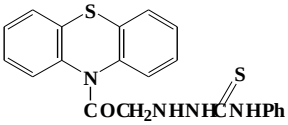
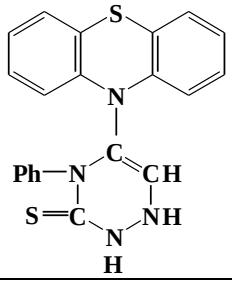
| Compd .No. | Structure | υ N-H $cm^{-1}$ | υ C-H Aromatic | υ C-H Aliphatic | υ C=O $cm^{-1}$ | υ C=N $cm^{-1}$ | υ C=C aromatic | Other band $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| 2 |  | - | 3060 W | 2950 W | 1690 VS 1970 VS | - | 1580 M | C-Cl 610 |
| 3 |  | 3336 M 3200 VW | 3057 VS | 2900 VW | 1670 S | - | 1600 M | - |
| 4 |  | 3211 3111 M | 3050 W | 2939 M | 1600 M | 1546 S | 1506 S | σ C=S1190 σ C—NH 1506 S-H 2588 |
| 5 |  | 3301 M 3132 M | 3020 VW | 2927 VW | - | 1606 S | 1544 S | σ c=s 1323 S σ C—NH 1450 S |

Table -3: Infrared data of compounds (6-9) (continued)

| Compd. No. | Alkyl halid | υ N-H $cm^{-1}$ | υ C-H Aromatic | υ C-H Aliphatic | υ C=N $cm^{-1}$ | υ C=C Aromatic | υ C=S $cm^{-1}$ | Other band $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| 6 | Chloropropane | 3210 W | 3060W | 2990W | 1630 S | 1610 S | - | - |
| 7 | Chlorobutane | 3182 M | 3037M | 2923 M | 1604 S | 1556 VS | - | - |
| 8 | Bromopentane | 3200 W | 3050 W | 2920 W | 1600 S | 1550 S | - | - |
| 9 | benzylchloride | 3200 M | 3050 M | 2900 W | 1602 S | 1500 VS | 1321 | - |

Table-4: Physical properties of compounds (10-15)

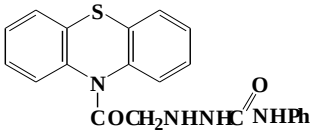
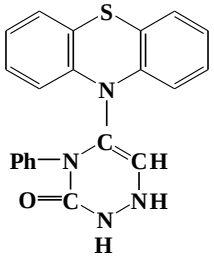
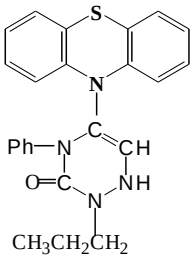
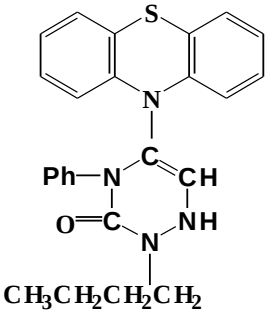
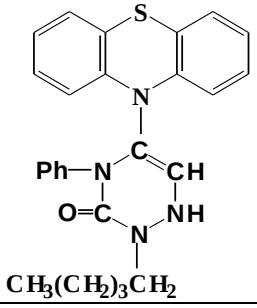
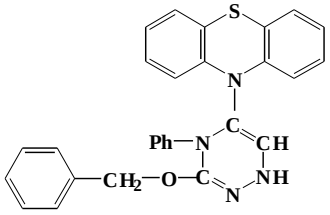
| Compd. No. | Structure | Chemical formula MWt | M. P.C$^{o}$ | % Yield | Colour of Cryst. |
|---|---|---|---|---|---|
| 10 |  | $C_{21}H_{18}N_4SO_2$ (446) | 200-202 | 55 | White |
| 11 |  | $C_{21}H_{16}N_4SO$ (372) | 212-214 | 46 | Gray |
| 12 |  | $C_{24}H_{22}N_4SO$ (414) | 190 | 31 | Beach |
| 13 |  | $C_{25}H_{24}N_4SO$ (428) | 195-197 | 30 | Beach |
| 14 |  | $C_{26}H_{26}N_4SO$ (442) | 203 | 29 | Beach |
| 15 |  | $C_{28}H_{22}N_4SO$ (462) | 183-185 | 20 | Beach |

Table -5: Infrared data of compounds (10-11)

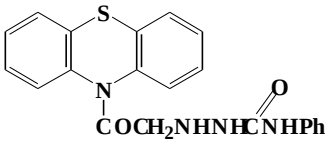
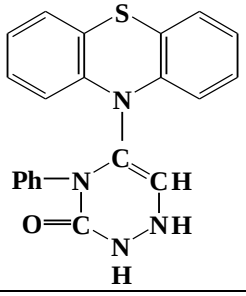
| Comp. No. | Structure | υ N-H $cm^{-1}$ | υ C-H Aromatic | υ C-H Aliphatic | υ C=O $cm^{-1}$ | υ C=N $cm^{-1}$ | υ C=C $cm^{-1}$ | Other bands $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| 10 |  | 3290 3210 | 3020 W | 2920 W | 1670 | 1610 | 1600 | Amid II 1650 Amid II 1600 |
| 11 |  | 3436 W | 3070 W | 2990 W | 1645 S | 1566 S | 1675 S | Broad O-H 3436 |

Table -6: Infrared data of compounds (12-15)

| Comp. No. | RX | υ N-H $cm^{-1}$ | υ C-H Aromatic | υ C-H Aliphatic | υ C=O | υ C=N $cm^{-1}$ | υ C=C $cm^{-1}$ | Other bands $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| 12 | chloropropane | 3436 M | 3010 W | 2870 W | 1700 M | 1571S | 1519M | σ C-N 1020 ,1070 σ N-$CH_2$ 2860 |
| 13 | chlorobutane | 3450 M | 3100VW | 2950 VS | 1703 S | 1610 M | 1600 M | σ C-N 1028, 1095 σ N-$CH_2$ 2852 |
| 14 | bromopentane | 3400 M | 3005 W | 2920 M | 1710 | 1650 | 1580 | σ C-N 1020, 1085 |
| 15 | benzylchloride | 3450 M | 3050 | 2923 | - | 1664 | 1590 | σ C-N 1026, 1100 σ N-$CH_2$ 2854 |

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