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# Synthesis of New N-Substituted Phenoxazine Derivatives

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## Abstract

This work comprises the synthesis of new phenoxazine derivatives containing N-substituted phenoxazine starting from phenoxazine (1). Synthesis of ethyl acetate phenoxazine (2) through the reaction of phenoxazine with ethylchloroacetate, which reacted with hydrazine hydrate to give 10-aceto hydrazide phenoxazine (3), then reacted with formic acid to give 10-[N-formyl acetohydrazide] phenoxazine (4). Reaction of compound (4) with phosphorous pentaoxide or phosphorus pentasulphide to gave 10-[N-methylene-1,3,4-oxadiazole] phenoxazine (5) and 10-[N-methylene-1,3,4-thiadiazole] phenoxazine (6).

**Key words:** phenoxazine, ethyl acetate phenoxazine, 10-aceto hydrazide phenoxazine.

## Introduction:

Heterocyclic compounds are cyclic compounds in which the ring atoms are of carbon and some other elements containing nitrogen, oxygen and sulfur, the most common other atoms such as boron, phosphorus or silicon compound also be members of heterocyclic ring. Some nonaromatic heterocyclic and some aromatic heterocyclic [1-4]. In 1887, the phenoxazine was made by Bernth [5] and though known for many years has not had a systematic study made of its chemistry. And till the last decade, little was known about the metabolism of phenoxazine in biological systems [6]. The heterocyclic oxygen atom of the phenoxazine nucleus places certain restriction on the aromaticity of this ring system, which appears to be somewhat less aromatic than the phenothiazine system for instance. The aromatic model shows that the phenoxazine nucleus is slightly folded along its short axis i.e., the axis passing through the two central hetero atoms. The dipole moment of phenoxazine which was found to be 1.93 D (benzene) [7] is also consistent with the non planarity of molecule. Phenoxazine nucleus is highly non-planer, i.e., folded along the axis passing through the two heteroatoms [8,9].

## Materials and Methods:

UV spectra were recorded on UV-visible spectrophotometer (SHIMADZU) UV-160 A. FT-IR spectra were recorded on (SHIMADZU)

FT-IR 8400 S spectrophotometer; solid samples were run as smears. Melting points were recorded using a (Gallen kamp) melting point apparatus with sample contained in open capillary glass tube in an electrically heated metal block apparatus. $^1$H-NMR spectra were recorded on Ultra Sheild 300 $MH_z$ with tetramethyl silane as internal standard and DMSO and methanol as solvents. Thin Layer chromatography (T.L.C.) were performed on pre-coated sheet with 0.25 mm Layer of silica-gel F 254. Spots were detected with iodine vapour.

### General Procedure for Synthesis of Phenoxazine and its Derivatives:

### Phenoxazine (1):

A mixture of (2g) $ZnCl_2$, (109g, 1mol) of o-aminophenol and 5 ml conc. $H_3PO_4$ was heated in a sand bath at 270-275 $^0$C for 4 hours. The reaction mixture was cooled and extracted with cyclohexane in soxhlet extraction apparatus, the solvent was removed and the formed colorless needles crystallized from ethanol m.p. 152-154 $^o$C, yield (54g,50%) IR: 3405 $cm^{-1}$ (N-H) str.

## Ethyl Acetate Phenoxazine (2):

A mixture of phenoxazine (1), (5g, 0.027 mol), ethylchloroacetate (3.5ml, 0.027 mol) in dry acetone (5 ml) and anhydrous $K_2CO_3$ (0.5 g) was refluxed for 24 hours, then cooled, filtered and solvent removed under reduced pressure. The resulting solid was monitored by (T.L.C) using ($CCl_4$:EtOH) (3:1) as eluent and recrystallized from ethanol, m.p (148 $^o$C), (1.3g, yield 34%).

## 10-aceto Hydrazide Phenoxazine (3):

A solutione of compounde (2) (2.5g, 0.009 mol) in ethanol (50 ml), hydrazine hydrate (0.5ml, 0.009 mol) was added and the reaction mixture was refluxed on a water bath for 2-3 hours. Reaction and purity of the final product was checked by (T.L.C) using ($CCl_4$:EtOH) (3:1) as eluent and recrystallized from ethanol, m.p (140 $^0$C), (1g, yield 81%).

## 10-[N-formylacetohydrazide] Phenoxazine (4):

A solution of compound (3) (2.87 g, 0.01 mol) in formic acid (20 ml) was refluxed for 20 minutes. The solvent was evaporated and the residue was recrystallized from methanol. The product was checked by (T.L.C) using ($CCl_4$: EtOH) (3:1) as eluent, m.p (124$^0$C), (0.4 g, 36%).

## 10-[N-methylene-1,3,4-Oxadiazole]Phenoxazine (5):

A solution of compound (4) (1 g, 0.001 mol) in o-xylene (50 ml), phosphorous pentaoxide (0.5 g) was added. The mixture refluxed for 1 hour. The solvent was evaporated, then water (10 ml) was added, and the mixture was extracted with chloroform. The solvent was evaporated and the residue was checked by (T.L.C) using ($CCl_4$ : EtOH) (3:1) as eluent and recrystallized from benzene or ethyl acetate, m.p. (116 $^0$C), yield (0.1 g, 71%).

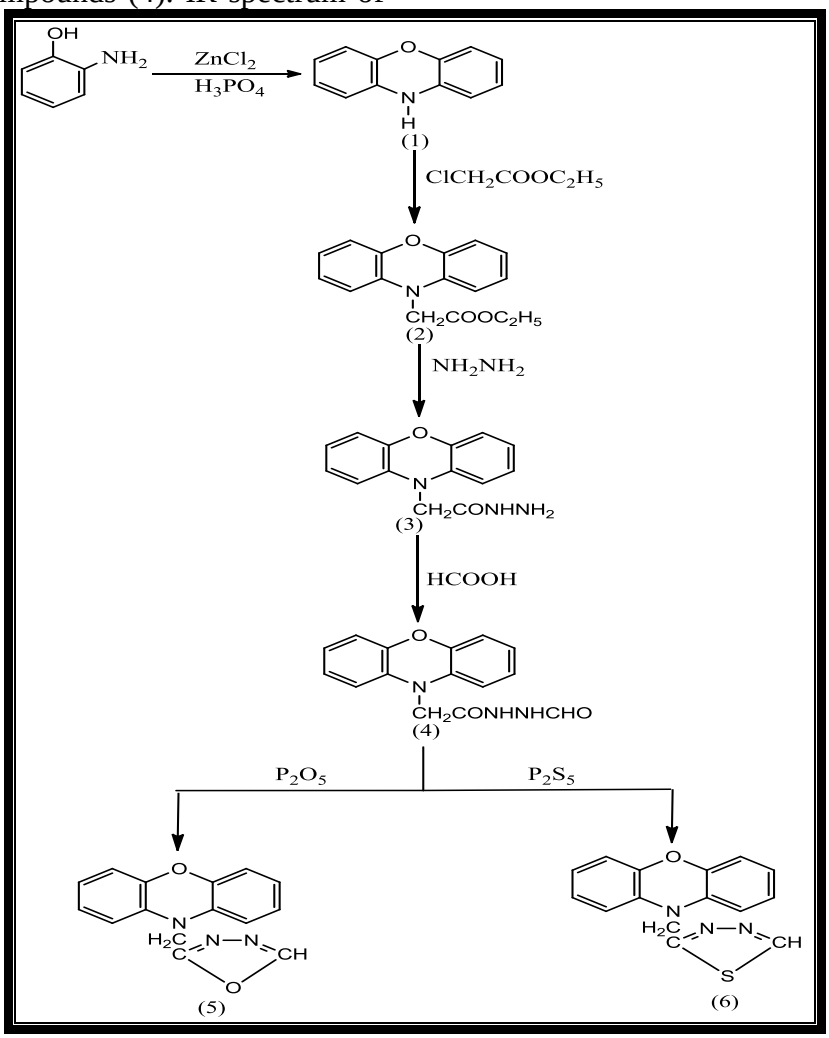
## 10-[N-methylene-1,3,4-thiadiazole]Phenoxazine (6):

Compound (6) was prepared by the same method described for the preparation of compound (5), using phosphorus pentasulphide, m.p. (142$^0$C), yield (0.1 g, 50%).

## Results and Discussion:

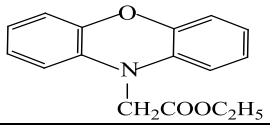
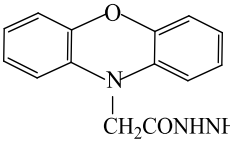
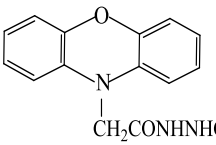
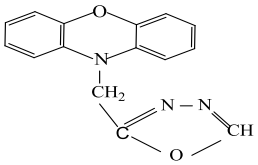
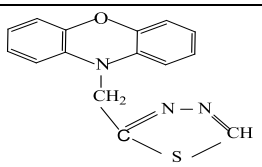
Phenoxazine was prepared by the reaction of o-aminophenol with zinc chloride in presence of phosphoric acid as showed in Scheme (1). Phenoxazine (1) showed strong stretching band at 3342 $cm^{-1}$ (N-H), strong stretching bands at 1570 $cm^{-1}$ and 1596 $cm^{-1}$ assigned to phenoxazine ring.The $^1$H-NMR spectrum [10] showed signal at δ

(6.7-7) ppm signals to aromatic protons and signal at δ (8.2) ppm a ssignal to (N-H) shown in Figure (1). The phenoxazine (1) was then converted to ethyl acetate phenoxazine (2) using ethylchloroacetate. IR spectrum of compound (2) showed the disappearance of (N-H) band at 3342 $cm^{-1}$ and showed a stretching band at 1629 $cm^{-1}$ (C=O). The IR spectrum also showed a band at 3090 $cm^{-1}$ (C-H) aromatic, at 2977 $cm^{-1}$ (C-H) aliphatic and 1585 $cm^{-1}$ (C=C). Compound (2) reacted with hydrazine hydrate to gave compound (3). The IR spectra of compounds (3) showed strong stretching band at 3397 $cm^{-1}$ (N-H), at 1640 $cm^{-1}$(C=O)str. and 1595 $cm^{-1}$ (C=C) as showed in Table (1). Compound (3) reacted with formic acid to gave compounds (4). IR spectrum of compounds (4) showed absorption band at 3406 $cm^{-1}$ (N-H), 1695 $cm^{-1}$ (C=O) str, 1583 $cm^{-1}$ (C=C) str. and $^1$HNMR spectra Figure (2) for compound (4) showed signal at (⇦ 6-6.5) ppm belong to (N-H) proton for amide, singal at ⇦ (2-2.5) ppm belong to ($CH_2$), singal at ⇦ (8.9-9.1) ppm belong to (CH) and signals at ⇦ (7.3-8) ppm belong to aromatic protons [11]. Compound (4) reacted with phosphorous pentaoxide or phosphorus pentasulphide to gave compound (5) and (6). IR spectrum of compounds (5) showed absorption strong bands at 1620 $cm^{-1}$ (C=N) str, 1585 $cm^{-1}$ (C=C) str., IR spectrum of compounds (6) showed absorption strong bands at 1627 $cm^{-1}$ (C=N) str, 1585 $cm^{-1}$ (C=C) str.




**Scheme (1) Synthetic path way for preparation of new Hetrocyclic compounds.**

## Table (1): Infrared spectral data of compounds (2-6)

| Compd. No. | Structure | υ C-H Aromatic | υ C-H Aliphatic | υ C=C $cm^{-1}$ | υ C=O $cm^{-1}$ | υ C=N $cm^{-1}$ | Other bands $cm^{-1}$ |
|---|---|---|---|---|---|---|---|
| 2 |  | 3090 w | 2977 w | 1585 s | 1629 s | - | - |
| 3 |  | 3085 m | 2923 w | 1595 s | 1640 s | - | N-H 3397 |
| 4 |  | 3080 m | 2991 w | 1583 s | 1695 s | - | N-H 3406 |
| 5 |  | 3041 m | 2885 m | 1585 s | - | 1620 s | C-O-C 1147 |
| 6 |  | 3030 m | 2923 m | 1585 s | - | 1627 s | C-S 712 |

## Table (2): physical properties of compounds (2-6)

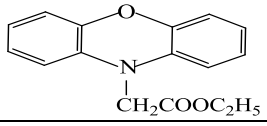
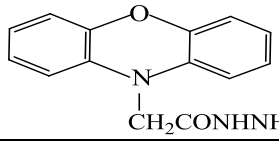
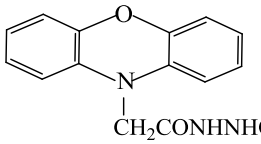
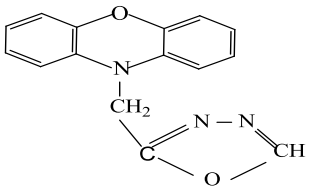
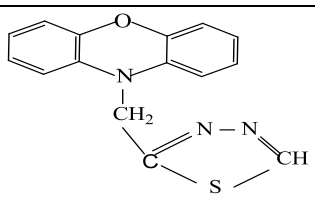
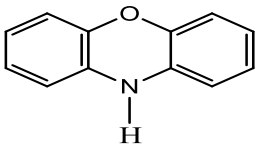
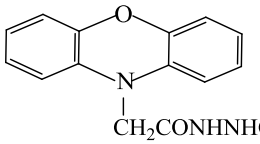
| Comp. No. | Structure | M.P. $^oC$ | %Yield | Color of crystal | Solvent |
|---|---|---|---|---|---|
| 2 |  | 148 | 34 | Yellowsh green | Ethanol |
| 3 |  | 140 | 81 | Off-White | Ethanol |
| 4 |  | 124 | 36 | Light Brown | methanol |
| 5 |  | 116 | 71 | Black | Ethylacetate |
| 6 |  | 142 | 50 | Black | Benzene |

**Table (3): $^1$H-NMR spectral data for compounds (1,4)**

| Comp. No. | Compound structure | δH aromatic ppm | δH other bands ppm |
|---|---|---|---|
| 2 |  | m(δ=6.7-7) | s(δ=8.2) (N-H) |
| 3 |  | m( δ=7.3-8 ) | s(δ=2-2.5) ($CH_2$), s( δ=6-6.5) ( N-H ), s(δ=8.9-9.1) (CH) |

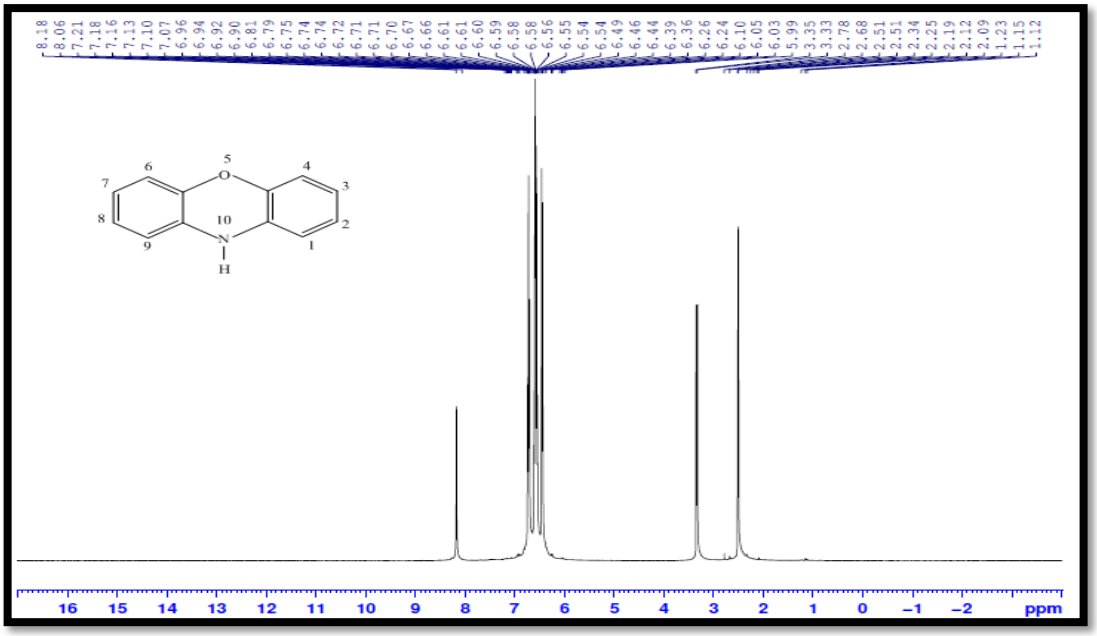


**Fig. (1): $^1$H-NMR spectrum of compound (1)**

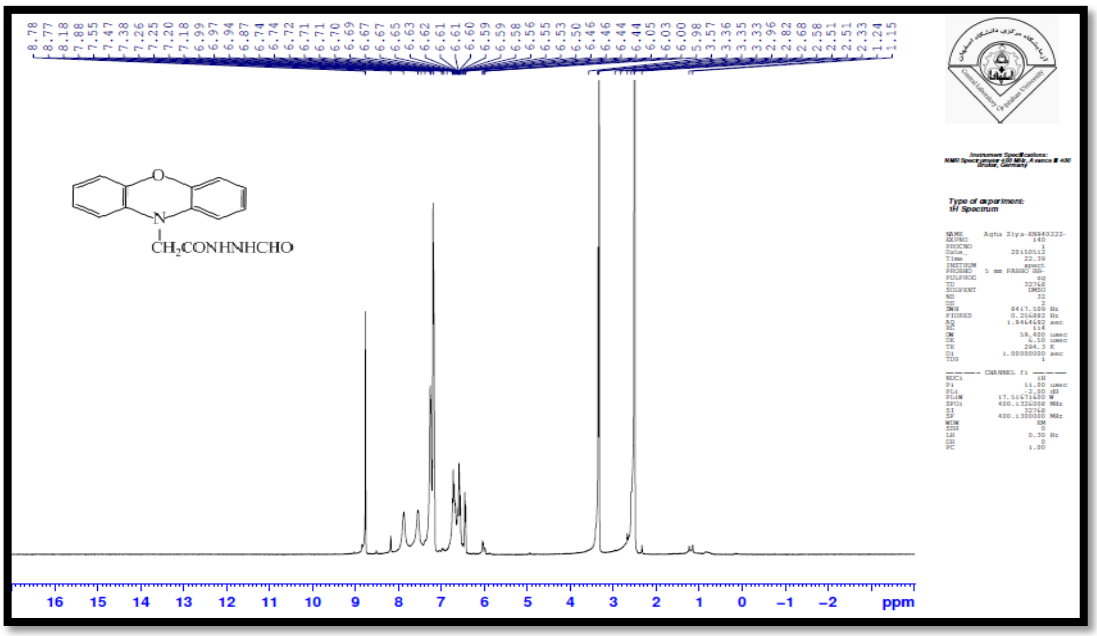


**Fig. (2): $^1$H-NMR spectrum for compound [4]**

## Conclusion:

Phenoxazine derivatives are an important type of nitrogen and oxygen containing heterocyclic compounds which have attracted considersion of medicinal chemist due to antimicrobial activites for this purpose new phenoxazine derivatives were synthesized. More than 5 derivatives were prepared and characterized by spectroscopic methods namely FT-IR and some of them with $^1$H-NMR.

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# تحضير مشتقات جديدة للفينوكسازين معوضة على ذرة النتروجين

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**الخلاصة :**

يتضمن البحث تحضير مشتقات جديدة من الفينوكسازين معوضة على ذرة النتروجين بدءا من الفينوكسازين (1). تحضير اثيل استيت فينوكسازين (2) بمفاعلة الفينوكسازين مع اثيل كلورو استيت ليعطي المركب (2)، الذي بدوره تفاعل مع الهيدرازين المائي ليعطي 10-اسيتو هيدرازايد فينوكسازين (3)، الذي تفاعل مع حامض الفورميك ليعطي 10-N-فورميل اسيتو هيدرازايد (4). وبتفاعل المركب (4) مع خماسي اوكسيد الفسفور او خماسي كبريتيد الفسفور اعطى 10-N- مثلين-1 ،3 ،4-اوكسادايازول فينوكسازين (5) و 10-N- مثلين-1 ،3 ،4-ثاياديازول فينوكسازين (6).

**الكلمات المفتاحية:** فينوكسازين، أثيل استيت فينوكسازين، 10-أسيتو هيدرازايد فينوكسازين.