

Synthesis of New 10-Amido phenoxazine Derivatives

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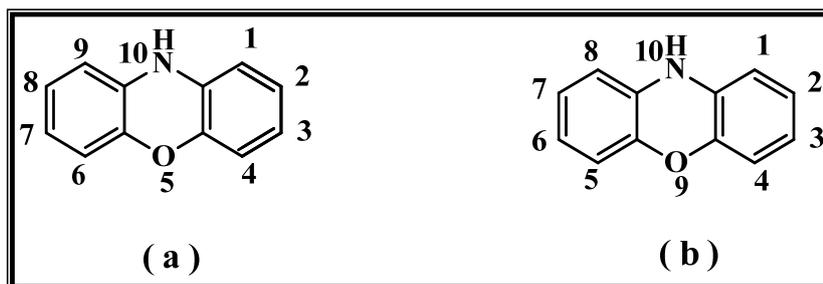
Abstract

This work includes synthesis of new phenoxazine derivatives containing N-substituted phenoxazine starting from phenoxazine (1).10-nitrosyl phenoxazine was prepared through the reaction of phenoxazine with sodium nitrite to give compound (2), which reacted with zinc in acetic acid to give 10-amino phenoxazine (3). Condensation of compound (3) with benzoyl chloride, isovaleryl chloride and 4-bromophenacyl chloride gave 10-amido phenoxazine derivatives (4-6).

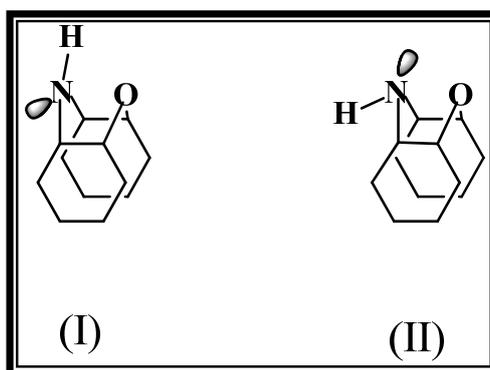
Keyword: phenoxazine, ethyl acetate phenoxazine, 10-aceto hydrazide phenoxazine.

Introduction

Heterocyclic compounds are cyclic compound in which the ring atoms consist of carbon and some other elements like nitrogen, oxygen or sulfur are by the most common other atom such as boron, phosphorus or silicon compounds also be members of heterocyclic ring[1-4]. In 1887 the phenoxazine was made by Bernth [5] and though known for many years it doesn't have a systematic study made of its chemistry. And till the last decade, a little was known about the metabolism of phenoxazine in biological systems [6]. The nomenclature and numbering of phenoxazine nucleus. At present only two systems (a) and (b) are widely used



The numbering system (a) has been adopted as being the most frequent and also approved in the "Revised Ring Index" (no.3290), used in chemical abstract and recommended by the IUPAC rules of organic nomenclature[7]. 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) [8] 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 [9,10]. Now the proton or the substituent at the nitrogen atom may be placed either between or out of the planes of the two lateral ring. Thus two geometrical configurations can be predicted for the phenoxazine ring, which on analogy to phenothiazine may be called *H-extra* (I) and *H-antra* (II) configuration.



Oxazine derivative have been reported to possess [11] antifungal, antibacterial, anticonvulsant, antiviral, analgesic, anticancer, anti inflammatory [12], antimalarial [13], antimicrobial [14]. Oxazine derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are used extensively in organic

synthesis due to the rapid development of bacterial agent to help in the battle against pathogenic.

Aim of the work

N-substituted phenoxazine have been reported to be biologically and industrially versatile compounds. Biologically, they are used in many drugs as antiviral, antibacterial, anticancer and fungicidal agents. In industry, most of phenoxazine dyes are derived from benzo phenoxazine e.g., Meldola blue or from more complex ring system containing the phenoxazine residue. The present work was directed toward the synthesis of new N-substituted phenoxazine derivatives expected to possess possible biological activity.

Material and Methods

FT-IR spectra were recorded on (SHIMADZU) FT-IR 8400 S spectrophotometer; solid samples were run in KBr disc, liquid were run as smears. UV spectra were recorded on UV-visible spectrophotometer (SHIMADZU) UV-160 A. $^1\text{H-NMR}$ spectra were recorded on Ultra Shield 300 MHz with tetramethyl silane as internal standard. Melting points were determined in a (Gallen kamp) melting point apparatus with sample contained in open capillary glass tube in an electrically heated metal block apparatus. Thin Layer chromatography (TLC) were performed on pre-coated plastic 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) [15]

A mixture of (109g, 1mol) of o-aminophenol, (2g, 0.018 mol) ZnCl_2 and 5 ml conc. H_3PO_4 was heated in a sand bath maintained at 270-275 $^\circ\text{C}$ for 4 hrs. 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 $^\circ\text{C}$, yield (54g,50%) IR: 3405 cm^{-1} (N-H) str.

10-nitroso-10H-phenoxazine (2) [16]

A mixture of phenoxazine (10g, 0.05 mole) and sodium nitrite (4.2 g) in (150 mL) of ethanol was refluxed for 2 hrs., after cooling (12mL) of concentrated HCl drop-wise was added. The brown precipitate obtained was filtered, dried and recrystallized from ethyl acetate. m.p. (172 $^\circ\text{C}$), yield (3.5g,56 %).

10-amino phenoxazine (3) [16]

A mixture of 10-nitrosylphenoxazine (9.0 g, 0.05mole) and zinc powder (5.0 g) in (25mL) acetic acid was stirred for 2 hrs., at 0 $^\circ\text{C}$. The filtered was poured on to about (500mL) of water. The brown precipitate obtained was filtrated, dried, recrystallized from ethanol. m.p. (190 $^\circ\text{C}$), yield(2g, 62 %).

10-Benzamido phenoxazine (4)

A mixture of 10-aminophenoxazine (0.5g,0.0027 mole) and (0.1mL) of benzoyl chloride with (0.2mL) of triethylamine in (10mL) of THF was stirred for (2hrs.) at room temperature. The reaction mixture was left overnight and the precipitate formed

was filtered and the filtrate dried and recrystallized from ethanol. m.p. (196 °C), yield(0.15g,50%).

Similarly, the following compounds were prepared similar to this procedure in this manner. The physical data are recorded in Table (1).

Result and Discussion

Phenoxazine was prepared by the reaction of o-aminophenol with zinc chloride in presence of phosphoric acid as shown 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} for (C=C) assigned to phenoxazine ring. The $^1\text{H-NMR}$ spectrum showed signal at δ (6.39-6.81) ppm, due to aromatic protons and signal at δ (8.2) ppm a signed to (N-H) as shown in figure (1). The phenoxazine (1) was then converted to 10-nitrosyl phenoxazine (2) using sodium nitrite. IR spectrum of compound (2) showed the disappearance of (N-H) band at 3342 cm^{-1} and showed a stretching band at 1271 cm^{-1} due to (NO). The IR spectrum also, showed a band at 3062 cm^{-1} (C-H) aromatic and 1587 cm^{-1} for (C=C). Compound (2) reacted with zinc powder in acetic acid to give compound (3) as shown in scheme (2). The IR spectrum of compound (3) showed a strong stretching band at 3386 cm^{-1} and 3370 cm^{-1} due to (NH₂) and 1593 cm^{-1} for (C=C) as shown in Table (2). Compound (3) reacted with benzoyl chloride, isovaleryl chloride and 4-bromophenacyl chloride to give 10-benzamide phenoxazine, 10-(3-methyl propenyl)amide phenoxazine and 10-(4-bromophenyl)amide phenoxazine compounds (4-6).

IR spectra of compounds (4-6) showed a strong absorption bands at (3342-3300) cm^{-1} for (N-H), at (1650-1697) cm^{-1} for (C=O), at (1583-1593) cm^{-1} for (C=C) str., $^1\text{HNMR}$ spectrum (Fig. 2) for compound (4) which showed a signal at (δ 8.7) ppm belong to (N-H) proton and signals at δ (6.5-8) ppm belong to aromatic protons.

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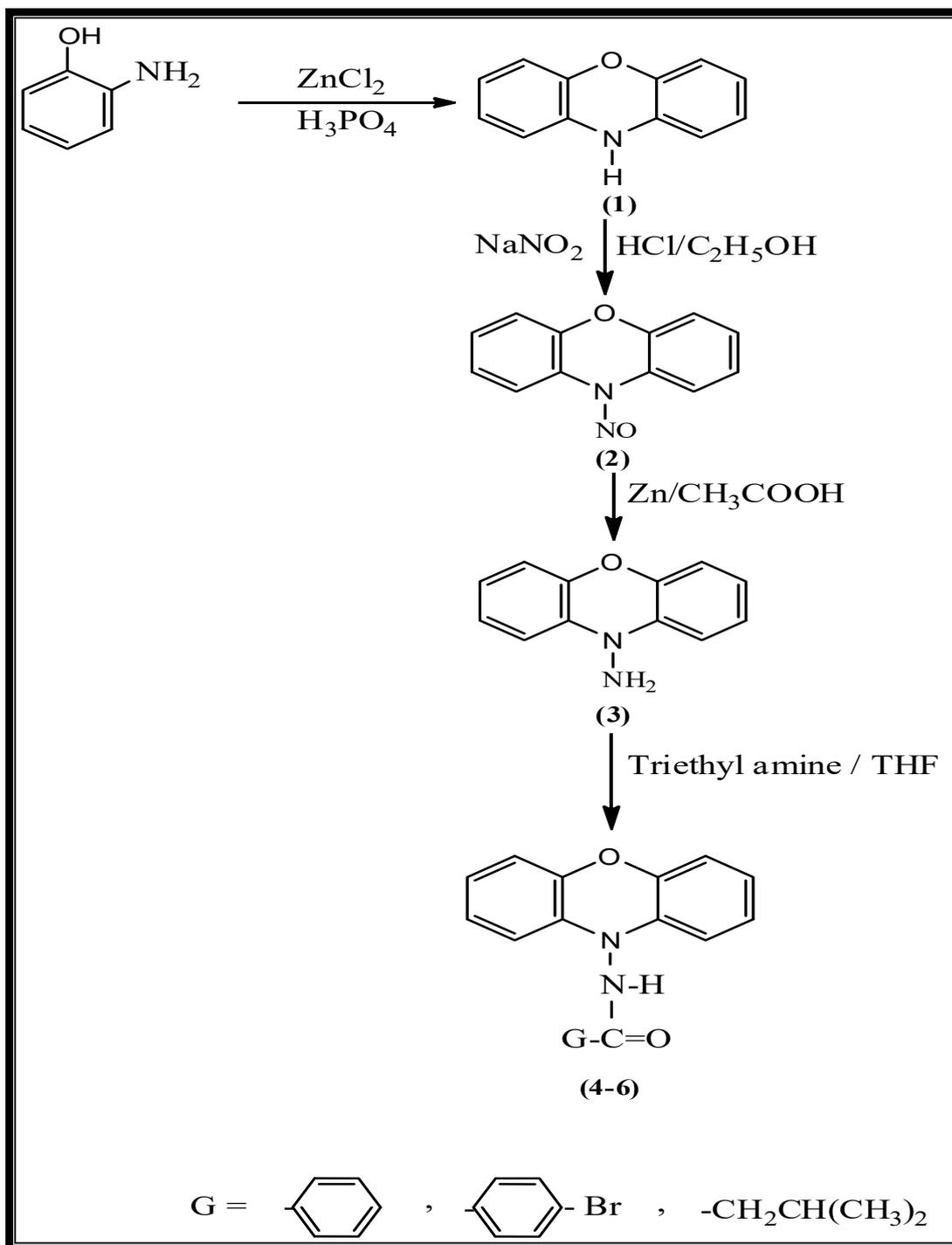
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Table (1) Physical properties of compounds (2-6)

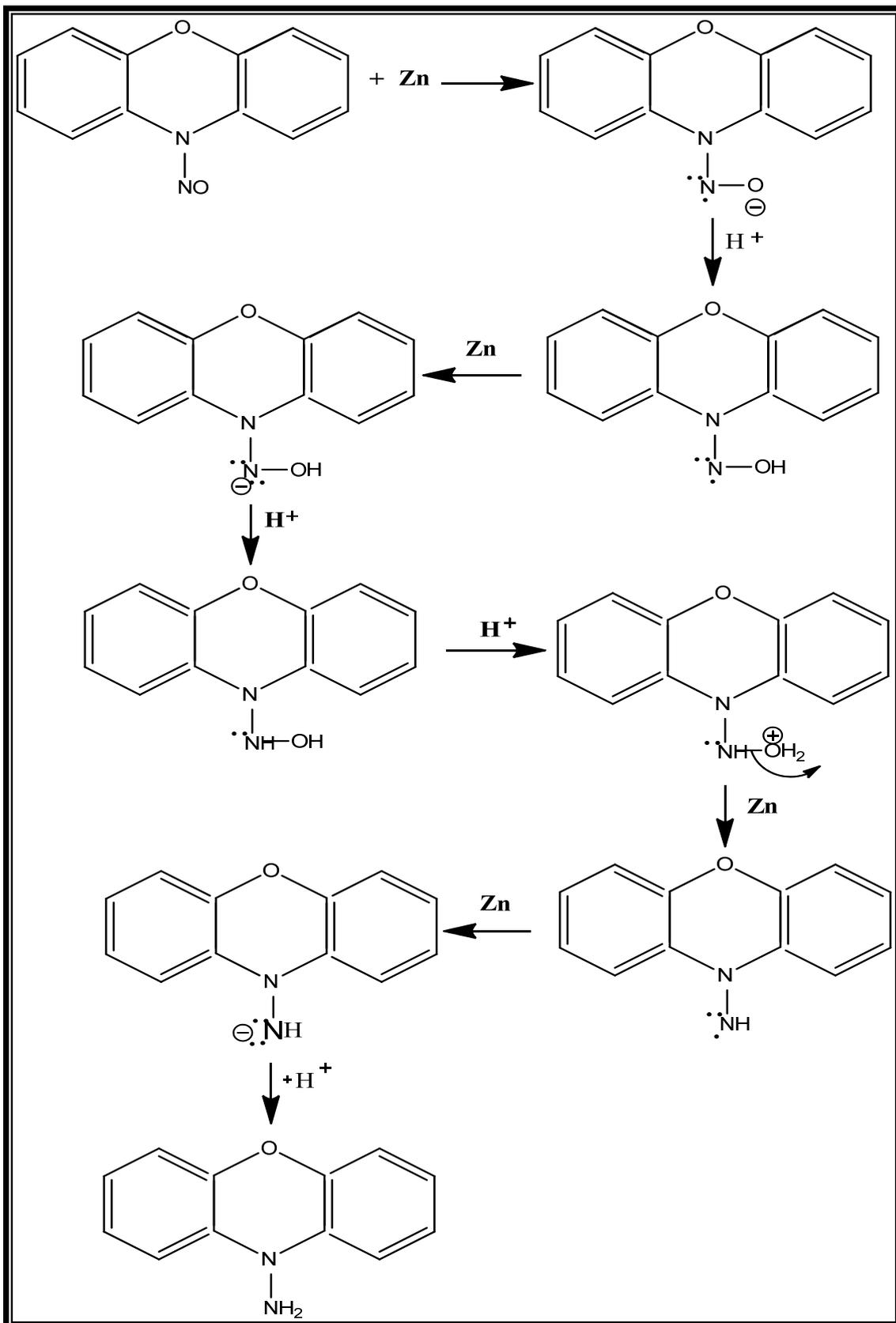
Comp. No.	Scientific name	Structure	M.P. °C	%Yield	Color of crystal	Solvent
2	10-nitroso-10H-phenoxazine		172	57	Brown	Ethanol
3	10-amino phenoxazine		190	62	Brown	Ethanol
4	10-Benzamido phenoxazine		196	50	Green	Ethanol
5	10-(3-methyl propenyl) amido phenoxazine		222	48	Black	Ethanol
6	10-(4-Bromophenyl) amidophenoxazine		130	90	Green	Ethanol

Table (2) Infrared spectra data of compounds (2-6)

Com. No.	Structure	ν N-H cm ⁻¹	ν C-H Aromatic	ν C=C cm ⁻¹	ν C=O cm ⁻¹	Other bands cm ⁻¹
2		-	3062 w	1587 s	-	NO 1271s C-O-C 1029 m
3		3386 m 3370 m	3062 m	1593 s	-	C-O-C 1112 m
4		3300 s	3055 m	1593 s	1683 s	C-O-C 1110 m
5		3342 m	3068 m	1589 s	1650 s	C-O-C 1119 m
6		3300 m	3083 w	1583 s	1697 s	C-O-C 1110 m



Scheme (1): Preparation of new Heterocyclic compounds



Scheme (2): Reaction mechanism for the reduction of 10- nitrosylphenoxazin

تحضير مشتقات جديدة من 10-أمينو فينوكسازين

إسراء طه إبراهيم
سعاد مصطفى الأعرجي

قسم الكيمياء / كلية العلوم / جامعة بغداد
استلم في: 22/تشرين الأول/2015، قبل في: 15/كانون الأول/2015

الخلاصة

يتضمن البحث تحضير مشتقات جديدة من الفينوكسازين وهي مشتقات معوضة على ذرة النتروجين مبتدأ من الفينوكسازين (1). حضر 10- نتروسل فينوكسازين من مفاعلة الفينوكسازين مع نتريت الصوديوم ليعطي المركب (2)، الذي بدوره يتفاعل مع الزنك في حامض الخليك ليعطي 10- أمينو فينوكسازين (3). فوعل المركب (3) مع كلوريد بنزويل، كلوريد أيزوفاليريل و كلوريد 4- برومو فينيسيل فأعطى مشتقات 10- أمينو فينوكسازين (4-6).

الكلمات المفتاحية: فينوكسازين , أثيل أستيت فينوكسازين, 1-أسيتو هيدرازيد فينوكسازين