PREPARATION AND CHARACTERIZATION OF SOME NEW OXAZEPINE COMPOUNDS

Natiq G. Ahmed[a]* and Hussein Y. Al-Hashimi[a]

Keywords: Mannich bases, Schiff bases, oxazepines; benzo[1,3]oxazepines.

The ketonic compound (**1**) is synthesized from equal moles of morpholine, 4-nitrobenzaldehyde, and 3-nitro acetophenone. Schiff base compounds (**2**)-(**4**), prepared by reacting (**1**) with different aromatic amines (4-aminoantipyrine, *p*-phenylenediamine, 2-aminopyridine), contain a set of one or more of azomethine (-C=N-) groups that have been used in the preparation of many heterocyclic compounds, which when reacted with maleic anhydride give 1,3-oxazepine compounds (a ring with seven atoms) (**5**)-(**7**), and seven membered ring benzo[1,3]oxazepine compounds (**8**)-(**10**) are obtained by reaction with phthalic anhydride. The synthesized compounds are identified using physical (melting points, colour change, thin layer chromatography) and spectral methods such as IR, UV, and NMR spectra). The biological effectiveness of some of the prepared compounds is measured.

* Corresponding Authors
E-Mail: natiq.ahmad@yahoo.com
Chemistry Department, College of Education, Mosul University, Mosul, Iraq

Introduction

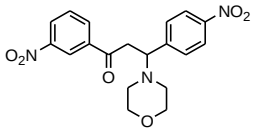
Mannich bases (β-amino ketones) are known to possess potent biological activities,[1] and are known for their use as additives in detergents, resins, polymers, surface active agents etc.[2] Schiff's bases, (RHC=N-R1, where R and R1 are alkyl, aryl, cycloalkyl or heterocyclic groups,[3]) are condensation products of primary amines with carbonyl compounds like Mannich bases exhibit a broad range of biological activities including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties.[4]

Oxazepine, un-saturated non-homologous seven membered heterocycle containing oxygen in position 1 and nitrogen in position 3, is prepared by the pericyclic cycloaddition of Schiff bases with maleic, phthalic, nitrophthalic and succinic anhydrides. Since oxazepine derivatives exhibit a vast variety of biological activities,[5] therefore some new oxazepine derivatives have been synthesized and studied for their biological activity.

Experimental

All reagents and chemicals are from BDH and Sigma-Aldrich, and have been used without further purification. Melting points are measured using hot stage Gallen Kamp melting point apparatus and are uncorrected (Maximum temperature 240 °C). The FT-IR spectra, in the range (4000-400) cm^{-1}, are recorded using KBr disk on Shimadzu FT-IR-8300 spectrophotometer. UV/VIS spectra are recorded on a Uv-Cary-100 spectrophotometer. ^1H NMR spectra are recorded on a BRUKER-400 MHz operating with TMS as an internal standard in $CDCl_3$ or DMSO-d_6 as a solvent. TLC is carried out by using alumina plates percolated with silica gel, supplied by Merck. Spots were detected with iodine vapour.

Synthesis of 3-morpholino-1-(3-nitrophenyl)-3-(4-nitrophenyl)propan-1-one (1)



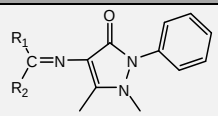
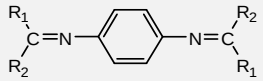
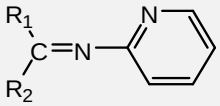
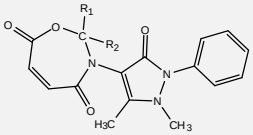
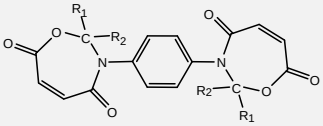
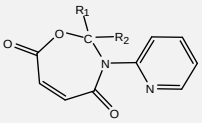
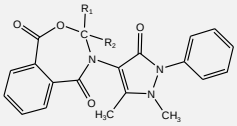
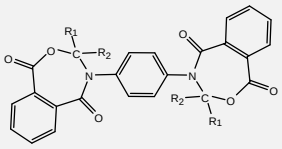
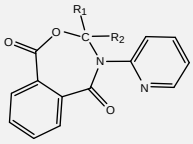
In a typical procedure,[6-8] an ethanolic solution (30 mL) of 4-nitrobenzaldehyde (1.51 g, 0.01 mol), 3-nitroacetophenone (1.65 g, 0.01 mol) and morpholine (0.88 mL, 0.01 mol) were mixed and continuously stirred for 4 h under ice cold condition. The solid formed is filtered and recrystallized using absolute ethanol. The purity of the compound is checked with TLC.

The obtained compound is off white in colour (77 %), m.p. 64-66 °C. Molecular formula $C_{19}H_{19}N_3O_6$. IR (KBr): 1689 cm^{-1} (C=O). UV-VIS (DMSO): 250 nm ($\pi \rightarrow \pi^*$), 325 nm ($n \rightarrow \pi^*$). ^1H NMR (400 MHz): δ = 7.8-8.16 (m, 8H, Ar-H), 3.32-3.35 (s, 4H, morpholine CH_2O), 2.48 (s, 4H, morpholino CH_2-N), 3.48 (s, 1H, CH), 2.67-2.72 (d, 2H, CH_2).

Synthesis of Schiff bases (2)- (4)

Schiff bases are prepared by adding few drops of glacial acetic acid with stirring to a solution of compound (**1**) (0.96 g, 0.0025 mol) in absolute ethanol (20 mL) followed by 0.0025 mol of 4-aminoantipyrine (**2**) or 2-aminopyridine (**4**) dissolved in 20 mL of absolute ethanol. For the preparation of compound (**3**), 0.005 mol of the compound (**1**) is mixed with (0.0025 mol) of *p*-phenylenediamine. The mixture is refluxed for 8-12 h with follow-up by TLC.

Table 2. Some physical properties of compounds (**2**)-(**10**).

Compound No.	Structure	Reaction Time (h)	Molecular formula and weight	m.p. in °C and colour	Yield %	R_f
2		10	$C_{30}H_{30}N_6O_6$ 570	191-193 Light orange	80	0.83
3		8	$C_{44}H_{42}N_8O_{10}$ 842	184-186 Yellow	77	0.76
4		12	$C_{24}H_{23}N_5O_5$ 461	94-96 Reddish orange	94	0.85
5		10	$C_{34}H_{32}N_6O_9$ 668	185-187 Reddish brown	73	0.61
6		10	$C_{52}H_{46}N_8O_{16}$ 1038	167-169 Light brown	65	0.95
7		10	$C_{28}H_{25}N_5O_8$ 559	134-136 Yellow	93	0.88
8		10	$C_{38}H_{34}N_6O_9$ 718	144-146 Reddish brown	82	0.66
9		10	$C_{60}H_{50}N_8O_{16}$ 1138	221-223 Desert	68	0.70
10		10	$C_{32}H_{27}N_5O_8$ 609	176-178 Yellow	54	0.82

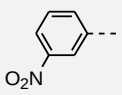
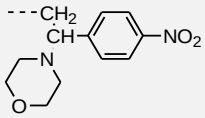
R_1 =  R_2 = 

Table 2. UV and IR spectral characteristics of compounds (**1**)-(**4**).

Comp. No.	ν (cm-1) IR (KBr)								λ_{max}, nm
	Ar C-H	R C-H	C=O	C=N	C-N-	C-O-C	$-NO_2$	Others	
1	3099	2962, 2924, 2852, 2819	1689	----	1247	1008, 1105	1342	----	325, 250
2	3090 3066	2999, 2968,2920, 2850	----	1645	1249	1020, 1107	1338	C=O 1689 conj. 1612 C=C conj.	302, 247
3	3101 3043	2983, 2881, 2847	----	1595	1192	1012, 1107	1338	----	338, 261
4	3043	2912, 2881, 2847	----	1626	1180	1008, 1105	1340	C=N 1597 endo	359, 276

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At the end of the reaction, solution is cooled to room temperature. The solvent is then evaporated to obtain the precipitate, which is recrystallized from absolute ethanol.

Synthesis of 1,3-oxazepine derivatives (5)-(7)

A mixture of Schiff base (**2**) or (**4**) (0.0004 mol) and 0.0006 mol of maleic anhydride in 20 mL of dry benzene is refluxed, and followed-up by TLC. At the end of the reaction, solution is cooled to room temperature and the solvent evaporated to obtain a precipitate which is washed with distilled water, filtered and recrystallized from absolute ethanol.[12,13]

The compound (**6**) is prepared by the same method except 0.0004 mol of the compound (**3**) and 0.0012 mol of maleic anhydride are used.

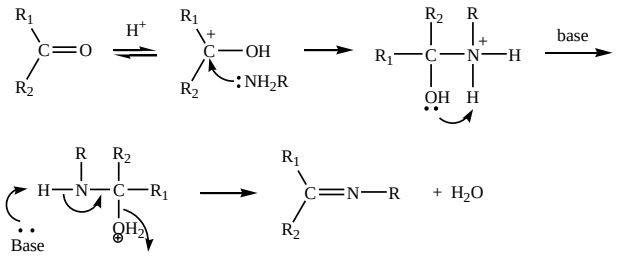
Synthesis of benzo[1,3]oxazepine derivatives (8)-(10)

A mixture of Schiff base (**2**) or (**4**) (0.0004 mol) and 0.0006 mol of phthalic anhydride in 20 mL of dry benzene is refluxed, and followed -up by TLC. At the end of the reaction, solution is cooled to room temperature and the solvent evaporated to obtain a precipitate, which is washed with distilled water, filtered and recrystallized from absolute ethanol.[12,14] The compound (**9**) is similarly prepared except 0.0004 mol of the compound (**3**) and 0.0012 mol of phthalic anhydride are used.

Physical properties and reaction time of compounds (**2**)-(**10**) are listed in Table 2.

Results and Discussion

A new ketone (**1**), a Mannich base, is synthesized from the reaction of 4-nitrobenzaldehyde, 3-nitroacetophenone and morpholine in ethanolic solution. The product is characterized using UV-VIS, IR and NMR spectra. Three new Schiff bases are synthesized from the reaction of compound (**1**) with 4-aminoantipyrine, 2-aminopyridine or *p*-phenylene diamine in absolute ethanol and in the presence of catalytic amount of acetic acid (Scheme 1).



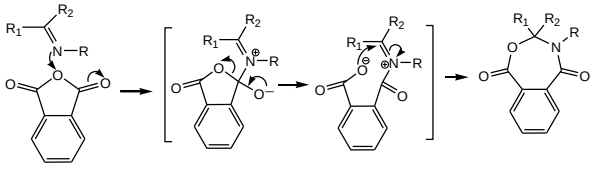
Scheme1. Mechanism of synthesis of Schiff base (**2**)-(**4**).

The main features of UV and IR spectra of the compounds **(1)-(4)** are given Table 2. The ^{1}H NMR spectrum of (**2**) showed the following peaks.

Compound (**2**): ^{1}H NMR (400 MHz): δ = 7.37-8.60 (m, 13H, Ar-H), 3.32 (s, 4H, morpholine CH_2O), 2.67 (s, 4H, morpholine CH_2N), 3.35 (t, 1H, CH), 3.24 (s, 3H, CH_3-N), 2.48 (s, 3H, CH_3-C=C), 2.72 (d, 2H, CH_2).

Oxazepines (**5**)-(**10**) are synthesized from the reaction of Schiff bases (**2**)-(**4**) with maleic or phthalic anhydride in dry benzene (Scheme 2).

The FT-IR spectrum,[13,14,18-20,22-24] of oxazepine compounds (**5**)-(**10**) showed the disappearance of peak of azomethine (C=N) group outside the ring. The new peaks which appears at 1689-1722 cm^{-1} can be attributed to the C=O group of ester and the peak at 1627-1693 is attributed to the C=O (amide) group. The UV/VIS Spectrum (in DMSO) shows absorption peak in the regions of 209-301 nm due to $\pi \rightarrow \pi^*$ and 294-354 nm due to $n \rightarrow \pi^*$ transitions.



Scheme 2. Mechanism of synthesis of compounds (**5**) – (**10**).

Biological Studies

Biological activity has been studied[25,26,27] for some of the synthesized compounds by studying their impact on the growth of *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. The biological activity of compounds is determined by measuring the diameter of the empty region around the well (inhibition zone). The organisms are activated in a nutrient growth medium at 37 °C for 24 h prior to the experiments. The results of preliminary screening tests (Table 3) indicated that compounds (**1**, **3**, and **10**) showed moderate activity and compounds (**2**, **5**, and **6**) showed slight activity against *Staphylococcus aureus*. Compounds (**1**, **2**, **3**, **5**, **6**, and **10**) are slightly active against *Escherichia coli*. Compound (**3**) is moderately active and compounds (**1**, **2**, **5**, **6**, and **10**) are slightly active against *Pseudomonas aeruginosa.*

Table 3. Antibacterial activities of some prepared compounds.

Comp. No.	S. Aureus Gr +Ve	E. Coli Gr -Ve	P. Aeruginosa Gr -Ve
1	++	+	+
2	+	+	+
3	++	+	++
5	+	+	+
6	+	+	+
10	++	+	+

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