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# Synthesis of Some Heterocyclic Compounds from Amidoxime and Imidate

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## ABSTRACT

Amidoxime (2) was prepared from the reaction of carbonitrile (1) with hydroxyl amine hydrochloride. Compound (2) treated with either acid chloride or anhydride at room temperature to obtain O-aroyl and O-acetyl amidoxime (3a-c). However, on heating compound (2), oxadiazole derivatives (4a-c) were obtained, respectively. 1,2,4-Oxadiazole-5-one (5) was obtained from the reaction of amidoxime with phosgene. Amidine (7) also prepared from imidiate reaction with ammonium chloride.

A number of heterocyclic compounds (8-10) were also prepared by the reaction of imidate (6) with either amino derivatives or azide. Imidate (6) was prepared from the reaction of carbonitrile with ethanol in the presence of hydrogen hydrochloride gas.

***Key words***: Heterocyclic compounds, Amidoxime, Imidate.

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# تحضير بعض المركبات الحلقية غير المتجانسة من الاميداوكزيم والايميدات

## الملخص

يتضمن البحث تفاعل الاميداوكزيم (2) (المحضر من تفاعل الكاربونتريل (1) مع هيدروكسيل امين هيدروكلوريد) مع كلوريد او انهيدريد الحامض، عند درجة حرارة الغرفة يعطى O-اريلول، O-اسيتيل اميداوكزيم (3a-c). وعند التسخين الى درجة الارتداد يعطى معوضات الاوكسادايازول (4a-c) وعند تفاعل الاميداوكزيم مع الفوسجين يعطي4,2,1 - اوكسادايازول -5-اون (5). اما الايميدين (7) فقد تم تحضيره من تفاعل الايميدات مع كلوريد الامونيم. كما تم تحضير عدد من المركبات الحلقية غير المتجانسة (8-10) من تفاعل الايميدات (6) المحضر من تفاعل الكاربونتريل (1) مع الايثانول بوجود غاز كلوريد الهيدروجين مع مشتقات الامينات والازايد.

**الكلمات المفتاحية:** المركبات الحلقية غير المتجانسة، اميداوكزيم، ايميدات.

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## INTRODUCTION

Versatile heterocyclic compounds were synthesized from carbonitrile. The reaction of carbonitrile with hydroxylamine hydrochloride gave amidoxime (Snoke and Popp, 1973; Maddison *et al.*, 1974; Basheer and Ezzat, 2006; Ezzat, 2003), whereas, the preparation of imidates (imino esters) could be achieved by the addition of dry hydrogen chloride to a mixture of carbonitrile and an alcohol (Freiter *et al.*, 1973; Dalko and Langlois, 1998; Sharma, 2001). Amidoximes and imidates were commonly used as intermediates in the synthesis of oxadiazole (Quillco *et al.*, 1962; William *et al.*, 1999; Bilek and Slouka, 2000), tetrazole (Basher and Ezzat, 2006), oxazole (White *et al.*, 2000), imidazole (McLaughlin *et al.*, 2003), benzimidazole (Grimmett, 1997) and benzoxazole (Sanjai *et al.*, 2001). Amidoxime derivatives have been found to possess versatile applications in the biological fields: as they manifested antineoplastic effects (Snoke and Popp, 1973), antipneumocystis activity (Boykin *et al.*, 1996), antimicrobial agent (Zhou, 2001), direct thrombin inhibitor (Clement and Lopian, 2003), antipeptide antibodies agents overlapping sequences differentially inhibit human (Cribb *et al.*, 1995), orally active fibrinogen receptor antagonists (Weller *et al.*, 1996) and as fungicides (Rheinheimer *et al.*, 2006). The possibility of using amidoxime resins to extract metals from aqueous media such as Uranium and Arsenic (Kato *et al.*, 1990.Kawai *et al.*, 2000; Kawai *et al.*, 2000).

## EXPERIMENTAL

Uncorrected melting points were determined using Electrothermal 9300 melting points apparatus. I.R. spectra were recorded on Infrared Spectrophotometer Model Tensor 27 Bruker Co., Germany, using KBr discs. UV spectra were measured on Shimadzu UV-1650 PC, UV-Visible Spectrophotometer.

### Synthesis of methyl-2-carbonitrile-(2H) quinoline-N- carboxylate (Snoke and Popp, 1973) (1)

Methyl chloroformate (0.064 mole) was added dropwise with stirring over a period of 30-60 minutes to a mixture of (0.032 mole) of a quinoline in 40 ml of methylene chloride and (0.096 mole) of potassium cyanide in 15 ml of water. The mixture were stirred for 3 hours and the two layers were separated. The organic layer was washed with water, 10% hydrochloric acid, 10% sodium hydroxide, and water then dried over magnesium sulfate. Evaporation of the solvent and recrystallization of the residue from ethanol gave the title compound. The physical properties and the spectral data were listed in Table (I).

### Synthesis of methyl-2-amidoxime-(2H) quinoline -N- carboxylate (Maddison *et al.*, 1974) (2)

A solution of (0.1 mole) of compound (1) in 100 ml 50% aqueous ethanol was added to (21.2 gm, 0.2 mole) sodium carbonate, thereafter (28 gm, 0.4 mole) hydroxyl amine hydrochloride was added. The reaction mixture was heated on a steam bath for 1.5 hr. The amidoxime which separated on cooling was filtered off and recrystallized from ethanol to give crystalline product. The physical and spectral data were indicated in Table (1).

### Synthesis of methyl 2-(O-aroyl amidoxime)-1-(2H) quinoline-N- carboxylate (3a-b)

Amidoxime (2) (0.005 mole) was mixed with 2 ml of benzoyl chloride (or p-nitro benzoyl chloride) dissolved in 25 ml of tetrahydrofuran under dry conditions. The reaction mixture was stirred for 4 hrs. at room temperature. The solid product was filtered off and recrystallized from ethanol. The physical constants and spectral data were illustrated in Table (1).

**Synthesis of methyl 2-(O-acetyl amidoxime)-1(2H) quinoline-N- carboxylate (3c)**

A mixture of amidoxime (2) (0.005 mole) and 2 ml of acetic anhydride was stirred at room temperature for 3 hrs. The solid product was filtrated off and recrystallized from ethanol. The physical constants and spectral data were listed in Table (1).

**Synthesis of 3-(N-methyl carboxylate-2H-quinoline-2-yl)-5-aryl-1,2,4-oxadiazole (4a-b)**

Amidoxime (2) (0.005 mole) was heated under reflux for 5 min. after the addition of 2 ml of benzoyl chloride (or p-nitro benzoyl chloride in 25 ml tetrahydrofuran and refluxed for 30 min. The product is solidified on cooling. The crude product was filtered off and crystallized from ethanol. The physical constants were indicated in Table (1).

**Synthesis of 3-(N-methyl carboxylate-2H-quinoline-2-yl)-5-methyl-1,2,4-oxadiazole (4c)**

Amidoxime (2) (0.005 mole) was heated under reflux for 5 min. with 3 ml of acetic anhydride, the product being solidify on cooling. The solid product was filtered off and recrystallized from ethanol. Spectral data and physical constant were listed in Table (1).

**Synthesis of 3-(N-methyl carboxylate-2H-quinoline-2-yl) -1,2,4- oxadiazole-5-one (5) (Bura Kevich *et al.*, 1972)**

A mixture of (0.005 mole) of amidoxime (2) and 2 ml of triethylamine in 50 ml of benzene was cooled to 5 °C then phosgene (1 gm) (Basher, 2000) was dissolved in 5 ml toluene was added. The mixture was allowed to stand for 40 hrs. and washed with 50 ml of water. The aqueous layer was extracted with benzene. The combined benzene fraction were dried over anhydrous magnesium sulfate and evaporated to give solid residue which was recrystallized from ethanol. The physical constants and the spectral data were indicated in Table (1).

**Synthesis of methyl-2-imidate 1-(2H) quinoline carboxylate hydrochloride (6)**

A mixture of compound (1) (0.1 mole) in 40 ml of absolute ethanol was saturated with dry hydrogen chloride gas. The solution was allowed to stand at room temperature for seven days. The imidate hydrochloride was precipitated and filtered. The physical and spectral data were illustrated in Table (2).

**Synthesis of methyl 2-imidine 1-(2H) quinoline carboxylate hydrochloride (7)**

Compound (6) (0.01 mole) was dissolved in enough amount of an ice-cold 50% sodium hydroxide solution to give an alkaline media then poured with 20 ml of diethyl ether was added, into separating funnel the mixture was shaken vigorously. The yellow layer is separated, washed with water until being neutral, dried over sodium sulphate, and concentrated to give the crude imidine. The latter was dissolved in 10 ml of 75% aqueous ethanol containing (0.02 mole) of ammonium chloride and heated at 70 °C for 4 hrs., cooled and diluted with 2-3 volumes of acetone. The unreacted ammonium chloride that separated was filtered and the filtrate concentrated. After standing over night at 0°C. white needles were separated. The melting point and IR spectral data were shown in Table (2).

### Synthesis of 5-(N-methyl carboxylate -2H- quinoline-2-yl) tetrazole (8)

A mixture of (0.01 mole) of compound (6) and (0.015 mole) of sodium azide was dissolved in 25 ml of acetic acid and refluxed for 24 hrs. The salt (sodium chloride) was filtered and the solvent was evaporated to give colorless needles. The physical constants are indicated in Table (2).

### Synthesis of 2-(N-methyl carboxylate -2H- quinoline-2-yl) -4-H,5-H-benzimidazole / imidazole (9a,10a)

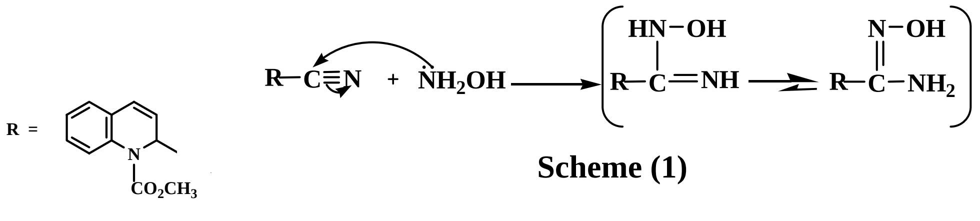
To a solution of (0.005 mole) of compound 6 in 10 ml of methanol was added with stirring a solution of (0.005 mole) of o-phenylenediamine or ethylenediamine in 10 ml methanol. After stirring for 30 min at 20-25 °C. the mixture was refluxed for 1hr. then cooled . The precipitate was filtered off and washed with water to give the product. The melting point and spectral data were shown in Table (2).

### Synthesis of 2-(N-methyl carboxylate -2H- quinoline- 2- yl) benzoxazole (9b,10b)

A mixture (0.005 mole) of compound (6) and (0.005 mole) of o-aminophenol or ethanol amine were dissolved in 10 ml of dry methanol was heated on a steam bath for 30 min., after cooling filtration, evaporation of the solvent affords the product. The physical constants and spectral data were indicated in Table (2).

## RESULTS AND DISCUSSION

Carbonitrile (1) was prepared by the addition of chlorofomate to a solution of quinoline and potassium cyanide in methylene chloride. It was identified by IR spectra which showed a main absorption bands at 2235 and 1733 cm$^{-1}$ assigned to C≡N and C=O bond streching respectively. The amidoxime (2) was synthesized through the condensation of the corresponding carbonitriles (1) with hydroxyl amine hydrochloride, the reaction mechanism could be illustrated as follow (scheme 1):-

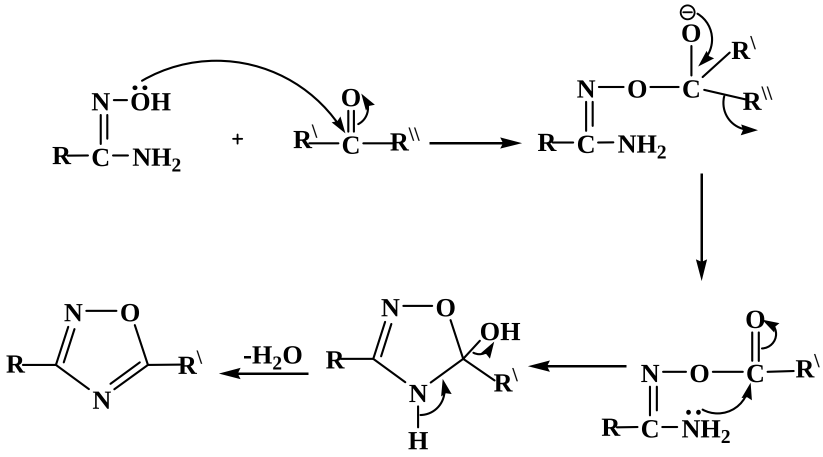


Scheme (1)

The IR spectra for this compound showed stretching vibration band at (1650 cm$^{-1}$, 3445 cm$^{-1}$) and (3645 cm$^{-1}$) which are attributed to C=N, N-H and O-H, respectively. The compounds (3a-c) were synthesized by the reaction of amidoxime (2) with acid chloride or acetic anhydride at room temperature. The obtained products were identified by the IR data. Their infrared spectra revealed the following bands, (1735-1745 cm$^{-1}$), (1655-1658 cm$^{-1}$ ) and (3357-3489 cm$^{-1}$) which were related to C=O, C=N, N-H groups respectively.

The U.V spectra for compounds (3a-c) showed lower wave length at (238-288 nm) due to the steric effect (Finer, 1977).

On the other hand, the compound (2) was converted to 1,2,4- oxadiazoles (4a-c ) under heating condition as shown in the following mechanism (Al-Barwary, 2006) (scheme 2):-



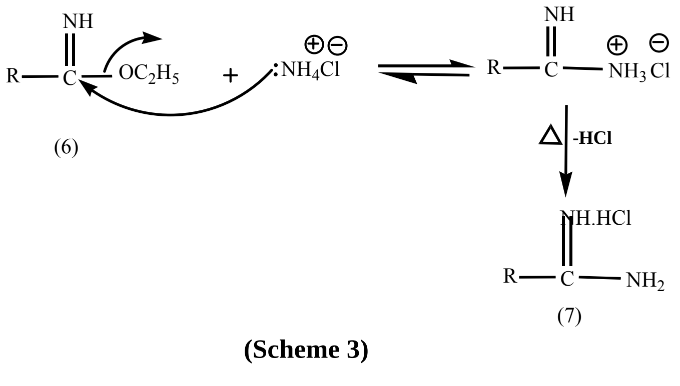
| 4 | R\ | R\\ |
|---|---|---|
| a | $C_6H_5$ | Cl |
| b | p-$NO_2C_6H_4$ | Cl |
| c | $CH_3$ | $OCOCH_3$ |

**(Scheme2)**

Compounds (4a-c&5) were confirmed by IR spectra in which their stretching vibration were observed at (1720-1748 $cm^{-1}$), (1627-1660 $cm^{-1}$) and (3362-3400 $cm^{-1}$) as these bands were referred to C=O, C=N and N-H respectively. In U.V spectra these compounds gave red shift at (232-286nm) and (276nm) respectively.

Highest attention was dedicated to the transformations of carbonitrile (1), to imidate hydrochloride (6) by its reaction with dry hydrogen chloride gas in an excess of dry ethanol (the Pinner synthesis) (Sandler and Karo, 1972). The IR spectrum for compound (6) showed absorption bands as follow, (1699 $cm^{-1}$ ) for C=N,( 1745$cm^{-1}$) for C=O and (3137 $cm^{-1}$) for N-H.

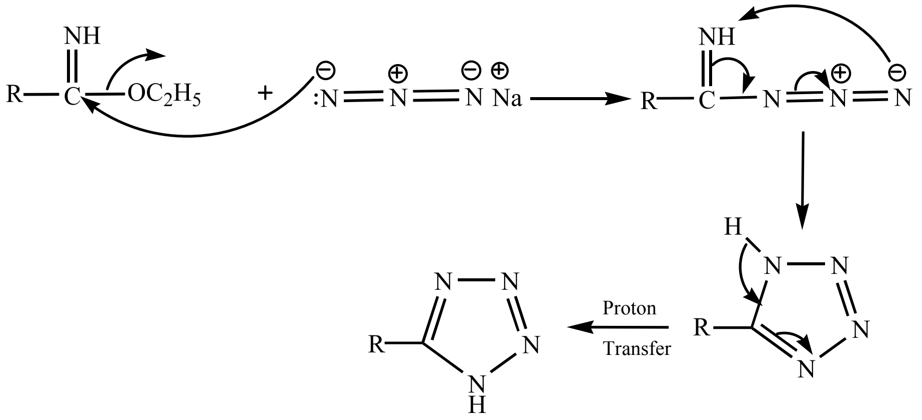
Compound (6) was readily converted to the amidine (7) when it was treated with ammonium chloride (King and Acheson, 1949) (scheme 3).



**(Scheme 3)**

The IR spectrum manifested the following bond stretching bands (1640 $cm^{-1}$) for C=N, (1750 $cm^{-1}$) for C=O and (3298 $cm^{-1}$) for N-H, while in U.V spectra this compound showed $\lambda_{max}$ at (240) due to the steric effect (Finer, 1977).

Tetrazole (8) was prepared by the acidic cyclization of imidate (6) with sodium azide (scheme 4).

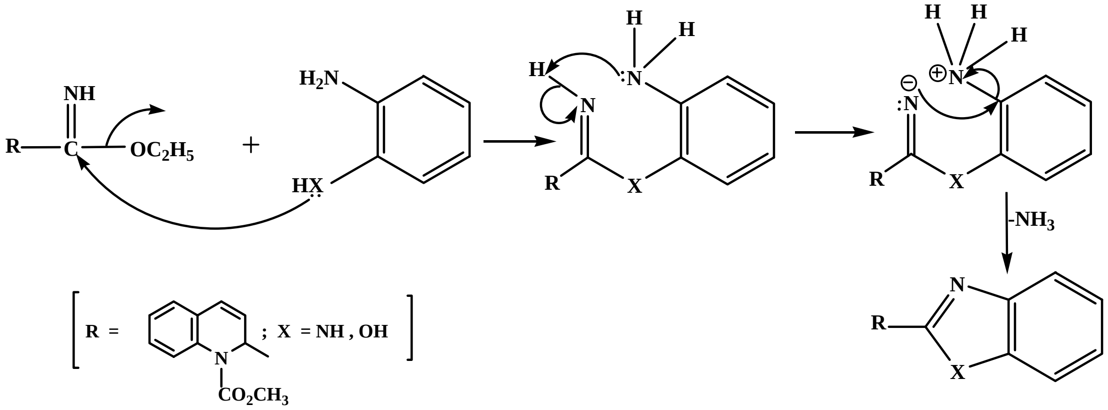


(8)

**(Scheme 4)**

The IR spectral data exhibited the major absorption bands at (1571 $cm^{-1}$), (1699 $cm^{-1}$), (1744 $cm^{-})^{1}$ and (3444 $cm^{-1}$)which are, respectively, assigned to N=N, C=N, C=O and N-H, on the other hand, this compound showed blue shift toward lower wave length in U.V spectrum at (238 nm ) due to the ring strain (Finer, 1977).

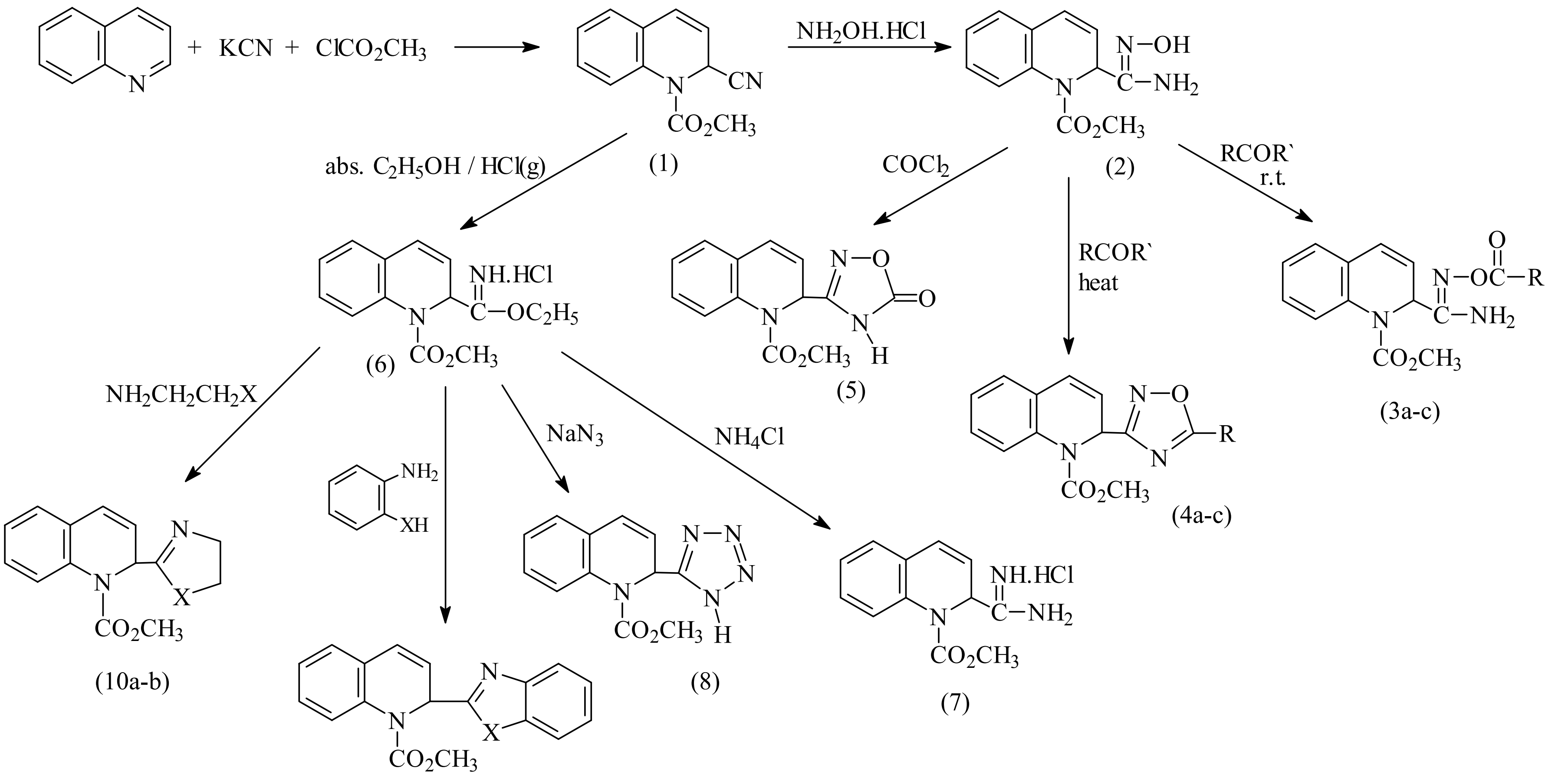
Imidate (6) was also transformed into benzoxazole (9a), oxazole (10a), benzimidazole (9b), and imidazole (10b) when it was reacted with various amines (scheme 5).



(9a-b)

**(Scheme 5)**

The IR spectra of compounds (9a,b), (10a,b) displayed the following, stretching vibrational absorption bands at (1699-1700$cm^{-1}$) and (1740-1745)$cm^{-1}$ which are related to C=N, C=O groups respectively, while the U.V spectra of these compounds showed $\lambda_{max}$ at (254-260nm) and (234-236 nm) respectively ,due to the ring strain (Finer, 1977).



| 3,4 | R | R` |
|---|---|---|
| a | $C_6H_5$ | Cl |
| b | p-$NO_2C_6H_4$ | Cl |
| c | $CH_3$ | $OCOCH_3$ |

| 9,10 | X |
|---|---|
| a | NH |
| b | O |

Table 1: Physical properties and spectral data for compounds (1-5)

| **Comp. No.** | **m.p. (°C)** | **Yield (%)** | **UV (EtOH) $\lambda_{max}$ (nm)** | **Colour** | **IR ν (cm$^{-1}$)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | **C≡N** | **C-N** | **C=O** | **C=N** | **N-H** | **O-H** |
| 1 | 55-57 | 75 | 258 | Pale brown | 2235 | 1340 | 1733 | - | - | - |
| 2 | 148-150 | 63 | 324 | White | - | 1384 | 1750 | 1650 | 3445 | 3645 |
| 3a | 122-124 | 70 | 240 | Pale brown | - | 1297 | 1745 | 1658 | 3368 | - |
| 3b | 152-154 | 74 | 288 | Pale yellow | - | 1385 | 1735 | 1656 | 3489 | - |
| 3c | 162-164 | 80 | 238 | Pale brown | - | 1338 | 1740 | 1655 | 3357 | - |
| 4a | 192-194 | 66 | 232 | Pale brown | - | 1385 | 1748 | 1660 | 3372 | - |
| 4b | 217-219 | 60 | 286 | Deep yellow | - | 1320 | 1736 | 1627 | 3366 | - |
| 4c | 153-155 | 83 | 236 | Yellow- wish white | - | 1376 | 1727 | 1636 | 3362 | - |
| 5 | 254-256 | 65 | 276 | Pale brown | - | 1365 | 1720,1735 | 1651 | 3400 | - |

Table 2: Physical properties and spectral data for compounds (6-10)

| **Comp. No.** | **m.p. (°C)** | **Yield (%)** | **UV (EtOH) $\lambda_{max}$ (nm)** | **Colour** | **IR ν (cm$^{-1}$)** | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | **C=N** | **C=O** | **N-H** | **N=N** | **C-O or C-N** |
| 6 | 78-80 | 85 | 272 | Pale yellow | 1699 | 1745 | 3137 | - | 1332 |
| 7 | 90-92 | 60 | 240 | Pale yellow | 1640 | 1750 | 3298 | - | - |
| 8 | 110-112 | 75 | 238 | Yellow | 1699 | 1744 | 3444 | 1571 | 1377 |
| 9a | 95-97 | 45 | 254 | Deep yellow | 1699 | 1745 | 3445 | - | 1333 |
| 9b | 203-205 | 36 | 260 | Orange | 1700 | 1745 | - | - | 1205 |
| 10a | 123-125 | 38 | 234 | Pale yellow | 1699 | 1740 | 3398 | - | 1328 |
| 10b | 85-87 | 31 | 236 | Yellow | 1700 | 1745 | - | - | 1121 |

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