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Synthesis of Three-Five and Seven Membered Ring Heterocyclic Compounds Derived from 2-[(2,6-Dichloroanilino) Phenyl]-Acetic Acid

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Abstract **- A new series of three-five and seven membered ring heterocyclic compounds were synthesized using 2-[(2,6-dichloroanilino)phenyl]-acethydrazide (3) as starting material. This carbohydrazide was condensed with numerous carbonyl compound to form the hydrazones (4-15) which some of them were used as precursor to synthesize heterocyclic compounds such as oxaziridines (16-20), 1,3-azetidinones (21-25), 1,3-oxazepin-4,7-diones (26-30), 1,3,4-oxadiazolines (31-36), 1,3,4-oxadiazoles (37-42) and 1,3-thiazolidines (43-47) by their reaction with different chemical reagents. The newly synthesized compounds were characterized on the bases of some physical and spectral data.**

Keywords **- hydrazone, oxaziridines , 1,3-azetidinone, 1,3,4-oxadiazoline, 1,3,4-oxadiazole, 1,3-thiazolidinone, 1,3-azepin-4,7-dione.**

I. INTRODUCTION

The hydrazones are one of the most important organic compounds that have been exclusively used for construction of a variety of heterocyclic compounds. It is well known that heterocyclic compounds are found as a contributing entity to the structure of many biological active compounds [1]. We have recently reported on a synthesis of some heterocyclic compounds derived from 2-[(2,6-dichloro anilino)phenyl]-acetic acid [2], in which the precursor is the hydrazide derivative of this compound. We, now, wish to report here on extension of the synthesis involves new series of three-five and seven membered heterocyclic moieties from the hydrazones that synthesized from the carbohydrazide derivative of the first compound.

Generally, the organic molecules containing an active heterocyclic moiety are used as antibiotic, such as, penicillin, cephalosporins, carbapenems, nocardicins and monobactams [1], in addition to a wide range of biological activity, such as antibacterial [3], antimicrobial [4], anti-inflammatory [5], anti-convulsant [6,7] and antifungal [8] activities.

II. EXPERIMENTAL SETUP

Melting points were determined with an open capillary tube by electro-thermal melting point apparatus 9300, and were uncorrected. Infrared spectra were recorded as KBr disc on FT.IR-Tensor 27- Bruker Co. Germany, 2003. ^{1}HNMR spectra were recorded on Bruker avance III 400 MHz spectrometer, using TMS as internal standard and (DMSO-d_6) as a solvent. The starting material 2-[(2,6-dichloroanilino)phenyl]-acetic acid (1) and its ethyl ester (2) and carbohydrazide (3) were synthesized according to our previous paper [2].

Synthesis of N'-(arylidene / alkylidene)-2-[(2,6-dichloro anilino)phenyl]-acethydrazide (4-15) [9]:

To a solution of the hydrazide (3) (0.01 mol) in absolute ethanol (10 ml) , one of aldehydes or ketones (or their alcoholic solution) was added with stirring at room temperature for ~ 30 min. The hydrazone was formed as precipitate. The solid product was filtered off, washed with hot ethanol then recrystallized from dioxane. The physical and IR spectral data were listed in Table I.

Synthesis of oxaziridines (16-20) [10]:

To a solution of the one of the hydrazones (4-7,9) (0.01 mol) in a mixture of methanolic sodium hydroxide (1 g in 15 ml methanol) and acetone (50 ml), hydrogen peroxide (5 ml, 30%) was added in regular batches with stirring at (20-25 ^{o}C). The turbidity of the reaction mixture was increased as the amount of the peroxide added increased. The stirring was continued for 24 hr.

The precipitate was filtered off, washed thoroughly with water until the output water became neutral, dried then recrystallized from ethanol to give white products. The physical and IR spectral data were listed in Table II.

Synthesis of 1,3-azetidinone compounds (21-25) [11]:

To a cold solution of one of the hydrazones (4-8) (0.01mol) in DMF (15 ml) at (0-5 ^{o}C), chloroacetyl chloride(0.01 mol,1.13 g) and triethylamine (0.01 mol) were added with stirring. The stirring was continued for further 2 hr at room temperature then the reaction mixture refluxed for 10 hr. The reaction mixture was filtered and the filtrate was added to a crushed ice. The resulted precipitate was filtered off, redissolved in cold ethanol to remove unreacted materials. The mixture was filtered and the filtrate was added to a crushed ice. The precipitate was filtered off, dried and recrystallized from dioxane. The physical and spectral data for compounds (21-25) were listed in Table III.

Synthesis of 1,3-oxazepin-4,7-dione compounds (26-30) [12]:

A solution of one of the hydrazone compound (4-8) (0.002 mol) and phthalic anhydride (0.002 mol, 0.3 g) in dry DMF was refluxed under dry conditions for 15 hr. The mixture was immediately filtered, and the filtrate poured on a crushed ice. The resulted precipitate was filtered off, redissolved in cold ethanol and filtered to remove the unreacted materials. The filtrate was poured on a crushed ice, and the resulted precipitate was filtered off, dried and recrystallized from ethanol-water. The physical and spectral data of synthesized compounds (26-30) were listed in Table IV.

Synthesis of 3-acetyl-1,3,4-oxadiazoline compounds (31-36) [13]:

A mixture of one of the hydrazones (4-9) (0.002 mol) and acetic anhydride (10 ml) was refluxed for 4 hr, then cooled and poured with stirring on a crushed ice until the oily material solidified. The precipitate was filtered off, washed thoroughly with water. The solid material was redissolved in cold ethanol and the resulted mixture was filtered to remove unreacted materials. The filtrate was poured on a crushed ice. The resulted precipitate was filtered off ,washed with water, dried and recrystallized from ethanol-water. The physical and spectral data of the synthesized compounds (31-36) were listed in Table V.

Synthesis of 1,3,4-oxadiazole compounds (37-42) [14]:

To a solution of one of the hydrazones (4-8,13) (0.002 mol) in glacial acetic acid (40 ml), lead dioxide (PbO_2) (0.002 mol, 0.48 g) was added. The mixture was refluxed for 10 hr then immediately filtered. The filtrate was cooled, poured with stirring on a crushed ice and the precipitate filtered off, washed thoroughly with water, redissolved in cold ethanol. The solution was filtered to remove unreacted materials, then the filtrate poured on a crushed ice to afford a precipitate. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol-water. The physical and IR spectral data of 1,3,4-oxadiazole compounds (37-42) were illustrated in Table VI.

Synthesis of 1,3-thiazolidin-4-one compounds (43-47) [14]:

A mixture of one of the hydrazones (4-8) (0.002 mol), thioglycolic acid (0.004 mol, 0.27 ml) and anhydrous zinc chloride (0.2 g) in DMF (25 ml) was refluxed for 24 hr. The mixture was filtered then the filtrate condensed and the left over material poured on a crushed ice. The resulted precipitate was filtered off, washed thoroughly with water, dried then redissolved in cold ethanol, and the resulted solution was filtered, to remove the unreacted materials, and the filtrate poured on a crushed ice. The precipitate was filtered off, dried and recrystallized from ethanol-water. The physical and spectral data of the synthesized compounds were illustrated in Table VII.

Synthesize of 2-[(2,6-dichloroanilino)phenyl]-acetyl chloride [15]:

To a solution of the acid (1) (0.01 mol, 3.1 g) in dry benzene (25 ml), thionyl chloride (0.015 mol, 1.1ml) was drop wise added with stirring for 1 hr. The reaction mixture was refluxed for 2 hr. The volatile materials were evaporated under reduced pressure to give red solid material (its m.p. is 120-122^{o}C).

III. RESULTS AND DISSCUSION

In continuation of our previous work directed to synthesize new heterocyclic compounds derived from 2-

[(2,6-dichloroanilino)phenyl]-acetic acid (1), we report herein the synthesis of other heterocyclic skeletons, containing three-five and seven membered ring moieties, derived from the same compound. We directed our effort toward synthesis of oxaziridine (16-20), 1,3-azetidinone (21-25), 2,4-oxazepin-1,5-dione (26-30), 3-acetyl-1,3,4-oxadiazoline (31-36), 1,3,4-oxadiazole (37-42) and 1,3-thiazolidin-4-one (43-47) compounds starting from substituted acetic acid hydrazide (3). The synthetic pathway leading to form the compounds (1-47) is illustrated in Scheme 1. The key intermediate in this synthetic strategy is the carbohydrazide (3), which is synthesized from the acid (1) via two steps according to our previous paper [2]. The first step involves the formation of the ester (2), while the second step involves conversion of the ester (2) to the carbohydrazide (3). The carbohydrazide (3) was condensed with various carbonyl compounds or their ethanolic solution, in presence of few drops of mineral acid, as catalyst, to produce the hydrazones (4-15). The IR spectra of these hydrazones showed absorption bands at (1610-1576) Cm^{-1} for C=N bond stretching and at (1691-1639) Cm^{-1} for the amidic C=O bond stretching, in addition to absorption bands at (3296-3251) Cm^{-1} for N-H bond stretching. The ^{1}HNMR spectrum of compound (8) showed the following chemical shifts δ (ppm) at: 1.89 (d, 3H, CH_3), 3.98 (s, 2H, CH_2), 6.19 (s, 1H, NH), 6.82-7.8 (m, 10H, Ar-H, CH=CH, N=CH), 8.15 (s, 1H, NHCO). The hydrazones were proved to be a versatile compounds for synthesis of a variety of heterocyclic compounds.

When the hydrazones (4-7, 9) allowed to oxidize by hydrogen peroxide (30%) in methanolic sodium hydroxide solution at 20-25 ^oC, the oxaziridines (16-20) were formed. The IR spectra of these compounds showed absorption bands at (1685-1637) for C=O bond stretching, and at (775-725) and (1267-1219) Cm^{-1} for N-O and C-O bond stretching respectively. The ^{1}HNMR spectrum of compound (18) showed the following chemical shifts δ (ppm) at: 3.24 (s, 2H, CH_2), 4.21 (s, 1H, CHNO), 6.31 (s, 1H, NH), 6.81-8.28 (m, 10H, Ar-H, furan-H), 8.44 (s, 1H, CONH).

Furthermore, when the hydrazones (4-8) stirred with chloroacetyl chloride and triethylamine in DMF at ambient temperature, the products were identified as 1,3-azetidinone compounds (21-25). The IR spectra of these compounds showed absorption bands at (1762-1685) Cm^{-1} for endocyclic C=O bond stretching and at (1664-1649) Cm^{-1} for the amidic C=O bond stretching, in addition to absorption bands at (772-748) Cm^{-1} for C-Cl bond stretching. The ^{1}HNMR spectrum of compound (23) showed the following chemical shifts δ (ppm) at: 3.69 (s, 2H, CH_2), 3.89 (s, 1H, CH-furan), 4.06 (s, 1H, CH-Cl), 6.38(s, 1H, NH), 6.86-8.03 (m, 10H, Ar-H and furan-H), 8.55 (s, 1H, NHCO).

On the other hand, the hydrazones (4-8) underwent cyclization reaction when treated with phthalic anhydride in DMF under dry condition to afford 1,3-oxazepin-4,7-dione compounds (26-30). The IR spectra of these compounds showed absorption bands at (1745-1732) Cm^{-1} for lactone C=O bond stretching and at (1709- 1645) Cm^{-1} for lactam C=O bond stretching, in addition to C-N bond stretching bands at (1302-1240) Cm^{-1}. The ^{1}HNMR spectrum of compound (30) showed the following chemical shifts δ (ppm) at: 1.23 (d, 3H, CH_3), 3.34 (s, 2H, CH_2), 6.30 (s, 1H, NH), 6.40-8.11 (m, 13H, Ar-H), 11.16 (s, 1H, CONH).

The refluxing of the hydrazones (4-9) in acetic anhydride led to formation of 3-acetyl-1,3,4-oxadiazoline compounds (31-36), while treatment of hydrazones (4-8,13) with lead dioxide in glacial acetic acid under refluxing condition afforded 1,3,4-oxadiazole compounds (37-42) via oxidation and cyclization processes [14].[189] The IR spectra of oxadiazolines (31-36) exposed the appearance of absorption bands at (1732-1718) and (1662-1219) Cm^{-1} for the C=O and C=N bonds stretching respectively, and at(1092-1010) and (1255-1219) Cm^{-1} for the symmetrical and asymmetrical C-O-C bonds stretching respectively. The ^{1}HNMR spectrum of compound (35) showed the following chemical shifts δ (ppm) at: 0.98 (d, 3H, CH_3), 2.50 (s, 3H, CH_3CO), 3.95 (s, 1H, CH-Ar), 6.54 (s, 1H, NH),7.13-7.72 (m, 9H, Ar-H, CH=CH). On the other hand, the IR spectra of the oxadiazoles (37-42) revealed the absence of stretching bands of the C=O bonds, and appearance of absorption bands at (1655-1577) for the C=N bond stretching, and at (1107-1070) and at (1240-1198) Cm^{-1} for the symmetrical and asymmetrical C-O-C bonds stretching.

The refluxing of the hydrazones (4-8) with thioglycolic acid in dry DMF in presence of anhydrous zinc chloride afforded 1,3-thiazolidin-4-one compounds (43-47). The IR spectra of these compounds showed absorption bands at (1736-1728) and (1678-1630) Cm^{-1} for lactam and amide C=O bond stretching respectively, and a characteristic bands at (883-847) Cm^{-1} for C-S-C bonds stretching.

Finally, we attempt to prepare the acid chloride of the acid (1), by refluxing the acid (1) with thionyl chloride, the product gained was, always, an intramolecular cyclization product [1-(2,6-dichlorophenyl)-indolin-2-one] (48), as identified by its IR spectrum. The IR spectrum of this compound showed absorption band at (1728) Cm^{-1} related to C=O bond stretching. Interestingly, when we attempt to synthesize the amides from the expected acid chloride, the resulted products have the same melting points and their color is red. This mean that the intramolecular cyclization process occurred before addition of the amines.

IV. REFERENCES

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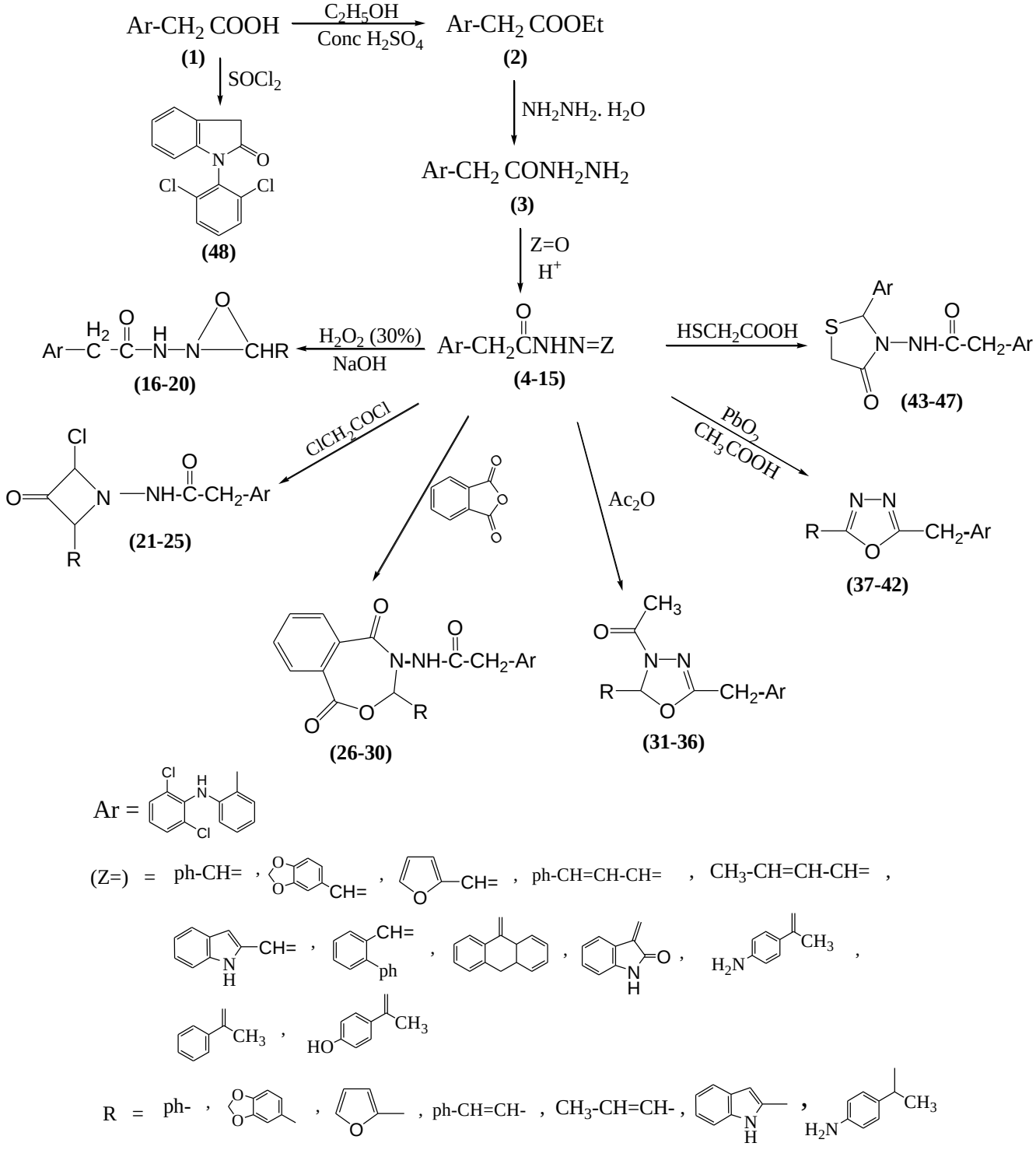

Ar-CH2 COOH
(1)
C2H5OH
Conc H2SO4
Ar-CH2 COOEt
(2)
SOCl2
NH2NH2. H2O
Ar-CH2 CONH2NH2
(3)
(48)
Z=O
H+
Ar-CH2CNHN=Z
(4-15)
H2O2 (30%)
NaOH
(16-20)
HSCH2COOH
(43-47)
ClCH2COCl
(21-25)
PbO2
CH3COOH
(37-42)
Ac2O
(26-30)
(31-36)
Ar =
(Z=) = ph-CH= , CH= , CH= , ph-CH=CH-CH= , CH3-CH=CH-CH= ,
CH= , CH= , , , ,
R = ph- , , , ph-CH=CH- , CH3-CH=CH- ,

Scheme 1

Table I

Physical and IR spectral data of the hydrazones (4-15)

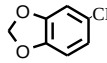
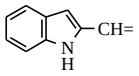
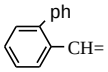
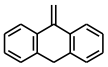
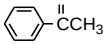
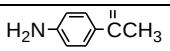
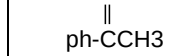
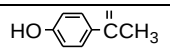
Compd. No.	Z=	M.P. °C	Yield %	IR ν (Cm^{-1})			
				N-H	C=O	C=N	others
4	Ph-CH=	255-257	89	3290	1641	1576	
5		281-283	93	3275	1649	1589	1050(C-O-C)
6		253-255	95	3290	1674	1587	1245(C-O-C)
7	Ph-CH=CH-CH=	212-214	80	3296	1674	1603	
8	$CH_3CH=CHCH=$	251-214	88	3251	1651	1576	
9		294-296	77	3275	1646	1610	
10		318-320	75	3290	1655	1589	
11		218-220	77	3255	1655	1589	
12		248-249	79	3255	1691	1608	1720(C=O)
13		222-224	82	3296	1664	1603	
14		220-223	72	3271	1664	1591	
15		226-228	79	3261	1639	1587	3518(OH)

Table II

Physical and spectral data of oxaziridines (16-20)

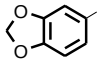
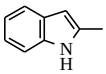
Compd. No.	R	M.P. °C	Yield %	IR ν (Cm^{-1})		
				C=O	N-O	C-O
16	Ph-	190-193	77	1647	758	1260
17		267-270	80	1637	754	1245
18		290-292	75	1646	752	1248
19	Ph-CH=CH-	207-209	83	1658	775	1219
20		255-257	77	1643	771	1267

Table III

Physical and spectral data of 1,3-azetidinones (21-25)

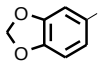
Compd. No.	R	M.P. °C	Yield %	Color	IR ν (Cm^{-1})				
					C=O Exo	C=O Amide	C-N	C-Cl	others
21	Ph-	99-101	65	Yellow	1720	1660	1250	748	
22		97-100	55	Faint brown	1715	1657	1255	750	C-O-C 1030
23		84-87	67	Brown	1726	1664	1363	748	C-O-C 1260
24	Ph-CH=CH-	130-132	77	Deep brown	1701	1649	1361	748	
25	CH_3CH=CH-	106-108	68	yellow	1685	1659	1300	772	

Table IV

Physical and spectral data of 1,3-oxazepin-4,7-diones (26-30)

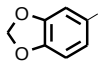
Compd. No.	R	M.P. (°C)	Yield %	Color	IR ν (Cm^{-1})			
					C=O lacton	C=O lactam	C-N	others
26	Ph-	136-138	75	Faint brown	1732	1672	1240	
27		228-230	77	Yellow	1745	1685	1255	C-O-C 1065
28		174-176	69	Greenish yellow	1745	1689	1282	C-O-C 1300
29	Ph-CH=CH-	151-153	76	Brown	1745	1645	1271	
30	CH_3CH=CH-	170-173	66	Deep yellow	1745	1660	1242	

Table V

Physical and IR spectral data of the 1,3,4-oxadiazolines (31-36)

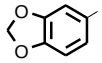
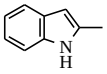
Compd. No.	R	M.P. °C	Yield %	Color	IR ν (Cm^{-1})			
					C=O	C-O Sym.	C-O Asym.	C=N
31	Ph-	121-123	75	Yellow	1732	1020	1242	1612
32		96-99	66	Yellow	1732	1032	1240	1651
33		108-110	75	Faint yellow	1732	1092	1240	1614
34	Ph-CH=CH-	99-102	60	Deep yellow	1732	1030	1255	1662
35	CH_3CH=CH-	113-115	55	Yellow	1718	1020	1240	1608
36		233-235	45	brown	1732	1012	1219	1614

Table VI

Physical and IR spectral data of the 1,3,4-oxadiazoles (37-42)

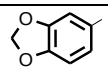
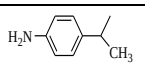
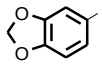
Compd. No.	R	M.P. °C	Yield %	Color	IR ν (Cm^{-1})			
					C=O	C-O Sym.	C-O Asym.	C=N
37	Ph-	121-123	75	Yellow	1732	1020	1242	1612
38		96-99	66	yellow	1732	1032	1240	1651
39		108-110	75	Faint yellow	1732	1092	1240	1614
40	Ph-CH=CH-	99-102	60	Deep yellow	1732	1030	1255	1662
41	CH_3CH=CH-	113-115	55	yellow	1718	1020	1240	1608
42		233-235	45	brown	1732	1012	1219	1614

Table VII

Physical and IR spectral data of 1,3-thiazolidin-4-ones (43-47)

Compd. No.	R	M.P. °C	Yield %	Color	IR ν (Cm^{-1})			
					C=O lactam	C=O amide	C-S-C	N-H
43	Ph-	120-123	70	orange	1736	1678	874	3248
44		121-123	65	yellow	1728	1630	872	3291
45		116-118	69	Faint brown	1726	1630	883	3249
46	Ph-CH=CH-	123-125	76	yellow	1736	1678	847	3211
47	CH_3CH=CH-	114-116	77	Yellowish brown	1730	1660	870	3278