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Synthesis of Pyrazolo [4,5]pyridazine and Isoxazolo [3,4d]pyridazine Derivatives

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Abstract □ Arylhydrazones of diethylacetondicarboxylate **3** was treated with formaldehyde to give 1-aryl-4,5,6-trihydropyridaine derivatives **4a-f** Cyclization of compound **4a-f** by hydroxylamine afforded [3,4d] 1,3,4,5-tetrahydropyridazine derivatives **5a-f**. Also cyclization of compound **4c** with semicarbazide gave 1-amidopyrazolo-5-one-1-aryl-3-carboxypyridazine **6**. On the other hand compound **3** reacted with ethylorthoformate to give diethyl-1,4-dihydro-1-arylpyridazine-4-one-2,5 dicarboxylate **7**, which on treatment with hydrazine, semicarbazide and thiosemicarbazide gave pyridazine, amido and thioamido derivatives. The spectral and antimicrobial data of these compounds **1-8** were studied.

Keywords □ Synthesis, pyrazolo[4,5] pyridazine, isoxazolo[3,4d] pyridazine, antimicrobial activity.

Synthesis of new compounds is described for pyridazine [4,5] derivatives which are an extention for the work done before[1], for the synthesis of azoles and fused azoles as both potential CNS re gulants and antimetabolite in purinebiochemical reactions. The treatment of arylhydrazones of diethylacetondicarboxylate **3** with formaldehyde in alcohol in presence of piperidine gave pyridazine derivatives **4** which are cyclized by hydroxylamine in ethanol and gave isoxazolo [3,4d] pyridazine derivatives **5**.

EXPERIMENTAL METHODS

All melting points are uncorrected. IR spectra (KBr disc) were recorded with a Pye Unicum Spectra-1000. ^{1}H-NMR spectra were recorded on a Wilmad 270 MHz Spectrometer in $(CD_3)_2SO$, $SiMe_4$ as an internal standard. Analytical analyses were carried out at Microanalytical center, Cairo University.

Preparation of diethylalpha-arylhydrazonoacetonedicarboxylates, 3

It was carried out as described before[1].

Preparation of 1,3,4,5-tetrahydropyridazine, 4a-f

0.01 mol of diethylalpha-hydrazonoacetondicarboxylate **3a-f** was treated with 3-5 m*l* CH_2O and 0.011 mol of piperidine were added. The reaction mixture was stirred then left overnight filter the precipitate and recrystallized from the proper solvent (Table I).

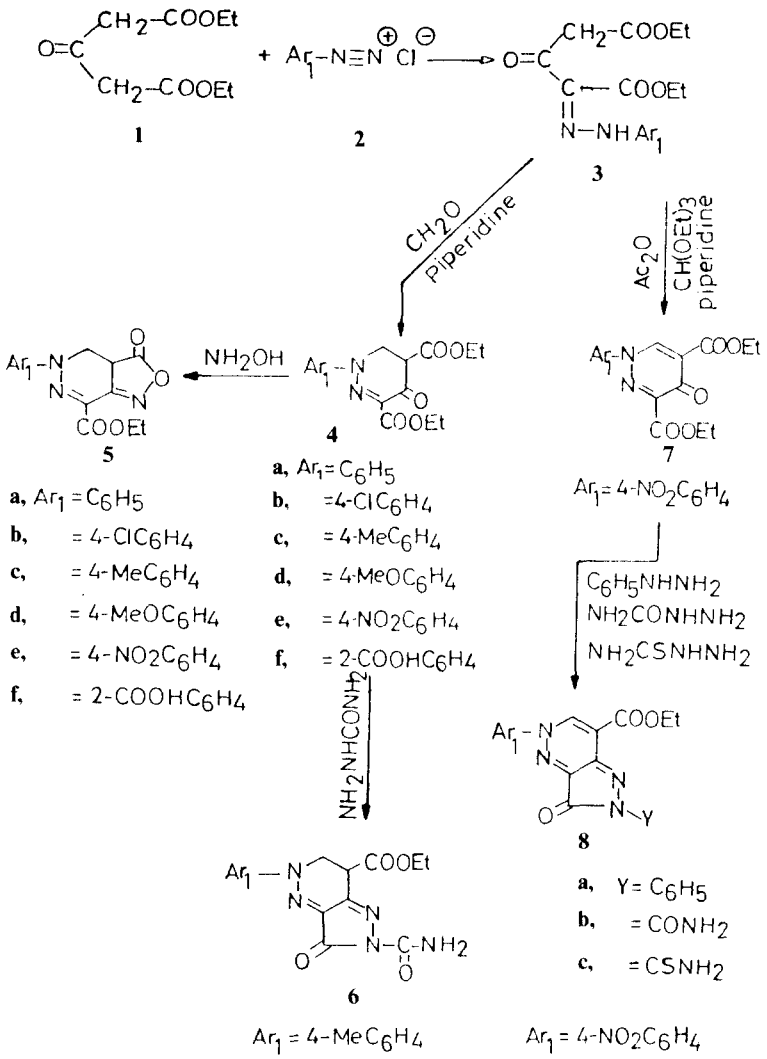
Preparation of isoxazolo[3,4-d]pyridazine derivatives, 5a-f

0.01 mol compound **4a-f** was treated with 0.01 mol hydroxylamine in 30 m*l* of ethanol containing 1g of sodium acetate. The reaction mixture was refluxed for 2 hrs cooled, filtered. The precipitate was washed well with water and recrystallized from the proper solvent (Table I).

Preparation of Pyrazolo[3,4-c]pyridazine, 6

When compound, **4** (0.01 mol) was treated with semicarbazide (0.01 mol) in 50 m*l* ethanol in the presence of 1g of sodium acetate. The reaction mixture was refluxed 3 hrs cooled, filtered washed with water and recrystallized (acetic acid). Table I.

Preparation of diethyl-1,4-dihydro-1-arylpyridazine-4-one-3,5-dicarboxylate, 7



Scheme 1

When 0.01 mol of compound **3** was mixed with 0.001 mol of triethylorthoformate and 1-2 drops of piperidine in presence of Ac_2O (10 ml). The reaction mixture was refluxed for 3 hrs then cooled, filtered and washed with water, recrystallized from the proper solvent (Table I).

Preparation of amidopyrazolo[3,4c]pyridazine, 8

0.01 mol of compound **7** was cyclized with NH_2-NH_2, semicarbazide and thiosemicarbazide (0.01 mol). The mixture was refluxed and treated as described in method and the amidopyrazolo [3,4d]-dihydropridazine was obtained (Table I).

Antimicrobial activity

An identified cultures of *Proteus vulgaris, Salmonella typhimurium, Bacillus cereus, Escherichia coli, Staphylococcus aureus, Helmenthosporium sp. Aspergillus wentii and Macrophomina phaseoli* were used as test organisms. The antimicrobial activity was assayed biologically. The inhibition zone of the test organisms by applying 25 mg of the chemical into a hole of 5 mm diameter were measured.

RESULTS AND DISCUSSION

The structures of these products were evidenced

Table I. List synthesized compounds 4a-f, 5a-f, 6, 7 and 8a-c

Compound No.	mp. ℃	Yield %	Molec. Form (Mol. Wt.)	Analysis Calc./Found C	H	N	Cl
4a	230	60	$C_{16}H_{18}N_2O_5$	60.37	5.69	8.8	
	alc.		(318.34)	60.00	5.80	8.2	
4b	222	60	$C_{16}H_{17}N_2O_5Cl$	54.48	4.86	7.9	10
	alc.		(325.77)	54.00	4.50	7.6	10.2
4c	218	65	$C_{17}H_{20}N_2O_5$	61.44	6.06	8.43	
	alc.		(332.35)	61.20	5.50	8.20	
4d	220	60	$C_{17}H_{20}N_2O_6$	58.61	5.78	8.04	
	alc.		(348.35)	58.90	5.20	8.00	
4e	158	65	$C_{16}H_{17}N_3O_7$	52.89	4.80	11.57	
	AcOH		(363.33)	52.50	4.50	11.00	
4f	200	60	$C_{17}H_{18}N_2O_7$	56.35	4.97	7.73	
	AcOH		(362.35)	55.70	4.70	7.00	
5a	135-7	60	$C_{14}H_{13}N_3O_4$	58.53	4.56	14.63	
	alc.		(287.28)	58.10	4.20	14.20	
5b	121	60	$C_{14}H_{12}N_3O_4$	52.27	3.76	13.06	11.02
	AcOH		(321.72)	52.70	3.20	13.00	11.10
5c	220	60	$C_{15}H_{15}N_3O_4$	59.80	5.02	13.94	
	alc.		(301.31)	60.20	5.20	13.50	
5d	196	60	$C_{15}H_{15}N_3O_5$	56.78	4.76	13.24	
	alc.		(317.31)	56.20	4.50	13.10	
5e	195	65	$C_{14}H_{12}N_4O_6$	50.61	3.46	16.86	
	AcOH		(332.27)	50.40	3.50	16.50	
5f	208	60	$C_{15}H_{13}N_3O_6$	54.38	3.96	12.68	
	alc.		(331.00)	54.30	4.10	12.20	
6	200	60	$C_{16}H_{14}N_5O_4$	56.47	4.12	20.54	
	AcOH		(340.00)	56.00	4.00	20.10	
7	194	60	$C_{16}H_{15}N_3O_7$	53.19	4.67	11.63	
	AcOH		(361.00)	53.00	4.20	11.00	
8a	228	60	$C_{20}H_{15}N_5O_5$	59.26	3.70	17.28	
	AcOH		(405.00)	59.00	3.50	17.00	
8b	295	60	$C_{15}H_{12}N_6O_6$	48.39	3.23	22.58	
	alc.		(372.00)	48.50	3.10	22.20	
8c	190	65	$C_{15}H_{12}N_6O_5S$	46.39	3.09	21.05	
	AcOH		(388.00)	45.90	3.10	20.91	

by their elemental and spectral data. The ^{1}H-NMR spectra for pyridazine derivative **4** revealed for the 1-aryl-4,5,6-trihydropyridazine, the aromatic protons at δ 6-8 ppm, the methyl group of the ethyl ester at δ 1.4 ppm triplete at δ 2-3 ppm and guartet for the CH_2 group. The methylene group at position 6, at δ 4.0 ppm. The CH at position 5 appears at δ 4.5 ppm. IR spectra of the compound **4** showed the carbonyl group at 1660 cm $^{-1}$ also the ester carbonyl at 1750 cm $^{-1}$ and at 1610 cm^{-1} for C=N. Also the ^{1}H-NMR spectra of compound **5** which is obtained by cyclization of pyridazinedicarboxylate with hydroxylamine revealed the aromatic protons at δ 6-8 ppm, the alkyl group CH_2-CH_3 at δ 1.4 and 2.3 ppm which appeared as triplet for CH_3 quartet for CH_2, at δ 4 ppm for CH_2 in pyridazine ring and at 4.5 for CH. The IR spectra showed the cyclic C=O in isoxazolone at 1740 cm^{-1}, the ester C=O at 1720 cm^{-1} and at 1620 for C=N in the ring.

On the other hand, the cyclization of pyridazine **4** with semicarbazide gave pyrazolo 1,3,4,5-tetra-

Table II. ^{1}H-NMR data of compound [δ/ppm in $(CD_3)SO$]

Compound No.	^{1}H-NMR δ ppm
4-a	1.4[t, 6H, 2-CH_3](Et. gp.); 2.8[q, 4H, 2-CH_2](Et. gp.); 6-8[m, 5H, ph]; 4.0 (d, 2H, 1-CH_2] and 4.5[s, 1H, CH].
4-b	1.3[t, 6H, 2-CH_3](Et. gp.); 2.7[q, 4H, 2-CH_2]; 6-8[m, 4H, C_6H_4]; 3.19[d, 2H, 1-CH_2] and 4.5[dd 1H, CH].
4-c	1.3[t, 6H, 2-CH_3]; 2.9[q, 4H, 2-CH_2](Et. gp.); 6-8[m, 4H, C_6H_4]; 3.8[d, 2H, 1-CH_2]; 4.5[dd, 1H, CH] and 2.28[s, 3H, CH_3-Ar].
4-d	1.4[t, 6H, 2-CH_3](Et. gp.); 2.8[q, 4H, 2-CH_2]; 6-8[m, 4H, C_6H_4]; 3.9[d, 2H, 1-CH_2]; 4.5[dd, 1H, CH] and 3.5[s, 3H, CH_3-O-Ar].
4-e	1.6[t, 6H, 2-CH_3](Et. gp.); 2.8[q, 4H, 2-CH_2](Et. gp.); 6-8[m, 4H, C_6H_4]; 3.9[d, 2H, 1-CH_2]; and 4.5[dd, 1H, CH].
4-f	1.4[t, 6H, 2-CH_3](Et. gp.); 2.8[q, 4H, 2-CH_2](Et. gp.); 6-8[m, 4H, C_6H_4]; 3.9[d, 2H, 1-CH_2]; 4.5[dd, 1H, CH] and 10.2[s, H, COOH].
5-a	1.4[t, 3H, 1-CH_3](Et. gp.); 2.3[q, 2H, CH_2]; 4[d, 2H, CH_2]; 6-8[m, 5H, C_6H_5] and 4.1[dd, H, CH].
5-b	1.5[t, 3H, 1-CH_3](Et. gp.); 2.4[q, 2H, CH_2](Et. gp.); 4[d, 2H, CH_2]; 6-8[m, 4H, 4-Cl-C_6H_4] and 4.2[dd, H, CH].
5-c	1.5[t, 3H, 1-CH_3](Et. gp.); 2.3[q, 2H, CH_2](Et. gp.); 4[d, 2H, CH_2]; 6-8[m, 4H, C_6H_4]; 2.28[s, 3H, CH_3-Ar] and 4.0[dd, H, CH].
5-d	1.4[t, 3H, 1-CH_3](Et. gp.); 2.3[q, 2H, CH_2](Et. gp.); 4[d, 2H, CH_2]; 6-8[m, 4H, C_6H_4]; 4.0[s, 3H, CH_3-O-Ar] and 4.15[dd, H, CH].
5-e	1.5[t, 3H, 2-CH_3](Et. gp.); 2.4[q, 2H, CH_2](Et. gp.); 4[d, 2H, CH_2]; 6-8[m, 4H, C_6H_4] and 4.20[dd, H, CH].
5-f	1.4[t, 3H, 1-CH_3](Et. gp.); 2.3[q, 2H, CH_2](Et. gp.); 4[d, 2H, CH_2]; 6-8[m, 4H, C_6H_4]; 10[s, 1H, COOH and 4.0[dd, 1H, CH].
6-a	1.4[t, 3H, 1-CH_3](Et. gp.); 2.3[q, 2H, CH_2](Et. gp.); 4[d, 2H, CH_2]; 9.5[s, 2H, NH_2] and 6-8[m, 4H, C_6H_4]; 2.28[s, 3H, CH_3-Ar] and 4.5[dd, H, CH].
7	1.4[t, 3H, 1-CH_3](Et. gp.); 2.3[q, 2H, CH_2](Et. gp.); 6-8[m, 4H, C_6H_4] and 8.6[s, H, CH].
8-a	1.3[t, 3H, 1-CH_3](Et. gp.); 2.3[q, 2H, CH_2](Et. gp.); 6-8[m, 10H, 2-C_6H_5] and 8.10[s, 2H, 2-CH].
8-b	1.3[t, 3H, 1-CH_3](Et. gp.); 2.3[q, 2H, CH_2](Et. gp.); 6-8[m, 5H, 1-C_6H_5] 8.2[s, 2H, 2-CH] and 9.5[s, 2H, NH_2].
8-c	1.3[t, 3H, 1-CH_3](Et. gp.); 2.3[q, 2H, CH_2](Et. gp.); 6-8[m, 5H, 1-C_6H_5] 8.1[s, 2H, 2-CH] and 9.4[s, 2H, NH_2].

Table III. Antimicrobial activity of the synthesized compounds against wide range of microorganisms. Data are expressed as mean diameter of inhibition zones of test organisms (mm), 0.0, not detected

Compound No.	Test organisms								
	Macroph. phaseoli	Staphy. aureus	Bacill. cereus	Proteus vulgaris	Salmonella typhimurium	E. coli	Fusarium oxysporium	Asperg. wentii	Helmentho-sporium sp.
4b	20	0	0	0	0	0	0	0	20
4d	0	25	25	0	30	0	30	20	0
5b	0	0	0	0	0	15	30	0	0
5f	0	0	0	35	0	0	0	0	0

No antimicrobial activities were detected against *Bacillus megaterium, Shigella flexxneri, Pseudomonas aeruginosa, Serratia Marcescens* and *Cunninghamella elegans*.

hydropyridazine derivative **6** which showed ^{1}H-NMR the aromatic protrons at δ 6-8 ppm, the alkyl group of CH_2-CH_3 guartet and triplet at δ 4 and at δ 2-3 ppm. The proton NH at δ 9.5 ppm. The proton of CH group of pyridazine at δ 4.5 ppm. The methylene of pyridazine at δ 4 ppm. The methine CH proton at δ 4.5 ppm. The IR of pyrazolopyridazine **6** showed the cyclic C=O at 1735 cm^{-1}, the ester carbonyl at 1720 cm^{-1}, the free NH_2 group at 3400 cm^{-1}, 1600 cm^{-1} and the amide carbonyl at 1670 cm^{-1}.

The treatment of arylhydrazones of ethylacetonedicarboxylate with ethylorthoformate[2] in acetic anhydride gave 7,1-arylpyridazine-3,5-dicarboxylate-4-one which its ^{1}H-NMR showed also the aromatic protons at δ 6-8 ppm, the alkylprotons of ester groups at 1.4 and 2.3, for the ethyl protons. The CH protons at position 6 at δ 8.6 ppm. The IR consistent with the suggested structure of these compounds.

The compound **7** on treatment with hydrazinesemicarbazide and thiosemicarbazide afforded the amidopyrazolo[3,4c] pyridazine which showed ^{1}H of the aromatic protons at δ 6-8 ppm, the alkylester group at δ 2-3 and 1.4 ppm also for the NH at δ 9.5 ppm, for compound **8b** and **8c** at 8.2, 8.1 ppm for the CH group. The data of NMR is tabulated in Table II.

Antimicrobial activities

The antimicrobial activity of compound **4b** and **4d** against wide variety of microorganisms are shown in Table III. Compound **5d** exhibited very poor antimicrobial activity against *Escherichia coli* and showed high antimicrobial activity against *Fusarium oxysporium*. Alternatively, it showed no activity against the other used test microorganisms. While, compound **5f** exhibited high antimicrobial activity against *Proteus vulgaris*, but showed no antimicrobial activity against the rest of the used test organisms.

On the other hand, compound **4d** showed antimicrobial activity against several bacteria; *Staphyllococcus aureus. Bacillus cereus* and *Salmonella typhimurium* as well as against two fungal species; *Fusarium oxosporium* and *Aspergillus wentii*. Such high antimicrobial activity of compound **4d** against wide range of microorganisms could be of applicable use. Compound **4b** exhibited moderate antimicrobial activity only against two fungal isolates *Helmenthosporium sp.* and *Macrophomina phaseoli*.

Conclusively, compound **5b**, **5f** and **4b** seem to be of no applicable use as antimicrobial agents, while compound **4d** could be used as antimicrobial agent against specific microorganisms of different taxa.

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