Synthesis and Reactions of Some New Pyridazinones

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Synopsis. 3-(*p*-Ethoxybenzoyl)acrylic acid (**1**) reacts with 3-methyl-1-phenyl-2-pyrazolin-5-one to give an addition compound **2**. The condensation of **2** with hydrazine hydrate affords 4,5-dihydro-3(2*H*)-pyridazinone (**3a**). Reaction of **3a** with dimethyl sulfate, diethyl sulfate, ethyl bromoacetate, $POCl_3$, and P_2S_5 gave the N-substituted pyridazinones **3b—d**, a dichloro derivative **5a**, and a dithione **7**. The behavior of the dichloro and the dithione derivatives was studied toward different reagents. The *in vitro* antibacterial screening reveals moderate activity against Gram-positive for compounds **3a** and **3c** while **4** and **7** are inactive.

A large number of pyridazinones are reported to exhibit bactericidal activities.[1-4] Direct methods for introduction of oxygenated substituents into aromatic rings are often quite limited. Anodic oxidation is potentially an excellent procedure for direct introduction of oxygen functionalities into aromatics.[5] In addition, efficiency of the anodic oxidation of para-substituted aromatic ethers[6] prompted the author to synthesize a new series of pyridazinones, through the nucleophilic addition of 3-methyl-1-phenyl-2-pyrazolin-5-one to 3-(*p*-ethoxybenzoyl)acrylic acid followed by cyclization of the adduct to give the corresponding dihydropyridazinone. The synthesis of various compounds (**2**—**9**) are outlined in Scheme 1.

Thus, the reaction of 3-(*p*-ethoxybenzoyl)acrylic acid[7] (**1**) with 3-methyl-1-phenyl-2-pyrazolin-5-one[8] in dry benzene gave 4,5-dihydro-α-[2-(4-ethoxyphenyl)-2-oxoethyl]-3-methyl-5-oxo-1-phenyl-1*H*-pyrazole-4-acetic acid (**2**). Structure[a] of the acid **2** was derived from its infrared spectrum which showed ν C=O (acid) at 1700, ν C=O at 1675 and ν C=N at 1605. The reaction of the acid **2** with hydrazine hydrate in boiling ethanol yielded 6-(*p*-ethoxyphenyl)-4-(5-oxo-2-pyrazolin-4-yl)-4,5-dihydro-3(2*H*)-pyridazinone (**3a**). The IR spectrum of **3a** showed ν C=O at 1655, ν C=N at 1605 and ν NH at 3430. Reaction of **3a** with dimethyl sulfate, diethyl sulfate, and ethyl bromoacetate gave the N-substituted products **3b—d**. The IR spectra of **3b—d** showed ν C=O at 1660—1630, ν C=N 1600—1585, and additional band at 1740 for **3d** attributable to ν C=O (ester). Condensation of **3a** with *p*-anisaldehyde in the presence of ethanolic KOH took place at the 5-position[9] to give 4,5,6-trisubstituted pyridazin-3(2*H*)-one (**4**). The IR specrum of **4** showed bands at 1650 (ν C=O), 1600 (ν C=N), and 3390 (ν NH).

This work reports on the behavior of the pyridazinone derivative towards nucleophilic reagents like phosphoryl chloride. Treatment of **3a** with $POCl_3$ gave the dichloro derivative **5a**. The IR spectrum of **5a** was devoid of ν C=O and showed ν C=N at 1605. The ^{1}H NMR (DMSO-d_6) of **5a** showed signals at δ=8.1—6.9 (9H, m, Ar-H), 3.9—2.7 (5H, m, CH_2CH+CH_2 of ethyl), 2.30 (3H, s, CH_3) and 1.32 (3H, t, CH_3 of ethyl). The dichloro derivative **5a** reacted with sodium methoxide to give the dimethoxy derivative **5b**. The IR spectrum showed ν C=N at 1610. Reaction of **5a** with hydrazine hydrate in ethanol gave the dihydrazino derivative **5c**. The IR spectrum showed ν C=N at 1600 and ν NH at 3170. Compound **5c** condensed with aromatic aldehydes namely benzaldehyde, *p*-anisaldehyde, and *p*-tolualdehyde and yielded the bis (hydrazone) derivatives **5d—f** which showed ν C=N at 1605—1600 and ν NH at 3420—3400. The reaction of the dichloro derivative **5a** with sodium azide gave compound **6**. The IR spectrum of **6** showed ν C=N at 1590. ^{1}H NMR (DMSO-d_6) of **6** showed signals at δ=8.08—7.2 (9H, m, Ar-H), 3.8—2.7 (5H, m, CH_2–, CH, +CH_2 of ethyl), 2.20 (3H, s, CH_3), and 1.32 (3H, t, CH_3 of ethyl). An alternative route for the preparation of compound **6** was the reaction of the dihydrazino derivative **5c** with nitrous acid to give the same compound **6**. The similarity of these compounds were identified by IR spectra and by mixed melting point determination with the sample prepared before.

Compound **3a** reacted with P_2S_5 in dry xylene to give the dithioxo derivative **7**. Compound **7** evidently exists in the mercapto–thioxo equilibrium. The IR spectrum exhibited bands for ν N–C=S at 1470, ν C=S at 1385, ν C=N at 1600 and band at 3420 evidently for ν SH. The ^{1}H NMR (DMSO-d_6) of **7** showed signals at δ=8.0—7.7 (10H, m, Ar-H+pyridazine proton), 3.43 (2H, q, CH_2 of ethyl), 3.30 (1H, s, pyrazolethione proton), 2.29 (3H, s, CH_3), and 1.34 (3H, t, CH_3 of ethyl). Treatment of **7** with dimethyl sulfate, diethyl sulfate, and/or methyl acrylate in dry acetone yielded the corresponding S-substituted derivatives **8a—c**, respectively. The IR spectra of **8** showed bands at 1605 (ν C=N) in addition to a strong band at 1725 of the ν C=O (ester) for compound **8c**. Compound **7** was easily oxidized to the cyclic disulfide **9** by iodine solution and the IR spectrum of **9** showed ν C=N at 1600.

Screening for an Antibacterial Activity. The prepared compounds **3a**, **3c**, **4**, and **7** were tested for *in vitro* antibacterial activity using the method described by Heatly.[6] The medium for screening was composed of (g 11000 ml) "Lab-lemco" beef extract, 1.0; yeast extract (Oxoid 120), 20; peptone (Oxoid L 37), 5.0; sodium chloride, 2.0, and agar, 15.0 (pH 7.0). Cylinders of known volume (0.1 ml) were placed on the solid medium seeded with a Gram-positive and Gram-negative test organism. A known constant volume (0.05 ml) of the compounds **3a**, **3c**, **4**, and **7** dissolved in SDS was introduced into each cylinder and allowed to diffuse through the agar at room temperature for 1 h and finally incubated at 37 °C for about 18—20 h. Clear circular zones of inhibition of the test organisms were formed around the holes containing compounds **3a** and **3c**. It

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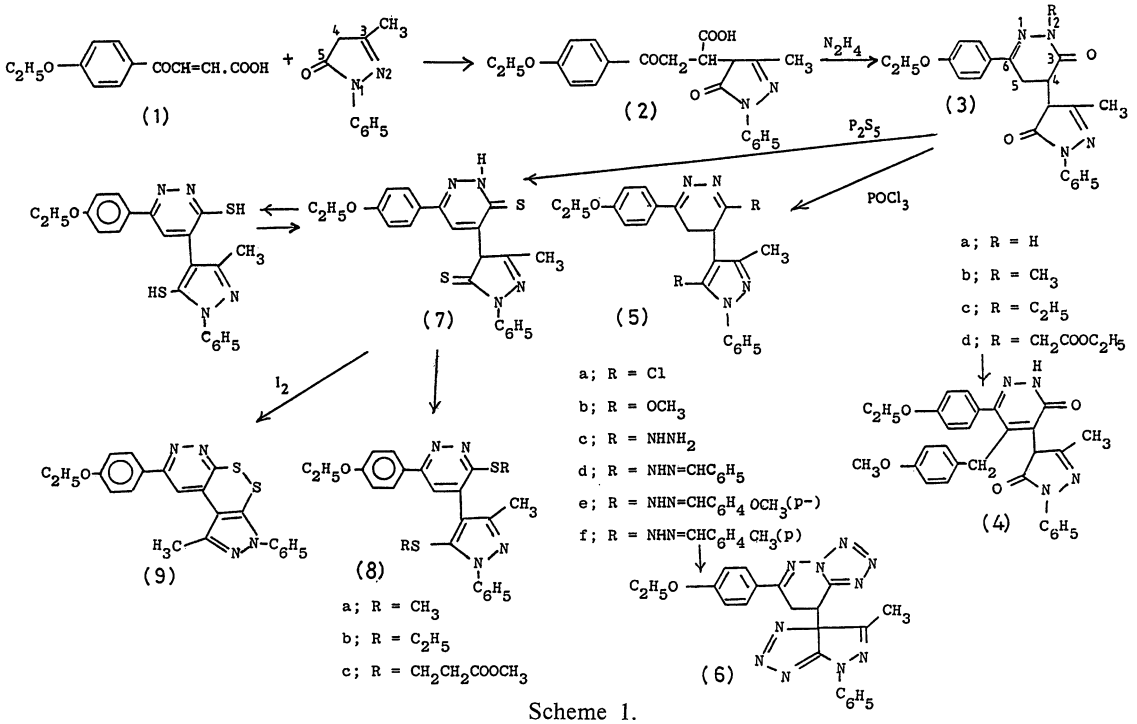
a) IR_{max} here and elsewhere in the paper in cm^{-1}.



Scheme 1.

Table 1. *In Vitro* Antibacterial Activities of Some of the Prepared Compounds[a)]

Compound	*Staphylococcus aureus*	*Echerichia Coli*	*Pseudomonas auregonosa*
3a	++	++	++
3c	++	++	+
4	−	−	−
7	−	−	−

a) (−) No antibacterial activity of the zone equal to 1 cm. (+) Mild activity with the diameter of the zone equal to 1 cm. (++) Moderate activity with the diameter of the zone equal to 1.8 cm.

is suggested that compounds **3a** and **3c** possess moderate activities against Gram-positive as shown in Table 1.

Experimental

All melting points are uncorrected. The IR spectra (KBr discs) were recorded on a Unicam SP 1200 spectrophotometer. The ^{1}H NMR spectra were obtained on a JEOL FX-100 Fourier transform instrument using tetramethylsilane as internal standard. Physical data of **2**—**9** are summarized in Table 2.

Preparation of Compound 2. To a solution of **1**[7)] (0.01 mol) in dry benzene (20 ml), 3-methyl-1-phenyl-2-pyrazolin-5-one[8)] (0.01 mol) was added and the reaction mixture refluxed for 10 h. The solid that separated on cooling was crystallized from ethanol to give **2**.

Preparation of Compounds 3a, 5c, and 5d—f. To a solution of **2**, **5a**, or **5c** (0.01 mol) in ethanol (20 ml), hydrazine hydrate, benzaldehyde, *p*-anisaldehyde, or *p*-tolualdehyde (0.01 or 0.02 mol) was added and the reaction mixture refluxed for 5 h. The solid that separated on cooling was crystallized from a suitable solvent to give **3a**, **5c**, and **5d—f**, respectively.

Preparation of Compounds 3b—d and 8a,b. A mixture of **3a** or **7** (0.01 mol), anhydrous potassium carbonate (0.03 mol), dimethyl sulfate, diethyl sulfate, or ethyl bromoacetate (0.03 mol), and dry acetone (50 ml) was refluxed for 20 h. After removing the excess solvent the products were crystallized from the proper solvent to give compounds **3b—d** and **8a,b**.

Preparation of Pyridazinone 4. A warm solution of **3a** (0.01 mol) in ethanol (20 ml) was treated with an ethanolic KOH solution (25 ml, 4%) and *p*-anisaldehyde (0.01 mol) was added portionwise with continuous shaking. The reaction mixture was refluxed for 2 h, cooled, poured into cold water and the solid obtained crystallized from the proper solvent to give **4**.

Preparation of Dichloro Derivative 5a. A mixture of **3a** (0.01 mol) and $POCl_3$ (10 ml) was gently refluxed for 30 min, cooled, and treated with crushed ice. The precipitated solid was filtered and crystallized from a suitable solvent to give **5a**.

Preparation of Dimethoxy Derivative 5b. The dichloro compound **5a** (0.01 mol) was added to sodium methoxide solution [from sodium (0.02 mol) in absolute methanol (50 ml)]. The mixture was refluxed for 2 h, then evaporated under reduced pressure. To the residue was added water (10 ml) and insoluble matter was filtered off and crystallized from suitable solvent to give **5b**.

Formation of Compound 6. (a) A mixture of **5a** (1.0 g), sodium azide (2.0 g), water (5 ml), and *N*,*N*-dimethylformamide (20 ml) was boiled for 2 h and cooled. The solid obtained upon dilution with water was filtered and crystallized from a suitable solvent to give **6** (in 55% yield).

(b) An aqueous solution of $NaNO_2$ (0.03 mol in 10 ml H_2O) was added dropwise with stirring to a solution of **5c** (0.01 mol) in 4 M (M=mol dm^{-3}) acetic acid (10 ml) and stirring was continued for 1 h. The solid formed was filtered and crystallized from a suitable solvent to give **6** (in 49% yield).

Preparation of Dithione 7. A solution of **3a** (0.01 mol) and P_2S_5 (0.03 mol) in dry xylene (50 ml) was boiled under reflux for 6 h. The reaction mixture was filtered while hot and then concentrated. The product which separated on cooling was crystallized from a suitable solvent to give **7**.

Preparation of Compound 8c. A solution of **7** (0.01 mol) and methyl acrylate (0.02 mol) in ethanol (20 ml) was treated with a few drops of 10% aqueous sodium hydroxide solution and the mixture heated under reflux for 12 h. The solid formed after cooling was crystallized from a suitable solvent to

Table 2. Physical Data of Various Compounds Prepared

Compound	Mp/°C (Solvent)	Yield/%	Mol formula	Analysis/% Found/Calcd		
				C	H	N
2	210 (Ethanol)	46	$C_{22}H_{22}N_2O_5$	F 67.20 C 66.99	5.40 5.62	6.90 7.10
3a	188 (Acetic acid)	60	$C_{22}H_{22}N_4O_3$	F 67.80 C 67.68	5.71 5.68	14.30 14.35
3b	183 (Benzene)	68	$C_{23}H_{24}N_4O_3$	F 68.40 C 68.30	6.11 5.98	13.75 13.85
3c	202 (Benzene)	59	$C_{24}H_{26}N_4O_3$	F 68.90 C 68.88	6.40 6.26	13.52 13.39
3d	180 (Benzene)	57	$C_{26}H_{28}N_4O_5$	F 65.62 C 65.53	5.78 5.92	11.83 11.76
4	199 [Benzene: Ethanol(1 : 1)]	50	$C_{30}H_{28}N_4O_4$	F 70.94 C 70.85	5.53 5.55	10.82 11.02
5a	160 (Methanol)	45	$C_{22}H_{20}Cl_2N_4O$	F 61.63 C 61.83	4.82 4.72	12.97 13.11
5b	135 (Pet.ether 80—100)	73	$C_{24}H_{26}N_4O_3$	F 68.91 C 68.88	6.30 6.26	13.52 13.39
5c	160 [Benzene: Ethanol(1 : 1)]	70	$C_{22}H_{26}N_8O$	F 63.40 C 63.14	6.32 6.26	26.51 26.78
5d	283 (Acetic acid)	68	$C_{36}H_{34}N_8O$	F 72.79 C 72.71	5.70 5.76	18.83 18.84
5e	260 (Acetic acid)	73	$C_{38}H_{38}N_8O_3$	F 69.84 C 69.71	5.63 5.85	16.89 17.11
5f	270 (Acetic acid)	70	$C_{38}H_{38}N_8O$	F 73.52 C 73.29	5.93 6.15	18.12 17.99
6	185 (Ethanol)	55	$C_{22}H_{20}N_{10}O$	F 59.83 C 59.99	4.52 4.58	31.87 31.80
7	241 (DMF)	69	$C_{22}H_{20}N_4OS_2$	F 62.92 C 62.83	4.83 4.79	13.52 13.32
8a	138 (Pet.ether 80—100)	63	$C_{24}H_{24}N_4OS_2$	F 64.43 C 64.26	5.62 5.39	12.50 12.49
8b	125 (Pet.ether 80—100)	57	$C_{26}H_{28}N_4OS_2$	F 65.83 C 65.51	5.92 5.92	11.81 11.75
8c	100 (Pet. ether 80—100)	71	$C_{30}H_{32}N_4O_5S_2$	F 60.60 C 60.79	5.29 5.44	9.73 9.45
9	239 (DMF)	76	$C_{22}H_{18}N_4OS_2$	F 63.43 C 63.13	4.32 4.34	13.58 13.39

give **8c**.

Formation of 1,2-Dithiin Derivative 9. A solution of iodine (0.02 mol) in 5% aqueous KI solution (100 ml) was added dropwise with stirring to a solution of **7** (0.01 mol) in 10% aqueous sodium hydroxide (10 ml) until the color of iodine persisted. The solid formed was filtered off and crystallized from a suitable solvent to give **9**.

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