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Synthesis and Biological Activity of some new Pyridazine Derivatives

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Summary. Condensation of β-aroyl-α-[1,3-diphenyl-5(4*H*)-oxo-pyrazol-4-yl] propionic acid with hydrazine hydrate affords 4,5-dihydro-3(2*H*)-pyridazinone (**2**). Reaction of **2** with $POCl_3$ and P_2S_5 gives a dichloro derivative (**7**) and a dithione (**4**). The behavior of the dichloro and dithione derivatives toward various reagents was studied. The *in vitro* antibacterial screening reveals moderate activities against certain bacteria.

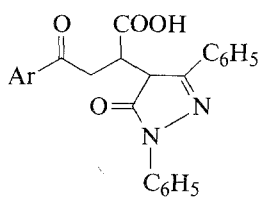
Keywords. Pyridazinone; Pyridazinethione; Chloropyridiazine.

Synthese und biologische Aktivität einiger neuer Pyridazinderivate

Zusammenfassung. Kondensation von β-Aroyl-α-[1,3-diphenyl-5(4*H*)-oxo-pyrazol-4-yl]-propionsäure mit Hydrazinhydrat ergibt 4,5-Dihydro-3(2*H*)-pyridazinon (**2**). Reaktion von **2** mit $POCl_3$ und P_2S_5 liefert ein Dichlorderivat (**7**) und ein Dithion (**4**). Das Verhalten dieser beiden Verbindungen gegenüber verschiedenen Reagentien wurde untersucht. Antibakterielles screening (*in vitro*) ergab mäßige Aktivität gegenüber verschiedenen Bakterienstämmen.

Introduction

A recent publication dealing with the synthesis and antibacterial screening of pyridazinones revealed that some of these compounds exhibited activities against *gram*-positive and *gram*-negative bacteria [1–4]. In continuation of our studies [5, 6] on the synthesis of new pyridazinone compounds, we now report the preparation of a new series of pyridazinones to screen their antibacterial activities. The syntheses of various compounds (**1**–**14**) are outlined in Scheme 1.



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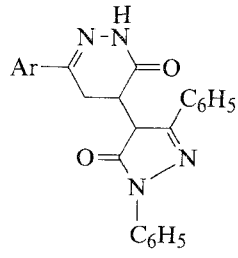

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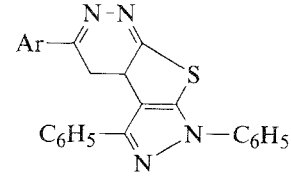

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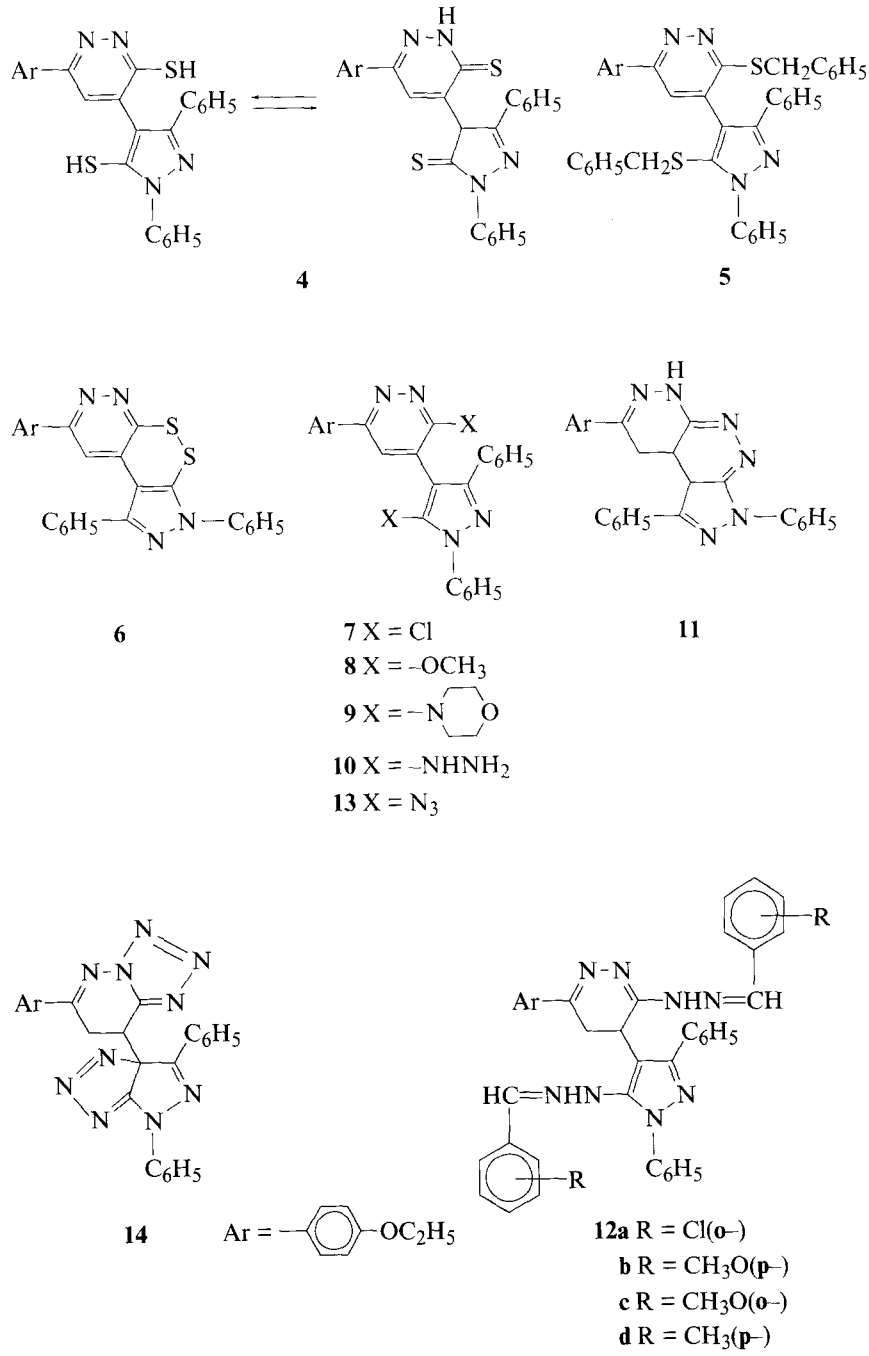

Scheme 1

Results and Discussion

The reaction of 3-(*p*-ethoxybenzoyl) acrylic acid [7] with 1,3-diphenyl-2-pyrazolin-5-one [8] in dry benzene gave 4,5-dihydro-α-[2-(4-ethoxyphenyl)-2-oxoethyl]-1,3-diphenyl-5-oxo-1 *H*-pyrazole-4-acetic acid (**1**). The structure of the acid **1** was derived from its infrared spectrum # which showed ν(C=O) (acid) at 1710, ν(C=O) at 1665,

and ν(C=N) at 1595. Reaction of **1** with hydrazine hydrate in boiling ethanol yielded 6-(*p*-ethoxyphenyl)-4-(5-oxo-2-pyrazolin-4-yl)-4,5-dihydro-3(2*H*)-pyridazinone (**2**). The IR spectrum of **2** showed ν(C=O) at 1660, ν(C=N) at 1600, and ν(NH) at 3430.

Compound **2** was reacted with *Lawsson* reagent in dry xylene. In an attempt to synthesize thienopyridazine, **3** instead dithioxo derivative **4** was obtained. Compound **4** evidently exists in a 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 a band at 3420 (ν(SH)). The ^{1}H NMR spectrum (*DMSO*-d_6) of **4** showed signals at $\delta = 7.7$–7.1 (15H, m, Ar–H + pyridazine proton), 3.43 (2H, q, CH_2 of ethyl), 3.30 (1H, s, pyrazolethione proton), and 1.34 (3H, t, CH_3 of ethyl) ppm.

The reaction of phenylmethanethiol with **7** gave a product identical with compound **5** obtained from the reaction of benzyl chloride with **4**. The IR spectrum of **5** showed ν(C=N) at 1605 and was devoid of ν(C=S). Compound **4** was easily oxidized to the cyclic disulfide **6** by iodine solution; the IR spectrum of **6** showed ν(C=N) at 1600. Treatment of **2** with $POCl_3$ gave the dichloro derivative **7**.

The IR spectrum of **7** was devoid of ν(C=O) and showed ν(C=N) at 1605. The ^{1}H NMR spectrum (*DMSO*-d_6) of **7** showed signals at $\delta = 7.7$–6.8 (14H, m, Ar–H), 3.9–2.7 (5H, m, $CH_2CH + CH_2$ of ethyl), and 1.32 (3H, t, CH_3 of ethyl) ppm.

The dichloro derivative **7** reacted with sodium methoxide to give the dimethoxy derivative **8**. The IR spectrum showed ν(C=N) at 1610. Reaction of **7** with morpholine in dry toluene resulted in dechloroamination, affording the dimorpholino derivative **9** which showed ν(C=N) at 1605. When compound **7** was allowed to react with hydrazine hydrate in ethanol, the dihydrazino derivative **10** was obtained instead of pyridazinopyridazine **11**. The IR spectrum showed ν(C=N) at 1600 and ν(NH) at 3170.

Condensation of the hydrazino derivative **10** with aromatic aldehydes (*o*-chlorobenzaldehyde, *p*-anisaldehyde, *m*-chlorobenzaldehyde, and benzaldehyde) gave the *bis*(hydrazone) derivatives **12a–d** which showed ν(C=N) at 1605–1600 and ν(NH) at 3420–3400. The reaction of the dihydrazino derivative **10** with nitrous acid gave compound **14**, presumably *via* azido derivative **13**. The IR spectrum of **14** showed ν(C=N) at 1590. An alternative route for the preparation of compound **14** was the reaction of the dichloro derivative **7** with sodium azide. The similarity of these compounds was identified by IR spectroscopy and mixed melting point analysis with the sample prepared before.

Screening for antibacterial activity

Compounds **2**, **4**, **5**, **8**, and **14** were tested for *in vitro* antibacterial activity using the method described by *Heatly* [9]. The medium for screening was composed of (g 11000 ml) "Lab-lemco" beef extract, 1.0; yeast extract (Oxoid 120), 20; peptone (Oxoid L37), 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 compounds **2**, **4**, **5**, **8**, and **14** dissolved in SDS was introduced into each cylinder, allowed to diffuse through the agar at room temperature for 1 h, and finally incubated at 37 °C for about 18–20 h. The zone of inhibition of bacterial growth around the disc was

Table 1. *In vitro* antibacterial activities of some of the prepared compounds[a]

Compound	Staphylococcus aureus	Echerichia coli	Pseudomonas auregonosa	Bacillus subtilis	Proteus
2	−	++	−	++	+++
4	−	+++	−	+	+++
5	−	++	+	+++	+
8	−	+	−	+	−
14	++	++	−	+++	+

[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 1.6 cm; (+++): good activity with the diameter of the zone equal to 2.1 cm

observed. The screening results given in Table 1 indicate that all the compounds exhibit antibacterial activities against various bacteria. Almost all compounds showed more inhibition against *E. coli*, *B. subtilis*, and *Proteus*, whereas inhibition towards *Staphylococcus aureus* and *Pseudomonas auregenosa* was less.

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 *TMS* as internal standard. Physical data are summarized in Table 2.

β-(4-Ethoxybenzoyl)-α-(1,3-diphenyl-5(4H)-oxo-pyrazolin-4-yl) propionic acid (**1**)

To a solution of 3-(*p*-ethyoxybenzoyl) acrylic acid (0.01 mol) in dry benzene (20 ml), 1,3-diphenyl-2-pyrazolin-5-one (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 **1**.

4,5-Dihydro-6-(4-ethoxyphenyl-4-[1,3-diphenyl-5(4H)-oxo-pyrazolin-4-yl]-3(2H) pyridazinone (**2**)

4,5-dihydro-3-hydrazino-6-(4-ethoxyphenyl)-4-(1,3-diphenyl-5-hydrazinopyrazolin-4-yl) pyridazine (**10**), 4,5-dihydro-3-(aryl methylene hydrazonyl)-6-(4-ethoxyphenyl)-4-(1,3-diphenyl-5-arylmethylene hydrazonylpyrazolin-4-yl) pyridazine (**12a–d**), *General procedure*

To a solution of **1**, **7**, or **10** (0.01 mol) in ethanol (20 ml), hydrazine hydrate, *o*-chlorobenzaldehyde, *p*-anisaldehyde, *m*-chlorobenzaldehyde, or benzaldehyde (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 **2**, **10**, and **12a–d**, respectively.

6-(4-Ethoxylphenyl)-4-[1,3-diphenyl-5(4H)-thioxo-pyrazolin-4-yl]-3(2H) pyridazinethione (**4**)

A solution of **2** (0.01 mol) and *Lawsson* reagent (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 ethanol to give **4**.

Table 2. Physical data of prepared compounds

Compound	Mp (°C) (solvent)	Yield (%)	Formula[a]
1	195 (Ethanol)	50	$C_{27}H_{24}N_2O_5$
2	136 (pet. ether 100–120)	58	$C_{27}H_{24}N_4O_3$
4	234 (Ethanol)	70	$C_{27}H_{22}N_4OS_2$
5	125 (Benzene)	72	$C_{41}H_{34}N_4OS_2$
6	235 (Benzene)	69	$C_{27}H_{20}N_4OS_2$
7	157 (Ethanol)	44	$C_{27}H_{22}Cl_2N_4O$
8	135 (Ethanol)	75	$C_{29}H_{28}N_4O_3$
9	185 (Ethanol)	63	$C_{35}H_{38}N_6O_3$
10	156 (Benzene)	67	$C_{27}H_{28}N_8O$
12a	266 (Acetic acid)	88	$C_{41}H_{34}Cl_2N_8O$
12b	260 (Ethanol)	80	$C_{43}H_{40}N_8O_3$
12c	275 (Acetic acid)	85	$C_{41}H_{34}Cl_2N_8O$
12d	279 (Ethanol)	86	$C_{41}H_{36}N_8O$
14	156 (Ethanol)	48	$C_{27}H_{22}N_{10}O$

[a] All compounds gave satisfactory elemental analyses (C, H, N)

6-(4-Ethoxyphenyl)-4-(5-benzylthioxy-1,3-diphenyl-pyrazolin-4-yl)-3-benzylthioxypyridazine (**5**)

(a): To a solution of sodium hydroxide (0.02 mol) and phenyl methanethiol (0.02 mol) in water (2.5 ml), cooled in ice, compound **7** (0.01 mol) and dioxan (0.6 ml) were added. The mixture was stirred for 2 h and the separated solid was crystallized from benzene to give **5** (63% yield).

(b): To a solution of sodium hydrogen carbonate (0.02 mol) and dithione **4** (0.01 mol) in water (10 ml), cooled in ice, benzylchloride (0.02 mol) and acetone (5 ml) were added. After stirring for 2 h at room temperature, the mixture was evaporated under reduced pressure. The separated solid was collected and crystallized from benzene to give **5** (72% yield).

8-(4-Ethoxyphenyl)-1,3-diphenylpyrazolo[3,4-c]dithiino[4,3-e]pyridazine (**6**)

A solution of iodine (0.02 mol) in 5% aqueous KI solution (100 ml) was added dropwise with stirring to a solution of **4** (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 benzene to give **6**.

3-Chloro-4,5-dihydro-6-(4-ethoxyphenyl)-4-(5-chloro-1,3-diphenyl-pyrazolin-4-yl) pyridazine (**7**)

A mixture of **2** (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 ethanol to give **7**.

4,5-Dihydro-3-methoxy-6-(4-ethoxyphenyl)-4-(5-methoxy-1,3-diphenyl-pyrazolin-4-yl) pyridazine (**8**)

Compound **7** (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 and then evaporated under reduced pressure. To the residue, water (10 ml) was added, insoluble matter was filtered off and crystallized from ethanol to give **8**.

4,5-Dihydro-3-morpholino-6-(4-ethoxyphenyl)-4-(5-morpholino-1,3-diphenyl-pyrazolin-4-yl) pyridazine (**9**)

A mixture of **7** (0.01 mol) and morpholine (0.025 mol) in 50 ml of dry toluene was refluxed for 3 h. The amine hydrochloride was filtered off and the organic filtrate was evaporated under reduced pressure. To the residue water (10 ml) was added; insoluble matter was filtered off and crystallized from ethanol to give **9**.

4,5-Dihydro-6-(4-ethoxyphenyl)-4-[1,3-diphenyl-triazolo(4,5-b)pyrazolin-4-yl]-tetrazolo[2,3-b]pyridazine (**14**)

(a): A mixture of **7** (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 ethanol to give **14** (48% 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 **10** (0.01 mol) in 4 *M* acetic acid (10 ml); stirring was continued for 1 h. The solid formed was filtered and crystallized from ethanol to give **14** (45% yield).

References

[1] Kamiya S, Nakamura A, Itai T, Koshinuma K, Okusa G (1966) Yakugaku Zasshi **86**: 1099
[2] Sayed GH, Ismail AA, Hashem Z (1984) Egypt J Chem **27**: 757
[3] Sayed GH, Ismail AA, Hashem Z (1984) J Chem Soc Pak **6**: 95
[4] Sayed GH, Ismail AA, El-Nagdy S, Mohamed SM (1986) Egypt J Chem **29**: 433
[5] Sayed GH, El-Mobayed M, El-Shekeil AG, Abdel-Ghani E (1990) Indian J Chem **29B**: 72
[6] Sayed GH, El-Mobayed M, El-Shekeil AG, Abdel-Ghani E (1991) Egypt J Chem **34**: 73
[7] Papa D, Schwenk E, Villani F, Klingsberg E (1948) J Am Chem Soc **70**: 3356
[8] Bal'yan Kh V, Shtangeev AL (1954) Zh Obshch Khim **24**: 238
[9] Capparelli MP, Deschepper RE, Swenton JS (1987) J Org Chem **52**: 4953

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