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Studies in the Vilsmeier-Haack Reaction, Part VII: Synthesis and Reaction of 3-Methyl-1-phenyl-4-acetyl Hydrazono 2-Pyrazoline-5-one(-5-thione)

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Summary. The keto (thio) tautomers **1**–**4** of the hydrazono pyrazolone, thiopyrazolone derivatives underwent simultaneous diformylation, chlorination (desulphurization) and ring closure under Vilsmeier reaction conditions giving the pyrazolo[3,4-c]pyrazole aminoacroleins (**5**, **6**). Treatment of **5** and/or **6** with proper reagents afforded the corresponding pyrazolo[3,4-c]pyrazoles with different heterocyclic systems at the 3-position.

The structures of these compounds were confirmed by elemental analysis, IR and ^{1}H-NMR spectroscopy. All synthesized compounds have been screened in vitro for their antibacterial activities against a number of Gram-positive and Gram-negative bacteria.

Keywords. Hydrazono-5-chloro pyrazole; Pyrazolo[3,4-c]pyrazole; Isoxazolylpyrazolo[3,4-c]-pyrazole; Pyrazolylpyrazolo[3,4-c]pyrazole; Physiological activity.

Untersuchungen zur Vilsmeier-Haack Reaktion, 7. Mitt.: Synthese und Reaktionen von 3-Methyl-1-phenyl-4-acetylhydrazono-2-pyrazolin-5-on(-5-thion)

Zusammenfassung. Die Keto-(Thio)-Tautomeren **1** – **4** der Hydrazonopyrazolon-/Thiopyrazolon-Derivate gingen unter Vilsmeier-Bedingungen zugleich Diformylierung, Chlorierung (Entschwefelung) und Ringschluß zu Pyrazolo[3,4-c]pyrazol-aminoacroleinen **5** und **6** ein. Aus **5** und/oder **6** konnten die entsprechenden Pyrazolo[3,4-c]pyrazole mit verschiedenen heterocyclischen Systemen in 3-Position erhalten werden. Die Strukturen der Verbindungen wurden mittels Elementaranalyse, IR und ^{1}H-NMR überprüft. Alle synthetisierten Verbindungen wurden in vitro bezüglich ihrer antibakteriellen Aktivität gegenüber einer Anzahl Gram-positiver und Gram-negativer Bakterien untersucht.

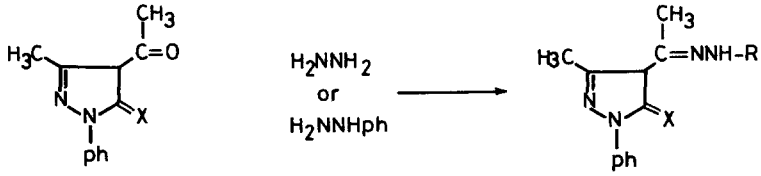
Introduction

The biological importance of pyrazolones [1, 2] as well as thiopyrazolones is well known. Also, a large number of hydrazones have shown amoebicidal activities [4–6]. Considering the foregoing benefits, it seems of interest that the presence of both the two systems viz. pyrazolo and hydrazono in a single compound might result in potent derivatives.

Results and Discussion

So, we wish to present herein the results of our efforts in the application of the Vilsmeier reaction [7, 11] on 4-acetyl hydrazono and/or phenyl hydrazono-2-pyr-

azoline-5-ones (-5-thiones) (**1–4**). The target starting materials were prepared from 4-acetyl by their condensation in boiling ethanol with hydrazine hydrate or phenyl hydrazine giving the corresponding hydrazones (**1–4**).



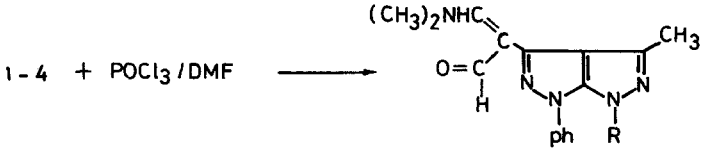
1, X=O ; R=H
2, X=O ; R=ph
3, X=S ; R=H
4, X=S ; R=ph

(1-4)

The ^{1}H-NMR spectra of **1–4** in $CDCl_3$ showed signals at δ 2.60 (s, CH_3 pyrazolone), 2.32 (s, CH_3 at 4-position), 8.20–6.86 (m, 10 *Ar*-H, 1 H pyrazolone 4-H), 6.05 (s, 2 H, NH_2), and 10.50 (s, NH) which were removed by D_2O treatment. The IR spectra showed bands at 1 620 cm^{-1} (C=H), 1 690 cm^{-1} (C=O), 1 290–1 275 cm^{-1} (C=S), 3 400–3 360 cm^{-1} (MH_2) and at 3 240 cm^{-1} (NH).

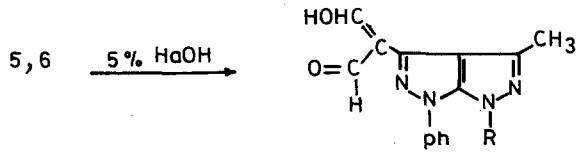
Compound **3**, **4** were also prepared by an alternative route. Thus, compounds **1**, **2** were subjected for thionation by P_2S_5 in dry pyridine giving **3**, **4**, respectively.

Vilsmeier reaction on **1–4** at room temperature (exothermic) simultaneously lead to the diformylation [7–10] of the 3-methyl group, chlorination (desulphurization) of 5-oxo (5-thio) position in addition to ring closure giving the corresponding fused pyrazolo[3,4-c]pyrazole aminoacroleins **5**, **6**.



5, R=H
6, R=ph

(5-6)



(7-8)

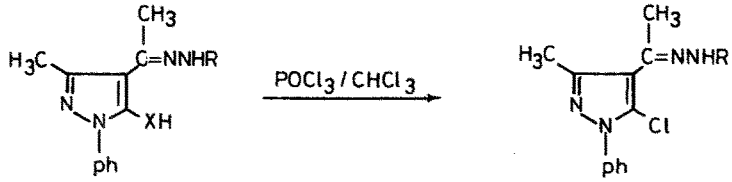
7, R=H
8, R=ph

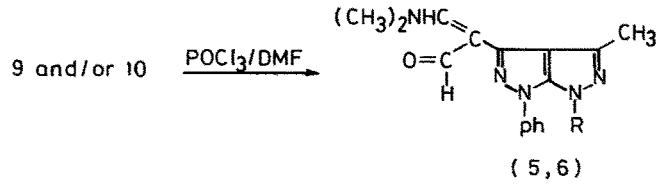
The ^{1}H-NMR spectra of **5**, **6** in $CDCl_3$ showed signals at 3.30–3.25 (s, -$N(CH_3)_2$), 2.40 (s, CH_3 at 4-position), 6.40 (s, 1 H acrolein methin), 9.32 (s, 1 H acrolein-CHO), 8.00–7.01 (m, 1 OH, *Ar*-H compound **6**), and at 9.90 (s, 1 H, NH compound **5**) which was removed by D_2O treatment. The IR spectra showed a band at 1 720 cm^{-1} (acrolein-CHO, vinylogous amide) and at 3 300 cm^{-1} (NH group compound **5**).

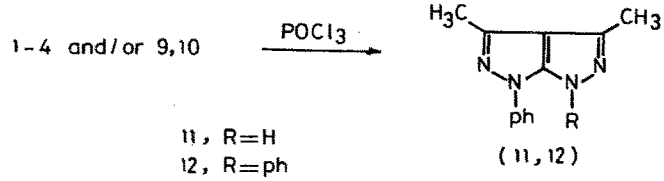
Also, the structure of **5**, **6** was confirmed by their conversion to the corresponding malonaldehydes **7**, **8** by warming with 5% NaOH.

The mechanistic course of the Vilsmeier reaction on compounds **1–4** may take place through the intermediates **9**, **10**; then ring closure can give **5**, **6** (see the formula scheme).

It is quite clear that chlorination of the 5-oxo (thio) position in **1–4** was affected by the action of $POCl_3$ in chloroform. Vilsmeier reaction on the chloro derivatives **9**, **10** simultaneously leads to the diformylation of the 3-methyl group and ring closure giving **5**, **6**. Also, ring closure of the chloro derivatives **9**, **10** as well as the hydrazono derivatives **1–4** was brough about by the action of excess $POCl_3$ at gentle reflux giving **11**, **12**.



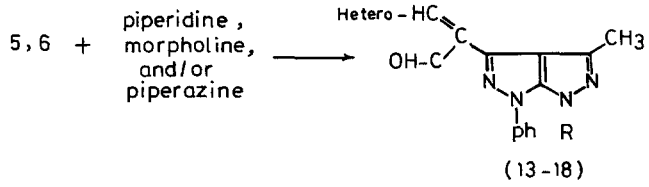




It must be pointed out that the preparation of **11**, **12** using $POCl_3$ neither improved the yield nor reduced the time of the reaction. However, compound **10** was previously prepared by Soliman et al. [12] from the reaction of 4-acetyl pyrazolone with phenylhydrazine in a refluxed mixture of acetic acid and hydrochloric acid for 24 hours. Condensation of **5**, **6** with some secondary heterocyclic amines in warmed ethanol gave the aminomethylenes **13–18**.

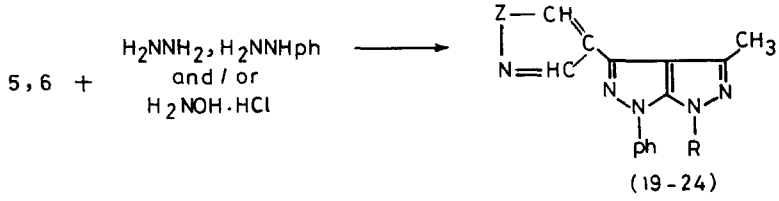
Also, interaction of **5**, **6** with hydrazine hydrate, phenylhdrazine and/or hydroxyl amine in refluxed ethanol afforded the pyrazolo-pyrazoles **19–24** with some heterocyclic systems at the 3-position.

The ^{1}H-NMR of compound **13** in $CDCl_3$ showed signals at 3.65 and 3.30 due to the piperidine ring ($-N-CH_2-$) besides signals due to the aromatic protons. The IR spectra of these compounds (**13–18**) indicated the presence of a band due



(13-18)

			Hetero
13,	R=H	;	piperidino
14,	R=H	;	morpholino
15,	R=H	;	piperazino
16,	R=ph	;	piperidino
17,	R=ph	;	morpholino
18,	R=ph	;	piperazino



(19-24)

19,	Z = NH	; R = H	22,	Z = NH	; R = ph
20,	Z = N-ph	; R = H	23,	Z = N-ph	; R = ph
21,	Z = O	; R = H	24,	Z = O	; R = ph

to $-$CHO (acrolein) at 1 710 cm^{-1} and a sharp absorption at 3 190 cm^{-1} (NH group) for compounds **13–15**.

The ^{1}H-NMR of compound **19** in $CDCl_3$ showed the absence of the signals due to $-N(CH_3)_2$ and $-$CHO and the presence of signals at δ 10.60, 10.59 [d, 2H, 2(NH) groups].

Physiology Activity

The compounds were tested in vitro for their growth inhibitory activities [13] against a variety of Gram-positive and Gram-negative strains of bacteria, namely *Staphylococcus aureus, Pseudomonas pyocyanea, Bacillus cereus, Proteus, Escherichia coli, Pasteurella, Klebsiella pneumoniae* and *Staphylococcus citreus.*

The culture medium was normal nutrient agar (NA), supplemented with 1 g yeast dm^{-3}, the tested compounds were dissolved in sterile polyethylene glycol at a concentration of 0.5% (*w/v*). The antibacterial activities were evaluated by the classical cup-plate technique [14, 15]. Pyrazolohydrazones, thiopyrazolohydrazono and chloropyrazolohydrazones (**1**, **2**, **3**, **4**, **9**, **10**) used as standard references.

The results revealed that the prepared compounds exhibite pronounced antibacterial activities against at least four of the test bacteria *Staphylococcus aureus,*

Table 1. Physical and analytical data of compounds **1–24**

Compound	M.P. °C	Yield %	Formula[a]
1	201–202	70	$C_{12}H_{14}N_4O$
2	191–192	76	$C_{18}H_{18}N_4O$
3	260–261	72	$C_{12}H_{14}N_4S$
4	158–159	75	$C_{18}H_{18}N_4S$
5	195–158	68	$C_{16}H_{17}N_5O$
6	110–112	65	$C_{22}H_{21}N_5O$
7	192–193	76	$C_{14}H_{12}N_4O_2$
8	92–93	73	$C_{20}H_{16}N_4O_2$
9	255–256	80	$C_{12}H_{13}N_4Cl$
10	166–168	83	$C_{18}H_{17}N_4Cl$
11	219–220	79	$C_{12}H_{12}N_4$
12	234–235	80	$C_{18}H_{16}N_4$
13	185–186	60	$C_{19}H_{21}N_5O$
14	255–257	65	$C_{18}H_{19}N_5O_2$
15	162–164	58	$C_{18}H_{20}N_6O$
16	120–121	62	$C_{25}H_{25}N_5O$
17	80–82	61	$C_{24}H_{23}N_5O_2$
18	98–99	64	$C_{24}H_{24}N_6O$
19	240–242	56	$C_{14}H_{12}N_6$
20	132–134	53	$C_{20}H_{16}N_6$
21	212–214	62	$C_{14}H_{11}N_5O$
22	95–97	58	$C_{20}H_{16}N_6$
23	85–87	64	$C_{26}H_{20}N_6$
24	90–92	61	$C_{20}H_{15}N_5O$

[a] Elemental analyses of C, H, N, S, and Cl gave results equal to those calculated within experimental error

Bacillus cereus, *Proteus*, and *Staphylococcus citreus* (cf. Table 2), the diameter of the inhibition zones ranged from 20–70 mm. It seems of interst to note that the thiono hydrazones **3**, **4** had enhanced antibacterial activities against all the organisms used.

Also, some of the prepared derivatives incorporated with heterocyclic nuclei at the 3-position of the pyrazolone moiety (**15**, **19**, **20**, **22**, **23**) had clearly antibacterial activities against almost all of the cultured used. Moreover, the best results were obtained with compound (**11**, **12**) against all bacteria used.

Experimental Part

All melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were obtained using a Pye-Unicam SP-200 G spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM-390 90 MHz instrument.

Table 2. Antibacterial activity of the prepared compounds; inhibition zones in mm

Compd. no.	*Staphylococcus aureus*	*Pseudomonas pyocanea*	*Bacillus cereus*	*Proteus*	*Escherichia coli*	*Pasteurella*	*Klebsiella pneumoniae*	*Staphylococcus citreus*
1	30	–	50	50	–	–	–	60
3	60	20	20	50	30	20	20	50
5	10	–	10	50	–	–	–	–
7	20	20	10	30	–	10	–	30
9	50	–	60	60	–	–	–	20
11	60	40	60	40	40	60	70	70
13	50	–	50	50	–	–	–	30
14	60	–	40	30	–	–	–	40
15	40	–	60	40	10	10	10	40
19	30	50	30	50	–	10	20	30
20	30	10	40	40	–	–	–	30
21	40	–	50	40	–	10	20	50
2	30	–	50	50	–	–	–	60
4	50	10	50	50	20	60	60	60
6	30	30	40	40	–	30	–	50
8	30	10	20	40	–	10	–	40
10	50	–	70	80	–	–	–	50
12	80	50	50	60	70	60	80	70
16	60	–	–	20	–	–	–	40
17	50	10	60	50	–	–	–	50
18	50	–	50	50	–	–	–	40
22	50	–	40	40	–	20	30	60
23	40	10	60	60	–	–	30	60
24	50	–	60	50	–	–	60	60

3-Methyl-l-phenyl-4-acetylhydrazono-2-pyrazolin-5-one(thione) (**1–4**)

A mixture of 3-methyl-l-phenyl-4-acetyl-2-pyrazoline-5-one (thione) (0.01 mol) and hydrazine hydrate and/or phenylhydrazine in 30 ml ethanol was refluxed for 3 h. The product obtained was filtered, washed well with cold ethanol and crystallized from ethanol. The physical and chemical data are quoted in Table 1.

3-(α-Dimethylaminomethylene-α-formylmethyl)-4-methyl-1-phenyl (or 6-phenyl) pyrazolo[3,4-c] pyrazole (**5**, **6**)

Method A. To dimethylformamide (5 ml) cooled to 0 °C $POCl_{36}$ (0.04 mol) was added and the reaction mixture left to stand for 20 min. To this the hydrazono pyrazolono (thione) (**1**, **2**, **3** and/or **4**) (0.02 mol) dissolved in *DMF* (5 ml), was added with stirring. The reaction mixture was left to stand for 10 min while stirring, then heated for 1 h at 50–60 °C. The cooled reaction mixture was poured into ice-cold water and treated with $NaHCO_3$ to *pH* 9. The orange solid that separated was filtered, washed thoroughly with cold water and crystallized from alcohol-benzene mixture.

Method B. To the mixture of dimethylformamide and $POCl_3$ (0.04 mol) at room temperature, hydrazone pyrazolone (thione) (**1–4**) (0.02 mol) were added portion wise with stirring. After the addition was over, the reaction mixture was left at room temperature with stirring for 1 h. The reaction mixture was worked up as in method A. The physical and chemical data are collected in Table 1.

3-(α-Hydroxmethylene-α-formylmethyl)-4-methyl-1-phenyl (or 6-phenyl) pyrazolo[3,4-c]pyrazole (**7**, **8**)

The acrolein derivatives (**5** or **6**) (1 g) taken in 5% NaOH (20 ml) were heated at 80 °C (40 min). It was then filtered off, cooled and acidified. The solid that separated was filtered, washed well with water and crystallized from ethanol. The physical and chemical data are listed in Table 1.

3-Methyl-1-phenyl-4-acethydryzono-5-chloro pyrazolo (**9**, **10**)

To (0.01 mol) of the hydrazono pyrazolone (thione) **1–4** in $CHCl_3$ (30 ml) was added (0.02 mole) of $POCl_3$. The reaction mixture was gently heated for 1 h. The solid that separated out was filtered and crystallized from $CHCl_3$. The physical and chemical data are presented in Table 1.

3,4-Dimethyl-1-phenyl (or 6-phenyl) pyrazolo[3,4-c]pyrazolo (**11**, **12**)

To the hyrazono pyrazolone (thione) (**1–4**) and/or hydrazono chloro pyrazole (**9**, **10**) (0.01 mol) was added $POCl_3$ (0.03 mol) with stirring. The reaction mixture was refluxed for 1 h. The solid that separated out was filtered, washed with chloroform and crystallized from ethanol.

3-(α-Heterocyclo-methylene-α-formylmethyl) pyrazolo[3,4-c]pyrazole (**13–18**)

To the acrolein derivatives (**5** or **6**) (0.01 mol) taken in ethanol (30 ml) was added (0.01 mol) of the secondary amine and the mixture gently heated on a water bath. The solid that separated after concentration was filtered, washed with cold water and crystallized from alcohol.

3-(4-Heterocyclo-)-4-methyl-1-phenyl (or 6-phenyl) pyrazolo[3,4-c]pyrazole (**19–24**)

To a solution of acrolein derivatives (**5** or **6**) in ethanol (30 ml) was added an equimolar quantity of hydrazine hydrate; phenylhydrazine and/or hydroxylamine hydrochloride, respectively. The reaction mixture was refluxed for 2 h, then concentrated and poured on to crushed ice. The product solid was

filtered, washed with cold water and crystallized from alcohol. The physical and chemical data are presented in Table 1.

3,4-Dimethyl-1-phenyl (or 6-phenyl) pyrazolo[3,4-c]pyrazolo (**11**, **12**)

To the hydrazoid pyrazolone (thione) (**1–4**) and/or hydrazono chloro pyrazole (**9**, **10**) (0.01 mol) was added $POCl_3$ (0.03 mol) with stirring. The reaction mixture was refluxed for 1 h. The solid that separated out was filtered, washed with chloroform and crystallized from ethanol.

3-(α-Heterocyclo-methylene-α-formylmethyl) pyrazolo[3,4-c]pyrazole (**13–18**)

To the acrolein derivatives (**5** or **6**) (0.01 mol) taken in ethanol (30 ml) was added (0.01 mol) of the secondary amine and the mixture gently heated on a water bath. The solid that separated after concentration was filtered, washed with cold water and crystallized from alcohol.

3-(4-Heterocyclo-)-4-methyl-1-phenyl (or 6-phenyl) pyrazolo[3,4-c]pyrazole (**19–24**)

To a solution of acrolein derivatives (**5** or **6**) in ethanol (30 ml) was added an equimolar quantity of hydrazine hydrate; phenylhydrazine and/or hydroxylamine hydrochloride, respectively. The reaction mixture was refluxed for 2 h, then concentrated and poured on to crushed ice. The product solid was filtered, washed with cold water and crystallized from alcohol. The physical and chemical data are listed in Table 1 for all synthesized compounds (**1–24**).

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