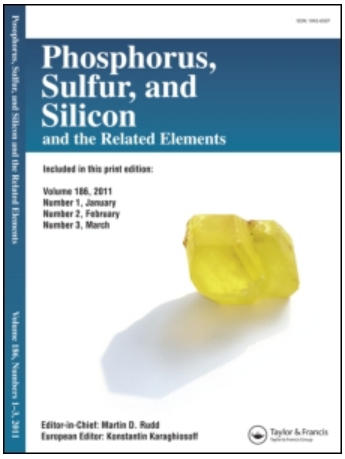

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STUDIES ON THE VILSMEIER-HAACK REACTION. PART III-REACTION OF 3-METHYL-1-PHENYL-4-ARYLIDENE-2-PYRAZOLIN-5-THIONE

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The 3-methyl group in 3-methyl pyrazolthione derivatives (2, 3) has been found to undergo diformylation by Vilsmeier reagent to give the aminoacroleins (4, 5). Treatment of 4,5 with some reagents affords the related 1-phenyl-4-arylidene-5-pyrazolthione derivatives (8–21) with different heterocyclic systems at the 3-position.

Key words: Pyrazolonethione; arylidene pyrazolonethione; bis piperazine; pyrazole and isoxazole

INTRODUCTION

The Vilsmeier reaction on 3-methyl-1-phenyl-5-pyrazolone was early reported.[1,2] Recently, considerable study has been directed in our laboratory toward the application of this reaction on some pyrazolone derivatives.[3,4] In spite of many reports on the synthesis and biological activity of pyrazolone derivatives,[5–7] as well as 5-thiopyrazolone,[8] none of these reports applied a Vilsmeier reaction on the 3-methyl group of the pyrazolthione.

RESULTS AND DISCUSSION

So, in continuation of our search for new sulfur heterocycles for biological screening, we describe herein the syntheses of several hitherto unreported heterocyclic compounds with different substituents at the 3-position. Many of these compounds are either isosters of or are structurally related to biologically active compounds. Thus, the present communication describes the application of the Vilsmeier reaction to 3-methylpyrazolthione derivatives (**2**, **3**).

These compounds were prepared by the condensation of the appropriate aromatic aldehyde with 3-methyl-1-phenyl-2-pyrazolin-5-thione[9] (**1**), or by thienation of the corresponding 3-methyl-1-phenyl-4-arylidene-5-pyrazolone derivatives.

Vilsmeier reaction on 2 or 3 was performed under usual conditions[10] and the expected aminoacrolein derivatives (4, 5) were obtained in good yields.

The structures of **4**, **5** were established by elemental analysis, ^{1}H NMR and IR

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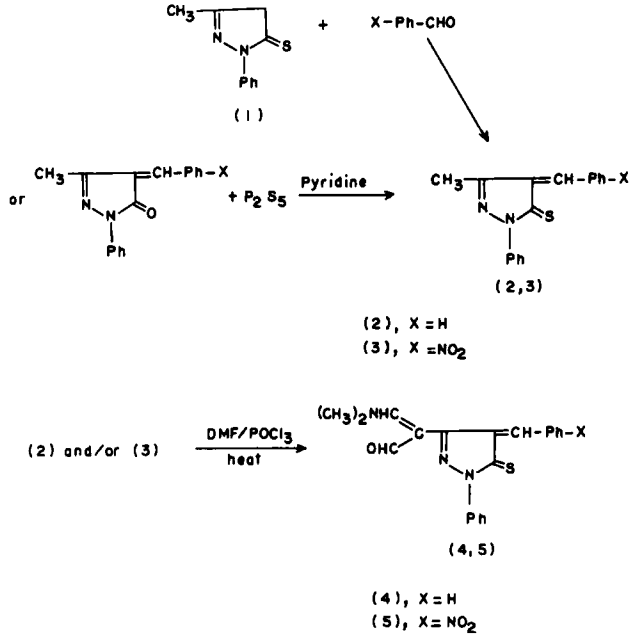
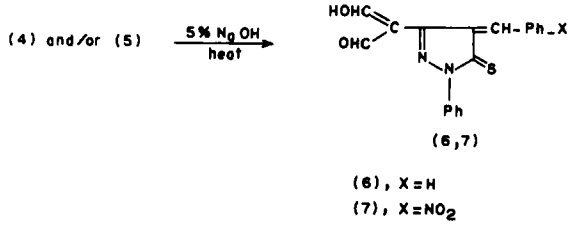


spectra and by their ready conversions with hot alkali (no evolution of dimethylamine) to the corresponding malonaldehydes (**6**, **7**).

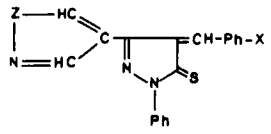


The ^{1}H NMR spectrum of 4 in $CDCl_3$ showed signals at δ3.01–2.90 (d, $-N(CH_3)_2$), δ8.6 (s, 1H acrolein -CHO) and at δ8.00–7.10 (m, 10 Ar-H, 1H acrolein methin and 1H—C=). The IR spectra showed a carbonyl absorption at 1680 cm^{-1} (acrolein —CHO, vinylogous amide) and at 1375 cm^{-1} for C=S group. Also, the structure of the compounds **6**, **7** were confirmed by their correct microanalytical data and IR, ^{1}H NMR spectroscopy are in accordance with their structures.

Encouraged by the findings of our earlier work[3] on the arylidene pyrazolones it was thought worthwhile to synthesise some new arylidene pyrazolthiones with some heterocyclic moieties at the 3-position, in order to study the effect of this replacement on the pharmacological activity.

On one hand, aminoacrolein derivatives (**4**, **5**) reacted easily in boiling ethanol with hydroxylamine, hydrazine and phenylhydrazine giving the corresponding compounds (**8–13**), respectively.

(4) and/or (5) —hydroxyl amine, hydrazine and phenylhydrazine→



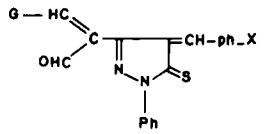
(8-13)

(8), X=H ; Z=O
(9), X=NO_2; Z=O
(10), X=H ; Z=NH
(11), X=NO_2; Z=NH
(12), X=H ; Z=N-Ph
(13), X=NO_2; Z=N-Ph

The structures of these compounds (**8–13**) were confirmed by their correct elemental analysis and IR spectra showed the absence of the carbonyl band related to the CHO group. The ^{1}H NMR spectra in $CDCl_3$ showed the absence of the signals due to —$N(CH_3)_2$ and the presence of the signals related to the rest of all the protons.

On the other hand, condensation of the aminoacrolein derivatives (**4, 5**) with some secondary heterocyclic amines in ethanol afforded the expected amino-methylenes (**14–19**), respectively.

(4) and/or (5) —piperidine, morpholine and piperazine→



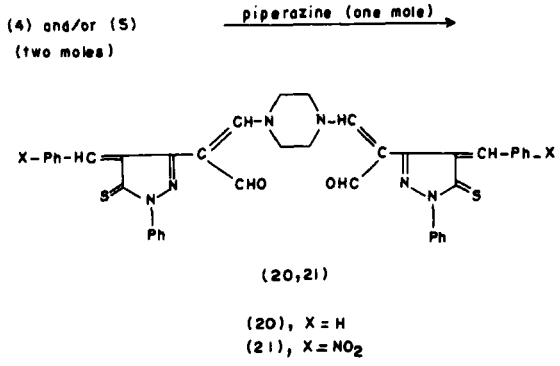
(14-19)

(14), X=H ; G=piperidino
(15), X=NO_2; G=piperidino
(16), X=H ; G=morpholino
(17), X=NO_2; G=morpholino
(18), X=H ; G=piperazino
(19), X=NO_2; G=piperazino

The structures of these products (**14–19**) were established from the correct microanalysis and IR spectra were in agreement with their structures indicating the presence of a sharp absorption at 1395 cm^{-1} (C=S) and at 1680 cm^{-1} (acrolein —CHO). The ^{1}H NMR spectrum in $CDCl_3$ showed the presence of signals at δ4.00–3.88 (d, —N—CH_2—) due to the piperidine ring (compound **14**), besides signals due to the other protons.

It must be pointed out that, when piperazine reacted with two moles of the aminoacrolein derivatives (**4, 5**) a bis-piperazine compounds (**20, 21**), were obtained.

The IR, ^{1}H NMR and microanalysis of these compounds (**20, 21**) were in accordance with their structures.



EXPERIMENTAL

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.

3-Methyl-1-phenyl-2-pyrazolin-5-thione (**1**): was prepared as reported previously.[8]

Substituted 3-methyl-1-phenyl-4-arylidene-2-pyrazoline-5-thiones (**2, 3**): were prepared according to the methods reported for arylidene pyrazolones.[11]

3-(α-Dimethylaminomethylene-α-formylmethyl)-1-phenyl-4-arylidene-2-pyrazolin-5-thiones (**4, 5**). To dimethylformamide (5 ml) cooled to 0°C $POCl_3$ (0.04 mole) was added with stirring and the mixture left to stand for 25 minutes. To this the thiopyrazolones (2) and/or (3) (0.02 mole) dissolved in DMF (5 ml) were added with stirring. The reaction mixture was left to stand for 10 min. while stirring, then heated to 60–80°C for 6 hrs. The cooled reaction mixture was poured into ice-water and treated with $NaHCO_3$ to pH 9. The deep red solid that separated was filtered, washed thoroughly with cold water and crystallized from methanol. The physical and chemical data are depicted in Table I.

TABLE I

Physical and analytical data of compounds (**2**)–(**21**)

Compound	m.p. (°C)	Yield %	Formula	Calcd. C	H	N	S	Found C	H	N	S
2	183–4	80	$C_{17}H_{14}N_2S$	73.38	5.03	10.07	11.51	73.19	5.10	10.17	11.56
3	212–3	84	$C_{17}H_{13}N_3O_2S$	63.15	4.02	13.00	9.90	63.08	4.00	13.01	10.00
4	171–3	50	$C_{21}H_{19}N_3OS$	69.80	5.26	11.63	8.86	70.01	5.30	11.62	8.99
5	167–9	53	$C_{21}H_{18}N_4O_3S$	62.06	4.43	13.79	7.88	62.10	4.40	14.00	7.98
6	151–2	40	$C_{19}H_{14}N_2S$	75.49	4.63	9.27	10.59	75.55	4.72	9.19	10.60
7	156–7	45	$C_{19}H_{13}N_3O_2S$	65.70	4.03	12.10	9.22	65.49	4.10	12.02	9.30
8	166–8	70	$C_{19}H_{13}N_3OS$	68.88	3.92	12.68	9.66	69.00	4.01	12.76	9.69
9	175–7	76	$C_{19}H_{12}N_4O_3S$	60.63	3.19	14.89	8.51	60.72	3.29	14.99	8.61
10	145–6	82	$C_{19}H_{14}N_4S$	69.09	4.24	16.96	9.69	69.06	4.23	16.79	9.68
11	138–9	85	$C_{19}H_{13}N_5O_2S$	60.80	3.46	18.66	8·53	61.00	3.56	18.60	8.60
12	135–6	69	$C_{25}H_{18}N_4S$	73.89	4.43	13.79	7.88	73.56	4.42	13.92	7.98
13	122–3	65	$C_{25}H_{17}N_5O_2S$	66.51	3.76	15.52	7.09	66.65	3.77	15.61	7.03
14	125–6	67	$C_{24}H_{23}N_3OS$	71.82	5.73	10.47	7.98	71.94	5.75	10.51	7.97
15	160–1	80	$C_{24}H_{22}N_4O_3S$	64.57	4.93	12.55	7.17	64.72	5.01	12.33	7.20
16	142–3	66	$C_{23}H_{21}N_3O_2S$	68.48	5.21	10.42	7.94	68.50	5.22	10.45	8.00
17	156–7	69	$C_{23}H_{20}N_4O_4S$	61.60	4.46	12.50	7.14	61.80	4.45	12.52	7.23
18	148–9	70	$C_{23}H_{22}N_4OS$	68.65	5.47	13.93	7.96	68.80	5.48	13.99	7.91
19	128–9	75	$C_{23}H_{21}N_5O_3S$	61.74	4.69	15.63	7.15	61.82	4.70	15.72	7.21
20	165–6	65	$C_{42}H_{34}N_6O_2S_2$	70.19	4.73	11.69	8.91	70.23	4.72	11.86	9.00
21	178–9	70	$C_{42}H_{33}N_7O_6S_2$	63.39	4.15	12.32	8.05	63.44	4.17	12.34	8.09

3-(α-Hydroxymethylene-α-formylmethyl)-1-phenyl-4-arylidene-2-pyrazolin-5-thiones (**6, 7**). The acrolein derivatives (**4** or **5**) (1 g) taken in 5% NaOH (20 ml) were heated to 80°C (50 min). It was then filtered off, cooled and acidified. The solid that separated was filtered, washed well with cold water and crystallized from aq. ethanol. The physical and chemical data are quoted in Table I.

3-(4-Isoxazolyl or pyrazolyl)-1-phenyl-4-arylidene-2-pyrazolin-5-thiones (**8–13**). To a solution of acrolein derivatives (**4** or **5**) in ethanol (40 ml) was added an equimolar quantity of hydroxylamine hydrochloride, hydrazine hydrate and/or phenylhydrazine, respectively. The reaction mixture was refluxed for 2 hrs., cooled, concentrated and poured onto crushed ice. The precipitate solid was filtered, washed with cold water and crystallized from aq. ethanol. The physical and chemical data are recorded in Table I.

3-(α-Piperidino, morpholino and/or piperazinomethylene-α-formylmethyl)-1-phenyl-4-arylidene-2-pyrazolin-5-thiones (**14–19**). To the acrolein derivatives (**4** or **5**) (0.01 mole) taken in ethanol (30 ml) was added (0.01 mole) quantity of the amine and the mixture gently heated on a water bath for half hour. The solid that separated after concentration and pouring onto ice cold water was filtered, washed with cold water and crystallized from methanol. The physical and chemical data are presented in Table I.

Formation of the dimers (**20, 21**). To the acrolein derivatives (**4** or **5**) (0.02 moles) taken in ethanol (30 ml) was added (0.01 mole) quantity of piperazine and the mixture gently heated on a water bath. The solid that separated was filtered, washed with cold water then with cold ethanol and crystallized from ethanol. The physical and chemical data are listed in Table I.

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