NEW PYRAZOLINE DERIVATIVES

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The biological activity of azoles, pyrimidines as well as pyrazolines are of interest[1 – 5]. Formation of pyrazolines and related compounds from hydrazine derivatives and α,β-unsaturated carbonyl compounds in very common[6]. Pyrazoline fused with different heterocyclic nuclei at position 4 and 5 have been reported[7]. Here we report the synthesis of some new monocyclic or fused azoles and pyrimidinones linked to C-4 or 5-chloro-3-methyl-1-phenylpyrazoline.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were carried out at Microanalytical Center, Cairo University, IR spectra (KBr) on Perkin–Elmer infrared 127B spectrophotometer. ^{1}H NMR spectra were obtained on Varian EM 360 (60 MHz) in $CDCl_3$ and mass spectra (Mat 311 A, 70 eV) were performed at Chemistry Department, Duisburg University, Germany.

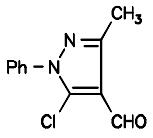
Preparation of α,β-Unsaturated Ketones *II – IV*; General Procedure

Equimolar portions (0.1 mol l^{-1}) of formyl compound[8] *I* and 3-methyl-1-phenylpyrazol-5-one or 2-methyloxazolone, respectively, were dissolved in ethanol (50 ml), then 0.5 ml of piperidine was added. The reaction mixture was allowed to reflux for 8 – 12 h, filtered hot, evaporated to one third of its volume, cooled, acidified with few drops of acetic acid and the product (*II* or *III*, respectively) precipitated on dilution with water. It was collected, washed by water and crystallized from appropriate solvents.

The above method has been applied to preparation of the ketones (*IVa – IVc*) by condensation of the formyl compound *I* with acetophenone derivatives; alcohol potassium hydroxide solution (0.15 mol l^{-1}) has been used as a basic catalyst. The structure of ketones *II*, *III* and *IVa – IVc* was confirmed on the basis of analytical and spectral data (Tables I and II).

Reaction of α,β-Unsaturated Ketones *II – IV* with Hydrazine Derivatives; General Procedure

Equimolar amounts of ketones *II – IV* and the hydrazine hydrate in boiling ethanol in presence of drops of acetic acid, phenylhydrazine with catalytic amount of piperidine (0.5 ml), hydroxylamine



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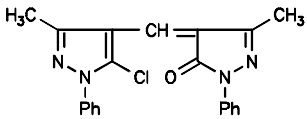

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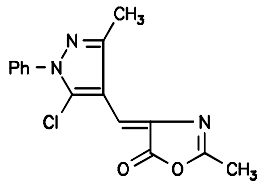

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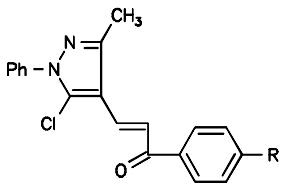

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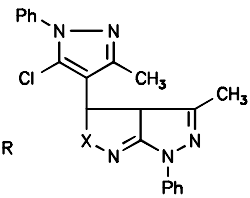

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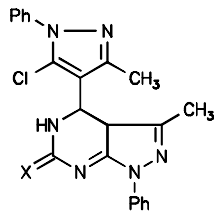

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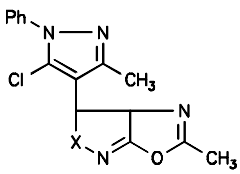
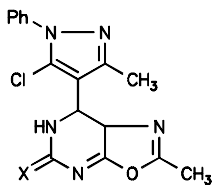


VII



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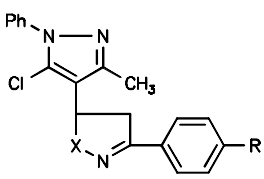
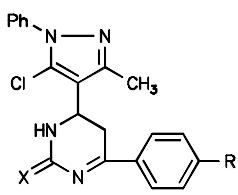


IX, R = H
XI, R = NO_2
XIII, R = OCH_3



X, R = H
XII, R = NO_2
XIV, R = OCH_3

In formulae *IV* : *a*, R = H
b, R = NO_2
c, R = OCH_3

VI, *VIII*, *X*, *XII*, *XIV* : *a*, X = O
b, X = S

V, *VII*, *IX*, *XI*, *XIII* : *a*, X = $NCOCH_3$
b, X = NC_6H_5
c, X = O

TABLE I
Physical characteristics of ketones *II – IV*

Compound	M. p., °C Yield, %	Formula (M. w.)	Calculated/Found			
			% C	% H	% Cl	% N
II[a]	185 – 187	$C_{21}H_{17}ClN_4O$	66.93	4.52	9.43	14.87
	80	(376.5)	66.91	4.85	9.40	14.85
III[b]	190 – 193	$C_{15}H_{12}ClN_3O_2$	59.70	3.98	11.77	13.93
	75	(301.5)	59.61	3.89	11.65	13.82
IVa[c]	115 – 117	$C_{19}H_{15}ClN_2O$	70.70	4.65	11.01	8.68
	75	(322.5)	70.62	4.50	10.88	8.53
IVb[c]	180 – 183	$C_{19}H_{14}ClN_3O_3$	62.04	3.81	9.66	11.43
	80	(367.5)	61.93	3.69	9.53	11.30
IVc[c]	160 – 164	$C_{20}H_{17}ClN_2O_2$	68.09	4.82	10.07	7.94
	65	(352.5)	67.97	4.70	9.98	7.82

Crystallized from [a] DMF, [b] methanol, [c] ethanol.

TABLE II
IR and ^{1}H NMR data for the ketones *II – IV*

Compound	IR[a], cm^{-1}	^{1}H NMR, ppm
II	1 730	1.29 s, 6 H (2 CH_3); 4.8 s, 1 H (ylidene); 7.1 – 7.8 m, 10 H (2 ArH)
III	1 725	1.28 s, 3 H (CH_3); 4.75 s, 1 H (ylidene); 7.1 – 7.8 m, 5 H (ArH)
IVa	1 730	1.3 s, 3 H (CH_3); 6.15 d, 1 H (ylidene); 6.3 d, 1 H (ylidene); 7.1 – 7.8 m, 10 H (2 ArH)
IVb	1 735	1.3 s, 3 H (CH_3); 6.1 d, 1 H (ylidene); 6.25 d, 1 H (ylidene); 7.1 – 7.8 m, 9 H (2 ArH)
IVc	1 735	1.3 s, 3 H (CH_3); 3.1 s, 3 H (CH_3–CO); 6.1 d, 1 H (ylidene); 6.2 d, 1 H (ylidene); 7.1 – 7.8 m, 9 H (2 ArH)

[a] (C=O).

TABLE III
Physical characteristics of compounds *V – XIV*

Compound	M. p., °C Yield, %	Formula (M. w.)	Calculated/Found			
			% C	% H	% Cl	% N
Va[a]	200 – 203	$C_{23}H_{21}ClN_6O$	63.82	4.86	8.21	19.42
	80	(432.5)	63.69	4.73	8.12	19.30
Vb[a]	160 – 162	$C_{27}H_{23}ClN_6$	69.45	4.93	7.61	18.01
	70	(466.5)	69.34	4.81	7.53	17.87
Vc[a]	205 – 207	$C_{21}H_{18}ClN_5O$	64.37	4.60	9.07	17.88
	50	(391.5)	64.15	4.47	8.98	17.74
VIa[b]	230 – 233	$C_{22}H_{19}ClN_6O$	63.08	4.54	8.48	20.07
	70	(418.5)	62.97	4.42	8.41	19.95
VIb[b]	210 – 212	$C_{22}H_{19}ClN_6S$	60.76	4.37	8.17	19.33
	73	(434.5)	60.68	4.25	8.12	19.21
VIIa[a]	220 – 223	$C_{17}H_{16}ClN_5O_2$	57.06	4.48	9.93	19.58
	80	(357.5)	56.97	4.37	9.84	19.51
VIIb[a]	185 – 188	$C_{21}H_{18}ClN_5O$	64.37	4.60	9.07	17.88
	85	(391.5)	64.26	4.51	8.96	17.76
VIIc[a]	215 – 217	$C_{15}H_{13}ClN_4O_2$	56.87	4.11	11.22	17.69
	50	(316.5)	56.78	4.02	11.08	17.58
VIIIa[b]	235 – 238	$C_{16}H_{14}ClN_5O_2$	55.90	4.08	10.33	20.38
	60	(343.5)	55.81	3.99	10.20	29.29
VIIIb[b]	245 – 247	$C_{16}H_{14}ClN_5OS$	53.41	3.89	9.87	19.47
	60	(359.5)	53.37	3.76	9.82	19.40
IXa[a]	140 – 142	$C_{21}H_{19}ClN_4O$	66.58	5.02	9.38	14.80
	70	(378.5)	66.47	4.88	9.30	14.68
IXb[a]	130 – 132	$C_{25}H_{21}ClN_4$	72.73	5.09	8.61	13.58
	75	(412.5)	72.69	4.97	8.52	13.46
IXc[a]	160 – 162	$C_{19}H_{16}ClN_3O$	67.56	4.74	10.52	12.44
	60	(337.5)	67.43	4.62	10.44	12.35
Xa[a]	140 – 143	$C_{20}H_{17}ClN_4O$	65.84	4.66	9.74	15.36
	60	(364.5)	65.74	4.52	9.70	15.29
Xb[a]	160 – 163	$C_{20}H_{17}ClN_4S$	63.07	4.47	9.33	14.72
	60	(380.5)	62.89	4.36	9.12	14.60
XIa[a]	165 – 168	$C_{21}H_{18}ClN_5O_3$	59.50	4.25	8.38	16.53
	70	(423.5)	59.41	4.11	8.29	16.47

TABLE III
(*Continued*)

Compound	M. p., °C Yield, %	Formula (M. w.)	Calculated/Found			
			% C	% H	% Cl	% N
XIb[a]	120 – 123	$C_{25}H_{20}ClN_5O_2$	65.57	4.37	7.76	15.30
	60	(457.5)	65.43	4.25	7.66	15.18
XIc[b]	210 – 212	$C_{19}H_{15}ClN_4O_3$	59.61	3.92	9.28	14.64
	75	(382.5)	59.48	3.78	9.17	14.57
XIIa[c]	160 – 163	$C_{20}H_{16}ClN_5O_3$	58.61	3.91	8.67	17.09
	45	(409.5)	58.47	3.80	8.56	16.98
XIIb[c]	170 – 172	$C_{20}H_{16}ClN_5O_2S$	56.40	3.76	8.34	16.45
	50	(425.5)	56.32	3.64	8.31	16.37
XIIIa[c]	180 – 183	$C_{22}H_{21}ClN_4O_2$	64.63	5.14	8.69	13.71
	70	(408.5)	64.51	5.03	8.57	13.58
XIIIb[b]	210 – 213	$C_{26}H_{23}ClN_4O$	70.51	5.20	8.02	12.66
	60	(442.5)	70.38	5.12	7.93	12.53
XIIIc[c]	175 – 177	$C_{20}H_{18}ClN_3O_2$	65.31	4.90	9.66	11.42
	62	(367.5)	65.22	4.78	9.52	11.31
XIVa[b]	232 – 234	$C_{21}H_{19}ClN_4O_2$	63.88	4.82	9.00	14.20
	74	(394.5)	63.75	4.67	8.89	14.07
XIVb[a]	185 – 187	$C_{21}H_{19}ClN_4OS$	61.39	4.63	8.64	13.64
	60	(410.5)	61.27	4.52	8.49	13.55

Crystallized from: [a] ethanol, [b] DMF, [c] methanol.

hydrochloride in 0.3 M alcoholic sodium hydroxide solution and urea or thiourea in presence of 0.05 M hydrochloric acid, were refluxed for 5 – 10 h. The product of *N*-acetyl pyrazoline derivatives has been obtained upon adding drops of cooled water to the concentrated solution, filtered, washed by diluted ethanol and then recrystallized.

The reaction mixture containing *N*-phenylpyrazoline, isoxazoline or pyrimidinone derivatives was concentrated and neutralized with acetic acid, hydrochloric acid and sodium hydroxide, respectively. The solid product was collected by filtration, washed with cooled water, dried and then crystallized from proper solvents. Most of these compounds have a brown to brownish orange colour, soluble in most polar solvents. Physical characteristics and selected IR and ^{1}H NMR data for these compounds are presented in Tables III and IV.

TABLE IV
Spectral data for compounds *V*, *VI* and *IX*

Compound	IR, cm^{-1}	^1H NMR, ppm
Va	1 690[a]	1.2 s, 6 H (2 CH_3); 2.2 s, 3 H (CH_3–CO); 5.1 – 5.3 d, 2 H (pyrazoline); 7.2 – 7.9 m, 10 H (2 ArH)
Vb	1 610[b]	1.2 s, 6 H (2 CH_3); 5.9 – 6.2 d, 2 H (pyrazoline); 7.1 – 7.9 m, 15 H (3 ArH)
Vc	1 615[b]	1.2 s, 6 H (2 CH_3); 5.1 – 5.2 d, 2 H (pyrazoline); 7.1 – 7.8 m, 10 H (2 ArH)
VIa	1 740[a] 3 400 – 3 300[c]	1.2 s, 6 H (2 CH_3); 3.4 b, 1 H (NH); 7.1 – 7.9 m, 12 H (2 ArH and pyrimidine H-3, H-4)
VIb	1 213[d] 3 400 – 3 300[c]	1.2 s, 6 H (2 CH_3); 3.4 b, 1 H (NH); 7.1 – 7.8 m, 12 H (2 ArH and pyrimidine H-3, H-4)
IXa	1 720[a]	1.2 s, 3 H (CH_3); 2.2 s, 3 H (CH_3–CO); 5.1 – 5.15 d, 2 H (pyrazoline H-4); 5.2 t, 1 H (pyrazoline H-5); 7.2 – 7.9 m, 10 H (2 ArH)
IXb	1 615[b]	1.2 s, 3 H (CH_3); 5.1 – 5.15 d, 2 H (pyrazoline H-4); 5.2 t, 1 H (pyrazoline H-5); 7.1 – 7.8 m, 15 H (3 ArH)
IXc	1 610[b]	1.2 s, 3 H (CH_3); 5.1 – 5.15 d, 2 H (pyrazoline H-4); 5.2 t, 1 H (pyrazoline H-5); 7.1 – 7.8 m, 10 H (2 ArH)

Bonds attributed as [a] (C=O), [b] (C=C), [c] (N–H), [d] (C=S).

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