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SYNTHESIS OF NITROGENOUS COMPOUNDS. *Part II*

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2,4-dioxohexenoates have been prepared by the condensation of ketones with ethyl oxalate to obtain new heterocycles for the study of structure activity relationship. A number of trisubstituted pyrazoles have been synthesized to study their potential use as antimicrobial and/or hypoglycemic agent.

Key words : Synthesis-Heterocyclic compounds.

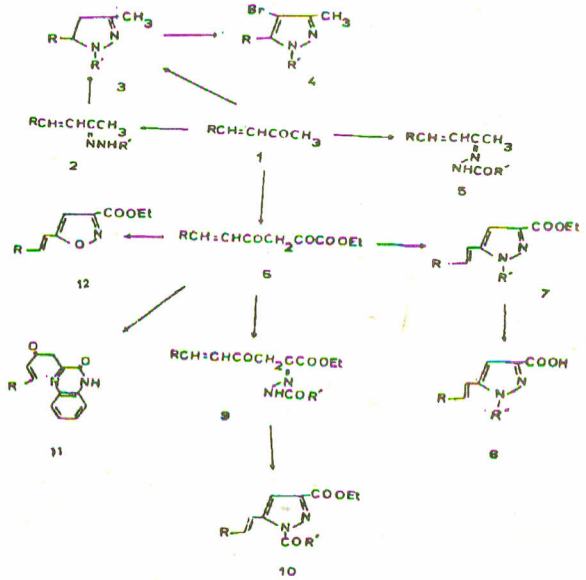
Introduction

The present investigation is a part of our systematic study [1-11] on the synthetic possibilities of 2,4-dioxohexenoates within the context of the preparation of new heterocycles. It has been reported [12-15] that many 3,5-dimethylpyrazoles showed potent hypoglycemic activity. Based on biological data reported by Soliman and coworkers [16-20] for 3,5-disubstituted pyrazoles, a possible structure-activity relationship for their hypoglycemic activity was established.

Condensation of ketones with arylhydrazines yielded the hydrazones. Heating of with ethanolic hydrogen chloride supplied the pyrazolines. Oxidation of with bromine water afforded the brominated pyrazoles. Reaction of with acylhydrazines furnished the hydrazones.

Alternatively, condensation of with ethyl oxalate gave the ethyl hexenoates which with hydrazines produced the pyrazole-3-esters, which were hydrolysed to the acids.

Esters on reaction with acylhydrazines afforded the hydrazones which were cyclized to the N-acylpyrazoles. With o-phenylenediamine, compounds [6] furnished the oxyquinoxalines, whereas, with hydroxylamine they gave rise to the isoxazole esters.



Materials and Methods

Experimental procedure. Melting points were taken in open glass capillaries and are uncorrected. IR absorption spectra were recorded in KBr on a Unicam SP-1025 spectrophotometer (υ_{max} in cm^{-1}), UV spectra in ethanol on a Unicam SP-1750 instrument (λ_{max} in nm) and ^1H nmr spectra in $CDCl_3$ on a varian HA 100 instrument using TMS as internal standard (chemical shift in δ, ppm).

4-Arylbut-3-en-2-ones (1). A solution of 2-furfuraldehyde or substituted benzaldehyde (0.1 mol) in acetone (45 ml) was treated dropwise with 2 ml of 10% NaOH solution during 30 min with stirring. The reaction mixture was stirred for another 2 hr, acidified with diluted HCl and extracted thrice with benzene. After removal of benzene, the desired ketone (1) was produced as yellow oil; yield 70%. The m-nitro derivative (1; R = m-$O_2NC_6H_4$) was obtained as yelow solid, m.p. 198° (yield 65%). IR: 1690 (C=O); ^1H-nmr: 1.38 (s, 3H, CH_3); 7.05-8.51 (m, 7H, -CH=CH and ArH) (Found: C, 62.7; H, 4.8; N, 7.3. $C_{10}H_9NO_3$ requires C, 62.8, H, 4.7; N, 7.3%). The appearance of the methyl group protons signal at low field (1.38) may be attributed to the electron attracting effect (-I_e) of the m-nitro-group. It forms an oxime derivative which crystallized from dilute ethanol in pale creem crystals; m.p. 138°; IR: 1600 (C=N), 3500 (OH); 860 and 1530-1350 (NO_2) (Found: C, 58.3; H, 5.0; N, 13.5. $C_{10}H_{10}N_2O_3$ requires C, 58.3; H, 4.9; N, 13.6%). The oxime derivative of the unsaturated ketone (1, R = p-$CH_3OC_6H_4$) has m.p. 132 and it was crystallized from dilute ethanol; IR: 1600 (C=N), 3480 (OH), 1580 (C=C, aromatic). (Found: C, 69.0; H, 7.0; N, 7.4. $C_{11}H_{13}NO_3$ requires C, 69.1; H, 6.8; N, 7.3%).

4-Arylbut-3-en-2-one-2-arylhydrazones (2). A mixture of the α,β-unsaturated ketone (1; 1 mmol) and the appropriate arylhydrazine (1 mmol) in ethanol (50 ml) was refluxed for 1 hr on a boiling steam-bath. Concentration and cooling of the reaction mixture furnished the hydrazone that crystallized from methanol in needles, yield 30-35% (Table 1).

1,5-Diaryl-3-methyl-2-pyrazolines (3). These pyrazolines were prepared by boiling the appropriate arylhydrazones (2; 1 mmol) with ethanol (25 ml) containing two drops of

hydrochloric acid for 3 hr. The reaction mixture was then concentrated and the deposited solid crystallized from dilute ethanol in needles, yield 25-30% (Table 2). Furthermore, these pyrazolines (3) were prepared, by refluxing the ketone (1; 1 mmol) with the appropriate arylhydrazine hydrochloride (1 mmol) in ethanol (35 ml) for 2 hr and working up as previously.

4-Bromo-1, 5-diaryl-3-methylpyrazoles (4). To an aqueous suspension of the foregoing pyrazolines (3; 1 mmol) in water (20ml), 5% bromine water (50 ml) was gradually added with stirring during 1 hr. and stirring continued for another 20 hr. The brominated pyrazoles which separated out were filtered off, washed successively with water, dried and recrystallized from dilute methanol in needles; yield 25-28% (Table 3).

4-Arylbut-3-en-2-one 2-acylhydrazones (5). A mixture of the α,β-unsaturated ketone (1; 1 mmol) and the appropriate acylhydrazine (1 mmol) in ethanol (25 ml) was heated under reflux on a boiling water bath for 1 hr. Concentration and cooling of the reaction mixture furnished the acylhydrazone that was crystallized either from methanol or benzene-methanol mixture in needles, yield 25-35% (Table 4).

TABLE 1. MICROANALYTICAL DATA FOR 4-ARYLBUT-3-EN-2-ONE 2-ARYLHYDRAZONES(2).

R	R'	Yield (%)	M.p. (°C)	Molecular formula	Calculated (%) C	H	N	Cl	Found (%) C	H	N	Cl
m-ClC_6H_4	-SO_2NH_2	35	212	$C_{16}H_{16}N_3O_2ClS$	54.9	5.6	12.0	10.2	54.9	5.7	12.1	10.1
m-ClC_6H_4	-NO_2	32	136	$C_{16}H_{14}N_3O_2Cl$	60.9	4.4	13.3	11.3	60.7	4.4	13.1	11.4
m-ClC_6H_4	-NO_2 (NO_2)	35	162	$C_{16}H_{13}N_4O_4Cl$	53.3	3.6	15.5	9.9	53.1	3.7	15.6	10.0
m-$NO_2C_6H_4$	-	30	154	$C_{16}H_{15}N_3O_2$	68.3	5.3	15.0	-	68.3	5.5	15.1	-
m-$NO_2C_6H_4$	-NO_2	32	118	$C_{16}H_{14}N_4O_4$	58.9	4.3	17.2	-	59.0	4.2	17.3	-
m-$NO_2C_6H_4$	-NO_2 (NO_2)	33	175	$C_{16}H_{13}N_5O_6$	51.8	3.5	18.9	-	51.7	3.5	19.0	-
p-$CH_3OC_6H_4$	-SO_2NH_2	33	165	$C_{17}H_{19}N_3O_3S$	59.1	5.5	12.2	-	59.0	5.6	12.2	-
p-$CH_3OC_6H_4$	-NO_2	35	162	$C_{17}H_{17}N_3O_3$	65.6	5.5	13.5	-	65.5	5.6	13.4	-
p-$CH_3OC_6H_4$	-NO_2 (NO_2)	34	138	$C_{17}H_{16}N_4O_5$	57.3	4.5	15.7	-	57.3	4.6	15.8	-

TABLE 2. MICROANALYTICAL DATA FOR 1,5-DIARYL-3-METHYL-2-PYRAZOLINES(3).

R	R'	Yield (%)	M.p. (°C)	Molecular formula	Calculated (%) C	H	N	Cl	Found (%) C	H	N	Cl
m-ClC_6H_4	-SO_2NH_2	30	160	$C_{16}H_{16}N_3O_2ClS$	54.9	4.6	12.0	10.2	55.6	4.5	12.0	10.3
m-ClC_6H_4	-COOH	30	133	$C_{17}H_{15}N_2O_2Cl$	64.9	4.8	8.9	11.3	64.8	5.0	9.0	11.2
m-ClC_6H_4	-NO_2	32	155	$C_{16}H_{14}N_3O_2Cl$	60.9	4.4	13.3	11.3	60.8	4.5	13.3	11.4
m-ClC_6H_4	-NO_2 (NO_2)	30	220	$C_{16}H_{13}N_4O_4Cl$	53.3	3.6	15.5	9.9	53.1	3.6	15.4	9.8
m-$NO_2C_6H_4$	-	25	175	$C_{16}H_{15}N_3O_2$	68.3	5.3	15.0	-	68.2	5.4	15.1	-
m-$NO_2C_6H_4$	-SO_2NH_2	29	172	$C_{16}H_{16}N_4O_4S$	53.3	4.4	15.6	-	53.3	4.0	15.5	-
m-$NO_2C_6H_4$	-NO_2	30	245	$C_{16}H_{14}N_4O_4$	58.9	4.3	17.2	-	58.9	4.4	17.3	-
m-$NO_2C_6H_4$	-NO_2 (NO_2)	32	199	$C_{16}H_{13}N_5O_6$	51.8	3.5	18.9	-	51.7	3.7	18.8	-
p-$CH_3OC_6H_4$	-SO_2NH_2	30	185	$C_{17}H_{19}N_3O_3S$	59.1	5.5	12.2	-	59.0	5.6	12.3	-
p-$CH_3OC_6H_4$	-COOH	31	204	$C_{18}H_{18}N_2O_3$	69.7	5.8	9.0	-	69.6	5.9	8.9	-
p-$CH_3OC_6H_4$	-NO_2	30	134	$C_{17}H_{17}N_3O_3$	65.6	5.5	13.5	-	65.6	5.7	13.3	-
p-$CH_3OC_6H_4$	-NO_2	30	200	$C_{17}H_{16}N_4O_5$	57.3	4.5	15.7	-	57.1	4.6	15.6	-

Ethyl 6-aryl-2, 4-dioxohexenoates (6). A mixture of 4-arylbut-3-en-2-one (1, 0.1 mol) and ethyl oxalate (0.1 mol) in dry ether (150 ml) was gradually added with shaking to an ice cold suspension of sodium ethoxide (0.1 mol) in dry ether (200 ml). After keeping the reaction mixture at room temperature for 24 hr. the separated sodium salt was filtered off, washed with ether , dried then acidified with cold dilute sulphuric acid. The desired titled ester was purified by recrystallization from methanol as a yellow orange needles, yield 75-90% (Table 5).

Ethyl 1-H/aryl-5-substituted-pyrazole-3-carboxylates (7). These trisubstituted pyrazole esters were obtained by refluxing a mixture of 6 (1 mmol) and the appropriate arylhydrazines, methylhydrazine or hydrazine (1 mmol) in ethanol (50 ml) on a boiling water bath for 3 hr. On concentration and cooling, the pyrazole esters separated out and were recrystallized from

TABLE 3. MICROANALYTICAL DATA FOR 4-BROMO-1,5-DIARYL-3-METHYLPYRAZOLES(4).

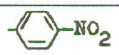
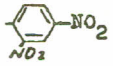
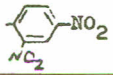
R	R'	Yield (%)	M.p. (°C)	Molecular formula	Calculated (%) C	H	N	Br	Found (%) C	H	N	Br
m-ClC$_6$H$_4$		26	102	$C_{16}H_{11}N_3O_2BrCl$	49.0	2.8	10.7	20.2	49.1	3.0	10.6	20.1
m-ClC$_6$H$_4$		25	92	$C_{16}H_{10}N_4O_4BrCl$	44.0	2.3	12.8	18.1	44.1	2.5	12.7	18.0
m-NO$_2$C$_6$H$_4$		28	173	$C_{16}H_{10}N_5O_6Br$	43.0	2.2	15.7	17.7	42.9	2.4	15.6	17.7

TABLE 4. MICROANALYTICAL DATA FOR 4-ARYL-BUT-3-EN-2-ONE-2-ACYLHYDRAZONES (5).

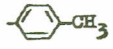
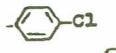
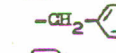
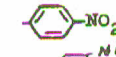
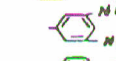
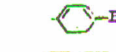
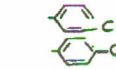
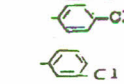
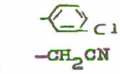
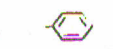
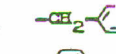
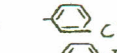
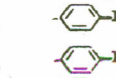
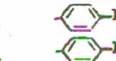
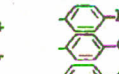
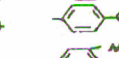
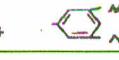
R	R'	Yield (%)	M.p. (°C)	Molecular formula	Calculated (%) C	H	N	Cl	Found (%) C	H	N	Cl
m-ClC$_6$H$_4$		30	154	$C_{17}H_{16}N_3OCl$	65.1	5.1	13.4	11.3	65.0	5.2	13.1	11.2
m-ClC$_6$H$_4$		28	156	$C_{18}H_{17}N_2OCl$	69.1	5.4	9.0	11.4	69.2	5.5	8.9	11.5
m-ClC$_6$H$_4$		30	101	$C_{17}H_{14}N_2OCl_2$	61.3	4.2	8.4	21.3	61.2	4.4	8.3	21.3
m-ClC$_6$H$_4$		35	126	$C_{18}H_{17}N_2OCl$	69.1	5.4	9.0	11.4	69.0	5.5	8.9	11.5
m-ClC$_6$H$_4$		25	150	$C_{17}H_{15}N_2OCl$	68.3	5.0	9.4	11.9	68.1	5.1	9.3	12.0
m-ClC$_6$H$_4$		35	204	$C_{17}H_{14}N_3O_3Cl$	59.4	4.1	12.2	10.3	59.3	4.2	12.1	10.4
m-ClC$_6$H$_4$		35	200	$C_{17}H_{13}N_4O_5Cl$	52.5	3.4	14.4	9.1	52.4	3.5	14.4	9.0
m-ClC$_6$H$_4$		30	124	$C_{17}H_{14}N_2OBrCl$	54.2	3.7	7.4	9.4	54.2	3.8	7.5	9.3
m-ClC$_6$H$_4$	-CH$_2$CN	25	146	$C_{13}H_{12}N_3OCl$	59.7	4.6	16.1	13.6	59.6	4.7	16.0	13.6
m-ClC$_6$H$_4$		30	92	$C_{17}H_{14}N_2OCl_2$	61.3	4.2	8.4	21.3	61.3	4.2	8.5	21.2
m-NO$_2$C$_6$H$_4$		30	198	$C_{16}H_{14}N_3O_2Cl$	60.9	4.4	13.3	11.3	60.8	4.5	13.5	11.3
m-NO$_2$C$_6$H$_4$		30	171	$C_{16}H_{14}N_3O_2Cl$	60.9	4.4	13.3	11.3	60.9	4.5	13.4	11.4
p-CH$_3$OC$_6$H$_4$	-CH$_2$CN	25	117	$C_{14}H_{15}N_3O_2$	65.4	5.8	16.3	-	65.3	6.0	16.2	-
p-CH$_3$OC$_6$H$_4$		28	166	$C_{19}H_{20}N_2O_2$	74.0	6.5	9.1	-	74.1	6.5	9.0	-
p-CH$_3$OC$_6$H$_4$		25	192	$C_{18}H_{18}N_2O_2$	73.5	6.1	9.5	-	73.5	6.3	9.4	-
p-CH$_3$OC$_6$H$_4$		30	188	$C_{19}H_{20}N_2O_2$	74.0	6.5	9.1	-	74.0	6.6	9.0	-
p-CH$_3$OC$_6$H$_4$		30	185	$C_{18}H_{17}N_2O_2Cl$	65.8	5.2	8.5	10.8	65.6	5.3	8.4	-
p-CH$_3$OC$_6$H$_4$		28	208	$C_{18}H_{17}N_2O_2Br$	58.1	4.6	7.5	-	58.0	4.7	7.6	-
p-CH$_3$OC$_6$H$_4$		30	201	$C_{18}H_{19}N_3O_2$	69.9	6.2	13.6	-	770.0	6.3	13.5	-
p-CH$_3$OC$_6$H$_4$		30	198	$C_{18}H_{17}N_3O_4$	63.7	5.0	12.4	-	63.6	5.2	12.5	-
p-CH$_3$OC$_6$H$_4$		28	199	$C_{18}H_{17}N_2O_2Cl$	65.8	5.2	8.5	10.8	65.8	5.3	8.4	11.0
p-CH$_3$OC$_6$H$_4$		25	206	$C_{19}H_{20}N_2O_3$	70.4	6.2	8.6	-	70.3	6.3	8.7	-
p-CH$_3$OC$_6$H$_4$		30	211	$C_{18}H_{16}N_4O_6$	56.3	4.2	14.6	-	56.3	4.4	14.5	-

TABLE 5. ETHYL 2,4-DIOXO-6-SUBSTITUTED-HEX-5-ENOATES(6).

R	Yield (%)	M.p. (°C)	Molecular formula	Calculated (%) C	H	Cl	Found (%) C	H	Cl
m-ClC_6H_4	80	100	$C_{14}H_{13}O_4Cl$	59.9	4.6	12.7	59.8	4.7	12.7
p-$CH_3OC_6H_4$	90	92*	$C_{15}H_{16}O_5$	—	—	—	—	—	—
2-Furyl	75	80**	$C_{12}H_{12}O_5$	—	—	—	—	—	—

* lit[23] m.p. 92° ** lit[23] m.p. 80

TABLE 6. MICROANALYTICAL DATA FOR ETHYL 1-H/ARYL-5-SUBSTITUTED PYRAZOLE-3-CARBOXYLATES(7).

R	R'	Yield (%)	M.p. (°C)	Molecular formula	Calculated (%) C	H	N	Cl	Found (%) C	H	N	Cl
m-ClC_6H_4	-SO_2NH_2	45	201	$C_{20}H_{18}N_3O_4ClS$	55.6	4.2	9.7	8.2	55.6	4.3	9.6	8.1
m-ClC_6H_4	-SO_2NH-(pyrimidin-2-yl)	40	204	$C_{24}H_{20}N_5O_4Cl$	56.5	3.9	13.7	77.0	56.5	4.0	13.6	7.1
m-ClC_6H_4	-CH_3	35	144	$C_{21}H_{19}N_2O_2Cl$	68.8	5.2	7.6	9.7	68.8	5.2	7.7	9.6
m-ClC_6H_4	-pyridyl	30	157	$C_{19}H_{16}N_3O_2Cl$	64.5	4.5	11.9	10.0	64.4	4.6	12.0	10.0
m-ClC_6H_4	CH_3	32	132	$C_{15}H_{15}N_2O_2Cl$	62.0	5.2	9.6	12.2	62.1	5.4	9.5	12.3
p-$CH_3OC_6H_4$	-SO_2NH_2	40	175	$C_{21}H_{21}N_3O_5S$	59.0	4.9	9.8	7.5	59.0	5.0	9.6	7.3
p-$CH_3OC_6H_4$	-CH_3	30	104	$C_{22}H_{22}N_2O_3$	72.9	6.1	7.7	-	72.7	6.3	7.7	-
p-$CH_3OC_6H_4$	-Cl	30	107	$C_{21}H_{19}N_2O_3Cl$	65.9	5.0	7.3	9.3	65.8	5.1	7.2	9.3
p-$CH_3OC_6H_4$		30	102**	$C_{21}H_{20}N_2O_3$								
p-$CH_3OC_6H_4$	-SO_2NH-(pyrimidin-2-yl)	40	188	$C_{22}H_{23}N_5O_5S$	59.4	4.6	13.9	-	59.3	4.8	13.8	-
p-$CH_3OC_6H_4$	-NO_2	50	136	$C_{21}H_{19}N_3O_5$	64.1	4.8	10.7	-	64.0	4.9	10.8	-
p-$CH_3OC_6H_4$		45	77	$C_{23}H_{20}N_4O_3$	69.0	5.0	14.0	-	68.9	5.2	13.8	-
p-$CH_3OC_6H_4$	H	40	112	$C_{15}H_{16}N_2O_3$	66.2	5.9	10.3	-	66.2	6.0	10.4	-
2-Furyl	-SO_2NH_2	45	193	$C_{18}H_{17}N_3O_5S$	55.8	4.4	10.9	-	55.9	4.4	10.9	-
2-Furyl	-Cl	40	138	$C_{18}H_{15}N_2O_3Cl$	63.1	4.4	8.2	10.4	63.0	4.5	8.1	10.5
2-Furyl	-NO_2	40	189	$C_{18}H_{15}N_3O_5$	61.2	4.3	11.9	-	61.0	4.4	11.8	-

* lit[23] m.p. 100°

TABLE 7. MICROANALYTICAL DATA FOR 1-H/ARYL-5-SUBSTITUTED PYRAZOLE-3-CARBOXYLIC ACIDS (8).

R	R'	Yield (%)	M.p. (°C)	Molecular formula	Calculated (%) C	H	N	Cl	Found (%) C	H	N	Cl
m-ClC_6H_4	-SO_2NH_2	60	254	$C_{18}H_{14}N_3O_2ClS$	58.1	3.8	11.3	9.6	58.0	3.9	11.3	9.5
m-ClC_6H_4	-SO_2NH-(pyrimidin-2-yl)	60	192	$C_{22}H_{16}N_5O_4ClS$	54.8	3.3	14.6	7.4	54.8	3.5	14.7	7.5
m-ClC_6H_4	-CH_3	50	121	$C_{19}H_{15}N_2O_2Cl$	67.4	4.4	8.3	10.5	67.5	4.4	8.4	10.4
m-ClC_6H_4	-pyridyl	50	118	$C_{17}H_{12}N_3O_2Cl$	62.7	3.7	12.9	10.9	62.5	3.9	13.0	10.8
m-ClC_6H_4	CH_3	50	166	$C_{13}H_{11}N_2O_2Cl$	59.4	4.2	10.7	13.5	59.3	4.3	10.6	13.4
p-$CH_3OC_6H_4$	-pyridyl	50	190	$C_{18}H_{15}N_3O_3$	67.3	4.7	13.1	-	67.3	4.7	13.0	-
p-$CH_3OC_6H_4$	-phenyl	52	128	$C_{19}H_{16}N_2O_3$	71.3	5.0	8.8	-	71.2	5.2	9.0	-
p-$CH_3OC_6H_4$	-C_6H_4-Cl	55	148	$C_{19}H_{15}N_2O_3Cl$	64.3	4.2	7.9	10.0	64.1	4.3	8.0	10.1
p-$CH_3OC_6H_4$	-C_6H_4-CH_3	50	107	$C_{20}H_{18}N_2O_3$	71.9	5.4	8.4	-	71.8	5.5	8.4	-
p-$CH_3OC_6H_4$	-SO_2NH-(pyrimidin-2-yl)	60	179	$C_{23}H_{19}N_5O_5S$	57.9	4.0	14.7	6.7	57.9	4.1	14.7	-
p-$CH_3OC_6H_4$		60	186	$C_{21}H_{16}N_4O_3$	67.7	4.3	15.1	-	67.7	4.5	15.0	-
p-$CH_3OC_6H_4$	H	50	237	$C_{13}H_{12}N_2O_3$	63.9	4.9	11.5	-	63.7	5.0	11.4	-
p-$CH_3OC_6H_4$	CH_3	55	132	$C_{14}H_{14}N_2O_3$	65.1	5.4	10.9	-	65.0	5.6	11.0	-
2-Furyl	-C_6H_4-CH_3	50	195	$C_{17}H_{14}N_2O_3$	69.4	4.8	9.5	-	69.3	4.9	9.4	-
2-Furyl	-C_6H_4-Cl	50	296	$C_{16}H_{11}N_2O_3Cl$	61.1	3.5	8.9	11.3	61.0	3.7	8.8	11.2
2-Furyl	-C_6H_4-NO_2	60	218	$C_{16}H_{11}N_3O_5$	59.1	3.4	12.9	-	59.0	3.5	12.8	-

ethanol in needles, yield 30-50% (Table 6).

1-H/Aryl-5-substituted-pyrazole-3-carboxylic acids (8). The foregoing ester 7 (0.5 g) was boiled with 2N ethanolic KOH (50 ml) for 3 hr. The reaction mixture was concentrated, diluted with water and acidified with dilute hydrochloric acid (1:1) to give the acid (8) which crystallized from dilute methanol in needles, yield 50-60% (Table 7).

Ethyl 2,4-dioxo-6-arylhex-5-enoate-2-acylhydrazones (9). An ethanolic solution (50 ml) of the appropriate acylhydrazine (1 mmol) was added to a solution of the ethyl hexenoate (6; 1 mmol) in ethanol (50 ml) containing two drops of glacial acetic acid and the reaction mixture left at room temperature for one day. The orange-yellow solid thus separated was filtered, washed with little ethanol and crystalized from chloroform-light petroleum (b.p. 40-60°) mixture to give the titled compounds as orange-yellow needles, yield 35-40% (Table 8).

Ethyl 1-acyl-5-substituted-pyrazole-3-carboxylates (10). These N-acylpyrazole esters were prepared by boiling the foregoing acylhydrazones (9; 0.5 g) with ethanol (75 ml) containing two drops of hydrochloric acid for 3 hr. on a steam bath. Concentration and cooling furnished the N-acylpyrazole that was filtered off, dried and crystallized from dilute methanol in needles, yield 30-40% (Table 8).

Oxyquinoxaline derivatives (11). A mixtue of the ethyl hexenoate (6; 1 mmol) and o-phenyl-enediamine (1 mmol) in ethanol (35 ml) was heated under reflux on a boiling water bath for 2 hr. The oxyquinoxaline derivative obtained afer concentration was filtered, washed with little ethanol and crystallized from ethanol in orange-red needles, yield 70-75% (Table 9).

Ethyl 5-substituted isoxazole-3-carboxylates (12). These

TABLE 8. MICROANALYTICAL DATA FOR ETHYL 2,4-DIOXO-6-ARYLHEX-5-ENOATE 2-ACYLHYDRAZONES (9) AND ETHYL 1-ACYL-5-SUBSTITUTED PYRAZOLE-3-CARBOXYLATES (10)

R	R'	Yield (%)	M.p. (°C)	Molecular formula	Calculated (%) C	H	N	Cl	Found (%) C	H	N	Cl
m-ClC_6H_4		35	108	$C_{21}H_{18}N_2O_4Cl$	65.2	4.8	7.0	8.9	63.4	4.6	7.1	9.0
m-ClC_6H_4		40	127	$C_{20}H_{18}N_3O_4Cl$	60.0	4.5	10.5	8.9	59.8	4.6	10.6	9.0
p-$CH_3OC_6H_4$		36	118	$C_{22}H_{22}N_2O_5$	67.0	5.6	7.1	-	67.0	5.8	7.0	-
2-Furyl		35	158	$C_{19}H_{18}N_2O_5$	64.4	5.1	7.9	-	64.4	5.2	7.8	-
2-Furyl		40	78	$C_{18}H_{17}N_3O_5$	60.9	4.8	11.8	-	60.7	4.9	11.8	-
1-Acylpyrazole-3-esters (10)												
m-ClC_6H_4		30	157	$C_{21}H_{17}N_2O_3Cl$	66.2	4.5	7.4	9.3	66.3	4.5	7.5	9.3
m-ClC_6H_4		40	129	$C_{20}H_{16}N_3O_3Cl$	62.9	4.2	11.0	9.3	62.8	4.4	10.9	9.2
p-$CH_3OC_6H_4$		35	86	$C_{22}H_{20}N_2O_4$	70.2	5.3	7.5	-	70.1	5.3	7.6	-
p-$CH_3OC_6H_4$		40	112	$C_{21}H_{19}N_3O_4$	66.8	5.0	11.1	-	66.7	5.2	11.0	-
2-Furyl		33	138	$C_{19}H_{16}N_2O_4$	67.9	4.8	8.3	-	67.8	5.0	8.1	-

TABLE 9. MICROANALYTICAL DATA FOR ETHYL 5-SUBSTITUTED-ISOXAZOLE-3-CARBOXYLATES (12) AND OXYQUINOXALINE DERIVATIVES (11).

R	Yield (%)	M.p. (°C)	Molecular formula	Calculated (%) C	H	N	Cl	Found (%) C	H	N	Cl
Isoxazole esters (12)											
m-ClC_6H_4	40	182	$C_{14}H_{12}NO_3Cl$	60.5	4.3	5.0	12.8	60.4	4.4	5.1	12.6
p-$CH_3OC_6H_4$	35	77*	———	—	—	—	—	—	—	—	—
Oxyquinoxaline derivatives (11)											
m-ClC_6H_4	75	243	$C_{18}H_{12}N_2O_2Cl$	66.8	3.7	8.7	11.0	66.7	3.9	8.8	11.0
p-$CH_3OC_6H_4$	75	278	$C_{19}H_{15}N_2O_3$	71.5	4.7	8.8	-	71.5	4.9	8.7	-
2-Furyl	70	191	$C_{16}H_{11}N_2O_3$	68.8	3.9	10.0	-	68.9	4.0	10.1	-

* lit.23 m.p. 77

compounds were obtained by boiling the 1, 3-diketoester (6; 1 mmol) in ethanol (25 ml) with hydroxylamine hydrochloride (1 mmol) and sodium acetate (1 mmol) in water (3 ml) for 2 hr. On concentration and cooling, the isoxazole ester separated out was filtered and crystallized from ethanol in needles, yield 35-40% (Table 9).

Discussion

The reaction of (1) with arylhydrazines furnished the hydrazones (2). Their i.r. spectra revealed bands at 3255-3140 cm^{-1} indicative of the NH group, at 1620-1585 cm^{-1} for an imine group, at 770-745 cm^{-1} due to mono-substituted benzene ring, at 1595-1485 cm^{1} characteristic for (C=C, aromatic, two bands at 1345-1335 cm^{-1} and 1190-1170cm^{-1} typical of the $-SO_2N$ group and the NO_2 group bands were observed at 845 and 1540-1350 cm^{-1}. The ^1H nmr ($CDCl_3$) spectra of these hydrazones (2) displayed singlet at δ2.36-2.38(CH_3) multiplet at 7.11-8.98 due to conjugated and aromatic ring protons singlet at δ9.14 ppm (NH, diappear on deuteration). In addition to these signals the p-methoxyphenyl derivatives showed a singlet due to the (CH_3O) group at δ 3.71-3.84 ppm. Hydrazones (2) on refluxing with ethanol containing drops of HCl underwent cyclization to the pyrazolines [3] which were also obtained by reaction of (1) with arylhydrazine hydrochlorides. Their i.r. spectra revealed bands due to saturated (C-H) bond of the methyl group at 2930-2835 cm^{-1} two bands for the $-SO_2N$ at 1350-1320 and 1195-1170 cm^{-1} and bands at 855 and 1550-1350 cm^{-1} for (NO_2) group. Their ^1H nmr ($CDCl_3$) spectra exhibited a singlet at δ 2.13-2.41 (CH_3 protons), multiplet at δ5.2 and 3.4 due to CH and $CH_2$of the pyrazoline ring and multiplet at 6.79-8.05 ppm for aromatic ring protons. In addition to these signals the p-methoxyphenyl derivatives gave a second methyl group protons as singlet at δ3.61-3.73 ppm. Oxidation of (3) with an excess of bromine water led to the formation of the brominated pyrazoles (4). Their ^1H nmr ($CDCl_3$) spectra showed singlet at δ2.21-2.33 (CH_3 protons); and the aromatic ring protons as a multiplet at 7.02-8.13 ppm and disappearance of the multiplet signals observed at 5.2 and 3.4 ppm in the spectra of pyrazolines (3). With acylhydrazines, ketones (1) generated the hydrazones (5). Their i.r. spectra revealed the carbonyl group band of the hydrazone part at 1665-1625 cm^{-1}, the NH group at 3395-3220 cm^{-1}, at 1610-1580 cm^{-1} characteristic for an imine group and at 1580-1490 cm^{-1} due to (C=C, aromatic). Their ^1H nmr ($CDCl_3$) spectra exhibited singlet at δ2.13-2.56, (CH_3)multiplet singnals at 6.85-7.95 due to conjugated and aromatic ring protons and singlet at δ8.91 ppm (NH proton disappeared on deuteration).

Compounds (1) on condensation with ethyl oxalate produced ethyl hexenoates (6). Their i.r. spectra displayed bands at 1735 cm^{-1} caused by the ester group, at 1640-1490 cm^{-1} (C=C, aromatic), at 1270-1015 cm^{-1} for (-C-O-C-) of ester group, while the (OH) group appeared at 3500-3480 cm^{-1}. Their ^1Hnmr ($CDCl_3$) spectra exhibited singnals at δ1.38 (triplet, 3H, $-CH_2CH_3$); 4.34-4.44 (quartet, 2H, $-CH_2CH_3$); 6.38, 6.68 (doublet, doublet, 1H, 1H, -CH=CH-); 6.56 (singlet, 1H, =CH-) and at 7.16-7.95 (multiplet, 5H, OH and aromatic ring protons) ppm. The signal at δ6.56 ppm. proves the enolic form of esters (6) and this explain their reaction with hydrazines to give the pyrazole-3-esters (7) and not the 5-esters.

The ethyl hexenoates (6) on reaction with hydrazines yielded the trisubstituted pyrazole esters (7). Their i.r. absorption spectra displayed carbonyl ester group band at 1735 cm^{-1} bands at 1260-1025 cm^{-1} due to (-C-O-C-) of ester group, at 1640-1480 cm^{-1} due to (C=C, aromatic), at 1350-1330) and 1190-1170 cm-1 for $-SO_2N$ group, at 3425-3240 cm^{-1} indicative of the NH group and the NO_2 group bands were observed at 850 and 1355 cm^{-1}. Their u.v. spectra showed two maxima stretching up to 204 and 318 nm and one minima at 254 nm. The structure of these esters (7) was further confirmed by measuring their ^1H nmr ($CDCl_3$) spectra that exhibited signals at δ1.25 (triplet) and 4.25 (quartet) for the ethyl ester group protons, conjugated and aromatic ring protons (multiple) at 6.81-7.65 ppm. Esters (7) underwent hydrolysis with ethanolic 2N KOH to the acids (8). Their i.r. spectra showed carbonyl group band at 1720 cm^{-1}, the OH group band in the region of 3500-3340 cm^{-1}, bands at 1610 cm^{-1} for (C=N) group, at 1600-1500 cm-1 indicative of (C=C, aromatic) and the (NO_2) group bands were observed at 870 and 1350 cm^{-1}.

Esters (6) reacted readily with acylhydrazines to generate the hydrazones (9). Their i.r. spectra revealed bands at 1650-1625 cm^{-1} caused by the carbonyl groue hydrazone part, at 3300-3150 cm^{-1} for the NH group, at 1735 cm^{-1} due to the carbonyl ester group, at 1620-1580 cm^{-1} indicative of the imine group and at 3500 cm^{-1} due to the OH group absorption. Hydrazones (9) on boiling with ethanol containingdrops of HCl underwent cyclization to N-acylpyrazoles (10). Their i.r. spectra displayed carbonyl ester group band at 1735 cm^{1}, carbonyl group band of the N-acyl part at 1675-1630 cm^{-1}, and bands due to (C=C, aromatic) were observed at 1580-1410 cm^{-1}.

With o-phenylenediamine, compounds (6) produced the oxyquinoxalines (11). Although ethyl 2, 4-dioxohexenoates may undergo attack either at 1, 2-carbonyls or at 2, 4-carbonyls, the resultant products were formulated as oxyquinoxalines. This behaviour is similar to the reaction of dehydroascorbic acid with o-phenylenediamine[21,22]. The possibility of attack on 2,4-positions of (6) is not acceptable since it will give a less favoured seven-membered

heterocycles. Their i.r. spectra exhibited bands at 1680 cm^{-1} for (OCN) group, at 1600-1480 cm^{-1} of (C=C, aromatic), at 1610 cm^{-1} due to (C=N) group, at 3500 cm^{-1} for (OH) group and at 2930 cm^{-1} due to (NH) group.

The hexenoates (6) reacted readily with hydroxylamine to furnish 5-substituted-isoxazole-3-esters (12). Their i.r. spectra exhibited the carbonyl ester group band at 1720 cm^{-1}, bands at 1580-1470 cm^{-1} characteristic for (C=C, aromatic), and at 1250-1010 cm^{-1} due to (-C-O-C-) of ester group.

Their ^{1}H-nmr ($CDCl_3$) spectra displayed signals at δ1.27 (triplet, 3H, $-CH_2CH_3$); 4.25 (quartet, 2H, $-CH_2CH_3$) and at 6.65-7.58 (multiplet, 7H, conjugated and aromatic ring protons) ppm. In addition to these signals the p-methoxyphenyl derivatives revealed a singlet due to the methoxyl group protons at δ3.81 ppm.

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