

Synthesis of Nitrogenous Compounds from δ -Unsaturated 1,3-Dicarbonyl Esters. Part I. Substituted Pyrazoles, Isoxazoles and Oxyquinoxalines.

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(Received 3rd November, 1987, Revised 17th March, 1988)

Summary: Condensation of 4-substituted-but-3-en-2-ones (1) with ethyl oxalate gave ethyl 6-aryl-2,4-dioxo- Δ^2 -hexenoates (2) and were interconverted to the methyl esters by alcoholysis. Compounds (2) were converted by hydrazine or arylhydrazine into the corresponding ethyl 1-H/aryl-5-substituted-pyrazole-3-carboxylates (3), which were hydrolysed to the acids (4). With hydroxylamine, the ethyl hexenoates (2) afforded 3,5-disubstituted-isoxazoles (5), whereas, with *o*-phenylenediamine they gave oxyquinoxaline derivatives (6).

The 1,3-diketo-esters (2) on reaction with acylhydrazines gave the acylhydrazones (7) which were cyclized to the corresponding *N*-acylpyrazoles (8). Reaction of (1) with arylhydrazines afforded the corresponding hydrazones (9) which on boiling with ethanol containing two drops of HCl underwent cyclization to the pyrazolines (10). Oxidation of (10) with an excess of bromine-water produced the brominated pyrazole derivatives (11). Furthermore, the condensation of the α,β -unsaturated ketones (1) with acylhydrazines furnished the corresponding hydrazones (12).

Introduction

Since previous studies indicated that several substituted 3,5-dimethylpyrazoles possessed potent hypoglycemic activity [1-4], additional compounds were synthesized [5-9]. Based on biological data reported by Soliman and co-workers [10-13], for 3,5-disubstituted pyrazoles, a possible structure-activity relationship for their hydroglycemic activity was established. The present study which is a continuation of previous work [5-9,14-16] describe the preparation of derivatives of 1,3,5-trisubstituted pyrazoles, hoping they might have beneficial hypoglycemic or antimicrobial activity. These compounds have, in addition to the carboxyl group on position 3, a substituted styryl group on position 5 and a variety of aryl substituted styryl groups on position 5 and a variety of aryl substituents

on position 1. Furthermore, it has been reported that many acid hydrazides such as cyanoacetic acid hydrazide [17] possess anti-tuberculous activity. These reports prompted us to synthesize some acylhydrazones of certain α,β -unsaturated ketones which might possess anti-tuberculous activity.

The Key intermediate, δ -unsaturated-1,3-dicarbonyl esters (2) required in the synthesis were prepared by the condensation of ethyl oxalate with 4-substituted-but-3-en-2-ones (1). The ethyl hexenoates (2) were interconverted to the methyl esters by alcoholysis and were utilized in the synthesis of new substituted pyrazoles (3), isoxazoles (4) and oxyquinoxalines (5) likely to be of medical importance.

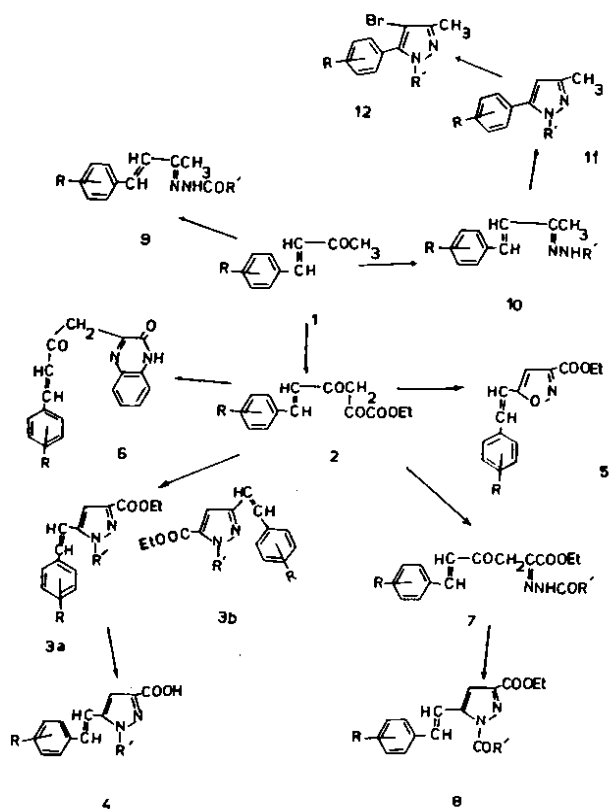
The I.R. spectra of (2) exhibited carbonyl absorption band at 1740 cm^{-1} , bands at $1640\text{--}1480\text{ cm}^{-1}$ due to (C=C, aromatic), at $1260\text{--}1030\text{ cm}^{-1}$ indicative of (-C-O-C-) of ester and (OH) group band at 3500 cm^{-1} . Whereas, their U.V. spectra showed two maxima stretching up to 226 and 324 nm and two minima up to 214 and 254 nm. Furthermore, their ^1H nmr (CDCl_3) spectra revealed at δ 1.35 (triplet, 3H, CH_2CH_3); 4.30 (quartet, 2H, CH_2CH_3); 6.50, 7.78 (doublet, doublet, 1H, 1H, -CH=CH-); 6.68 (singlet, 1H, =CH-) and at 7.20-7.72 (multiplet, 5H, OH and aromatic ring protons) ppm. In addition to these signals the p-tolyl derivative (2; $\text{R}=\text{p-CH}_3\text{C}_6\text{H}_4$) gave a singlet signal of CH_3 group protons at δ 2.48 ppm. The signal at 6.68 proves the enolic form of these esters and this explains their reaction with hydrazines to give the pyrazole 3-esters (3a) and not the 5-esters (3b).

With hydrazine and arylhydrazines, the δ -unsaturated-1,3-dicarbonyl esters (2), furnished the pyrazole-3-esters (3a). That these trisubstituted pyrazoles were obtained pure from the reaction medium is evidence that only one of the two carbonyl groups in 2 (actually C-2 carbonyl group being more reactive than the C-4 carbonyl) gets preferably attacked by the nucleophilic reagent such as hydrazine to give the corresponding hydrazone intermediate which simultaneously undergoes ring closure with the elimination of a water molecule from hydroxyl group of the enolized C-4 carbonyl and the imino-proton of the hydrazone part forming the 3-esters (3a) and not the 5-esters (3b). The I.R. spectra of compounds (3) showed characteristic carbonyl

ester group absorption band at 1740 cm^{-1} , bands at $1260\text{--}1025\text{ cm}^{-1}$ due to (-C-O-C-) of ester group and at $1620\text{--}1490\text{ cm}^{-1}$ characteristic for (C=C, aromatic). Besides these above bands, bands appeared in the region of $1190\text{--}1170$ and $1350\text{--}1330\text{ cm}^{-1}$ were due to SO_2N group, and the (NO_2) group bands were observed at 850 and 1350 cm^{-1} and the (NH) group at $3270\text{--}3150\text{ cm}^{-1}$. The esters (3) underwent hydrolysis with ethanolic 2N KOH to give the corresponding acids (4). Their I.R. spectra included carbonyl group absorption band at 1720 cm^{-1} and (OH) group band in the region of $3500\text{--}3300\text{ cm}^{-1}$.

The ethyl hexenoates (2) reacted readily with hydroxylamine to give ethyl 5-substituted-isoxazole-3-carboxylates to which are assigned the formula (5). This confirms to our experience regarding the reactivity of the carbonyl group attached to the ethoxycarbonyl group towards the ordinary carbonyl reagents. It is also in agreement with Soliman et al. [18] suggestion for ethyl 5-styryl-isoxazole-3-carboxylate. Their I.R. spectra displayed absorption bands at 1740 cm^{-1} for carbonyl ester group and bands in the region of $1640\text{--}1490\text{ cm}^{-1}$ characteristic for (C=C, aromatic). Furthermore, their U.V. spectra included two maxima stretching up to 218 and 290 nm and a minimum near 242 nm. The shift of absorption bands to shorter wavelengths in case of p-tolyl derivative (5; $\text{R}=\text{p-CH}_3$) may be attributed to electron repelling effect ($+I_s$) of the methyl group.

However, on reaction with o-phenylenediamine, compounds (2) furnished the oxyquinoxaline deri-



vatives (6). Their I.R. spectra exhibited absorption bands at 1680 cm^{-1} characteristic for (OCN) group, at $1600\text{--}1490\text{ cm}^{-1}$ indicative of (C=C, aromatic), at 1610 cm^{-1} due to (C=N) group, at 3500 cm^{-1} for (OH) group and at 2920 cm^{-1} due to (NH) group.

Furthermore, the reaction of (2) with acylhydrazines furnished the corresponding acylhydrazones (7).

Their I.R. spectra displayed bands at $1645\text{--}1630\text{ cm}^{-1}$ indicative of the carbonyl group of the hydrazone part, carbonyl ester group at 1735 cm^{-1} , (NH) group at $3250\text{--}3140\text{ cm}^{-1}$, (OH) group absorption at 3500 cm^{-1} and (C=N) group at $1600\text{--}1580\text{ cm}^{-1}$. Moreover, their U.V. spectra included

three maxima stretching up to 204, 244 and 296 nm and two minima up to 222 and 254 nm.

Cyclization of the foregoing hydrazones (7) by refluxing with ethanol containing drops of HCl afforded the corresponding N-acylpyrazoles (8). Their I.R. spectra exhibited carbonyl ester group band at 1740 cm^{-1} , carbonyl group band of N-acyl part at $1670\text{--}1640\text{ cm}^{-1}$ and bands in the region of $1585\text{--}1410\text{ cm}^{-1}$ indicative of (C=C, aromatic). Whereas, their U.V. spectra showed two maxima stretching up to 220 and 294 nm and a minimum near 254 nm.

Condensation of substituted benzaldehyde with dimethyl ketone generated the α,β -unsaturated ketones (1). Their ^1H nmr (CDCl_3) spectra gave the methyl protons as singlet at δ 2.33 and multiplet signals at δ 6.45–7.62 ppm due to (–CH=CH– and aromatic ring protons). With acylhydrazines, the ketone (1) supplied the corresponding acylhydrazones (9). Their I.R. spectra displayed the carbonyl group band of the hydrazone part at $1660\text{--}1620\text{ cm}^{-1}$, bands at $3390\text{--}3220\text{ cm}^{-1}$ indicative of (NH) group, at $1610\text{--}1580\text{ cm}^{-1}$ due to (C=N) group and at $1580\text{--}1490\text{ cm}^{-1}$ characteristic for (C=C, aromatic). The structure of these acylhydrazones (9) was further confirmed by measuring the mass spectra of compound (9; $\text{R}=\text{p-CH}_3$; $\text{R}'=\text{p-O}_2\text{N C}_6\text{H}_4$) (see Table 1), where it gave a small molecular ion peak at m/z 323. The base peak appeared at m/z 157 and was due to the $\text{C}_{11}\text{H}_{11}\text{N}^+$ ion followed by all expected fragments produced from its structure.

Table-1: Mass spectral data of compounds (9; R=p-CH₃C₆H₄; R'=p-O₂NC₆H₄), and (10, R=p-CH₃C₆H₄; R'=p-O₂NC₆H₄)

Compound	m/z values of principal fragments (relative intensity, %)
4-p-Tolyl but-3-en-2-one- 2-p-nitrobenzoylhydrazone (9, R=p-CH ₃ ; R'=p-O ₂ NC ₆ H ₄)	323(M, 9), 322(M-1, 9), 232(M-C ₇ H ₇ , 9), 173(C ₁₁ H ₁₃ N ₂ , 46), 157(C ₁₁ H ₁₁ N, 100), 150(C ₇ H ₄ NO ₃ , 39), 128(C ₉ H ₆ N, 14), 115(C ₈ H ₅ N, 9), 104(C ₇ H ₄ O, 19), 91(C ₇ H ₇ , 13), 76(C ₆ H ₄ , 16), 50(C ₄ H ₂ , 8).
4-p-Tolylbut-3-en-2-one- 2-p-nitrophenylhydrazone (10), R=p-CH ₃ ; R'=p-O ₂ NC ₆ H ₄)	295(M, 100), 294(M-1, 31), 248(M-HNO ₂ , 3), 204(M-C ₇ H ₇ , 21), 158(C ₁₁ H ₁₂ N, 59), 143(C ₁₁ H ₁₁ , 8), 136(C ₆ H ₄ N ₂ O, 16), 128 (C ₉ H ₆ N, 11), 115(C ₈ H ₅ N, 59), 105(C ₆ H ₅ N ₂ , 13), 91(C ₇ H ₇ , 54), 78(C ₆ H ₆ , 15), 63 (CH ₄ + HNO ₂ , 22), 51(C ₄ H ₃ , 12), 50 (C ₄ H ₂ , 10).

Furthermore, their ¹H nmr (CDCl₃) spectra exhibited the methyl group protons as singlet at δ 2.15-2.50, multiplet signals 6.9-7.85 due to conjugated and aromatic rings protons and the (NH) proton was observed at δ 8.85 ppm (disappeared on deuteration).

The reaction of 4-substituted-but-3-en-2-one (1) with arylhydrazines afforded the corresponding arylhydrazones (10). Their I.R. spectra included bands at 3260-3130 cm⁻¹ indicative of (NH) group, at 1610-1580 cm⁻¹ for (C=N) group, two bands at 1350-1330 cm⁻¹ and 1190-1170 cm⁻¹ characteristic for SO₂N< group and the (NO₂) group bands were observed at 850 and in the region of 1540-1340 cm⁻¹. Furthermore, the ¹H nmr.

(CDCl₃) spectra of these hydrazones (10) gave the (CH₃) group protons as singlet at δ 2.37-2.48, multiplet signals at 7.0-8.91 due to conjugated and aromatic rings protons, and the (NH) proton as singlet at δ 9.13 ppm (disappeared on deuteration). The structure of these hydrazones (10) was further confirmed by measuring the mass spectra of compound (10, R=p-CH₃, R'=p-O₂NC₆H₄) (see Table 1). It produced a large molecular ion peak at m/z 295 and it was the base peak, followed by all the fragments expected from its structure. Hydrazones (10) on refluxing with ethanol containing drops of HCl underwent cyclization to the pyrazolines (11). Their I.R. spectra displayed bands due to saturated (C-H) bond of the methyl group at 2935-2840 cm⁻¹, two bands characteristic for the SO₂N<

Table-2: Microanalytical data of ethyl 6-aryl-2,4-dioxohex-5-enoates (2)

R	Yield %	M.p. °C	Molecular formula	Calculated (%)			Found (%)		
				C	H	Cl	C	H	Cl
p-CH ₃	55	108	C ₁₅ H ₁₆ O ₄	69.2	6.2	-	69.1	6.3	-
p-Cl	60	116	C ₁₄ H ₁₃ O ₄ Cl	59.9	4.6	12.7	59.8	4.8	12.6
<u>Methyl esters</u>									
p-CH ₃	65	96	C ₁₄ H ₁₄ O ₄	68.2	5.7	-	68.0	5.8	-
p-Cl	65	136	C ₁₃ H ₁₁ O ₄ Cl	58.5	4.1	13.3	58.5	4.3	13.4

group at 1355-1325 cm⁻¹ and 1190-1170 cm⁻¹ and the (NO₂) group bands were observed at 850 and in the region of 1550-1350 cm⁻¹. Their ¹H nmr (CDCl₃) spectra gave the methyl group protons as singlet at δ 2.42, multiplet signals at 7.01-8.51 ppm due to conjugated and aromatic rings protons. In addition to these signals, the p-tolyl derivatives gave a second methyl group protons as singlet at δ 2.40-2.50 ppm. Oxidation of the pyrazolines (11) corresponding brominated pyrazole derivatives (12), where bromination takes place in both the 4-position of the pyrazole nucleus and the p-position of the N-phenylpyrazole ring when free. Their ¹H nmr (CDCl₃) spectra exhibited the (CH₃) group protons as singlet at δ 2.31 and the aromatic rings protons as multiplet at δ 7.01-8.10 ppm.

Experimental

General. melting points were taken in open glass capillaries and are uncorrected. IR absorption spectra were recorded with a Unicam SP 1025 recording spectrophotometer using potassium bromide pellets (ν_{\max} in

cm⁻¹). UV spectra were measured in ethanol on a Unicam SP 1750 instrument (λ_{\max} in nm), PMR spectra in CDCl₃ on a Varian HA 100 MHz instrument using TMS as internal standard (chemical shift in δ ppm) and mass spectra on a Varian M66 spectrophotometer at 70 eV.

Ethyl-6-aryl-2,4-dioxohexenoates (2):

A mixture of 4-aryl-but-3-en-2-ones (1; 0.1 mol) and ethyl oxalate (0.1 mol) in dry ether (100 mL) was gradually added with shaking to an ice cold suspension of sodium ethoxide (0.1 mol) in dry ether (150 mL). After keeping the reaction mixture at room temperature for one day, the separated yellow sodium salt was filtered off, washed with ether, dried then acidified with cold dilute sulphuric acid. The titled esters were purified by recrystallization from ethanol in yellow needles, yield 55-65% (see Table 2).

The methyl esters were obtained by refluxing the foregoing ethyl hexenoates (1 g) with methanol (25 mL) containing one drop conc. H₂SO₄ and recrystallized from methanol in yellow needles (see Table 2).

Table-3: Microanalytical and spectral data of ethyl 1-H/aryl-5-substituted pyrazole-3-carboxylates (3)


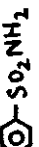
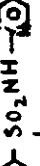



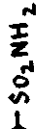





R	R'	Yield %	M.p. °C	Molecular formula	Calculated (%)			Found (%)			KBr ν_{\max} (cm^{-1})	
					C	H	N	C	H	N		
P-CH ₃	H	40	158	C ₁₅ H ₁₆ N ₂ O ₂	70.3	6.3	10.9	70.1	6.4	11.0	-	1740
P-CH ₃		38	94	C ₂₁ H ₂₀ N ₂ O ₂	75.9	6.0	8.4	75.8	5.9	8.4	-	1740
P-CH ₃		42	209	C ₂₁ H ₂₁ N ₃ O ₄ S	61.3	5.1	10.2	61.2	5.3	10.1	8.0	1740
P-CH ₃		40	208	C ₂₅ H ₂₃ N ₃ O ₄ S	61.4	4.7	14.3	61.3	4.6	14.2	6.3	1740
P-CH ₃		36	116	C ₂₃ H ₂₀ N ₂ O ₂	71.9	5.2	14.6	72.0	5.2	14.5	-	1740
P-CH ₃		50	247	C ₂₁ H ₁₉ N ₃ O ₄	66.8	5.0	11.1	66.7	5.1	11.0	-	1740
P-Cl	H	42	142	C ₁₄ H ₁₃ N ₂ O ₂ Cl	60.8	4.7	10.1	60.6	4.7	10.0	-	1740
P-Cl		40	156	C ₂₀ H ₁₇ N ₂ O ₂ Cl	68.1	4.8	7.9	68.0	5.0	8.0	-	1740
P-Cl		45	230	C ₂₀ H ₁₈ N ₃ O ₄ SCl	55.6	4.2	9.7	55.6	4.3	9.6	7.5	1740
P-Cl		43	154	C ₂₄ H ₂₀ N ₅ O ₄ SCl	56.5	3.9	13.7	56.4	4.0	13.5	6.4	1740
P-Cl		45	263	C ₂₂ H ₁₇ N ₃ O ₄ Cl	65.3	4.2	13.8	65.2	4.4	13.9	-	1740
P-Cl		43	151	C ₂₀ H ₁₆ N ₂ O ₂ Cl ₂	62.0	5.2	7.2	62.1	5.1	7.3	-	1740
P-Cl		50	162	C ₂₀ H ₁₆ N ₃ O ₄ Cl	60.4	4.0	10.6	60.2	4.1	10.7	-	1740
P-Cl		48	245	C ₂₀ H ₁₅ N ₄ O ₆ Cl	54.2	3.4	12.7	54.1	3.5	12.8	-	1740

Table-4: Microanalytical and spectral data of 1-H/aryl-5-substituted pyrazole-3-carboxylic acids (4)



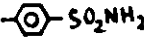


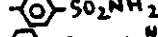
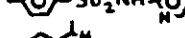

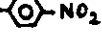
R	R'	Yield %	M.p. °C	Molecular formula	Calculated (%)			Found (%)			ν _{max} (cm ⁻¹)
					C	H	N	C	H	N	
p-CH ₃	H	66	290	C ₁₃ H ₁₂ N ₂ O ₂	68.4	5.3	12.3	68.3	5.5	12.4	1720
p-CH ₃		70	112	C ₁₉ H ₁₆ N ₂ O ₂	75.0	5.3	9.2	75.1	5.5	9.2	1720
p-CH ₃		65	245	C ₂₀ H ₁₈ N ₂ O ₂	75.5	5.7	8.8	75.4	5.8	8.9	1720
p-CH ₃		68	207	C ₁₉ H ₁₇ N ₃ O ₅	59.5	4.4	11.0	59.4	4.6	10.9	1720
p-Cl	H	65	286	C ₁₂ H ₉ N ₂ O ₂ Cl	58.0	3.6	11.3	58.1	3.7	11.4	1720
p-Cl		68	133	C ₁₈ H ₁₃ N ₂ O ₂ Cl	66.6	4.0	8.6	66.5	4.2	8.7	1720
p-Cl		66	131	C ₁₉ H ₁₅ N ₂ O ₂ Cl	67.4	4.4	8.3	67.3	4.6	8.1	1720
p-Cl		69	212	C ₁₈ H ₁₄ N ₃ O ₅ Cl	53.5	3.5	10.4	53.3	3.7	10.3	1720
p-Cl		70	189	C ₂₂ H ₁₆ N ₅ O ₄ Cl	54.8	3.3	14.5	54.8	3.5	14.5	1720
p-Cl		63	169	C ₂₀ H ₁₃ N ₄ O ₂ Cl	63.8	3.5	14.9	63.9	3.5	14.8	1720
p-Cl		60	169	C ₁₈ H ₁₂ N ₂ O ₄ Cl	58.5	3.3	11.4	58.3	3.5	11.5	1720

Table-5: Microanalytical data of ethyl 5-substituted isoxazole-3-carboxylates (5).

R	Yield %	M.p. °C	Molecular formula	C	Calculated (%)			Found (%)			
					H	N	Cl	C	H	N	Cl
p-CH ₃	45	156	C ₁₅ H ₁₅ NO ₃	70.0	5.8	5.5	-	70.0	5.9	5.6	-
p-Cl	45	128	C ₁₄ H ₁₂ NO ₃ Cl	60.5	4.3	5.1	12.8	60.3	4.3	5.0	12.9
<u>Methyl esters</u>											
p-CH ₃	50	95	C ₁₄ H ₁₃ NO ₃	69.1	5.4	5.8	-	69.0	5.6	5.7	-
p-Cl	50	128	C ₁₃ H ₁₀ NO ₃ Cl	59.2	3.8	5.3	13.5	59.1	4.0	5.2	13.5

Ethyl 1-H/aryl-5-substituted-pyrazole-3-carboxylates (3):

1-H/Aryl-5-substituted pyrazole-3-carboxylic acids (4):









These trisubstituted pyrazole esters were obtained by refluxing the 1,3-diketo-ester (2; 1 mmol) in ethanol (50 mL) for 3 hr on a steam bath. On concentration and cooling, the pyrazole esters separated out and were recrystallized from ethanol dilute ethanol in needles, yield, 35-50% (see Table 3).

The foregoing pyrazole esters (3; 0.5 g) was boiled with ethanolic 2N KOH (30 mL) on a water-bath for 3 hr. The reaction mixture was concentrated, diluted with water, acidified with dilute hydrochloric acid, the solid mass that separated out was filtered off and recrystallized from dilute ethanol in needles, yield 60-70% (see Table 4).

Table-6: Microanalytical and spectral data of 3-substituted-2-oxyquinoxalines (6).

R	Yield %	M.p. °C	Molecular formula	Calculated (%)			Found (%)			KBr. ν_{\max} (cm^{-1})		
				C	H	N	Cl	C	H		N	
p-CH ₃	73	269	C ₁₉ H ₁₆ N ₂ O ₂	75.0	5.3	9.2	-	75.0	5.4	9.0	-	1680
p-Cl	75	273	C ₁₈ H ₁₃ N ₂ O ₂ Cl	66.6	4.0	8.6	10.9	66.5	4.1	8.5	10.1	1680

Table-7: Microanalytical data of ethyl 6-aryl-2,4-dioxohex-5-enoate-2-acylhydrazones (7); and 3,5-disubstituted-N-acylpyrazoles (8).

R	R'	Yield %	M.p. °C	Molecular formula	Calculated (%)				Found (%)			
					C	H	N	Cl	C	H	N	Cl
p-CH ₃		38	120	C ₂₂ H ₂₂ N ₂ O ₄	69.8	5.8	7.4	-	69.6	6.0	7.3	-
p-CH ₃		36	113	C ₂₂ H ₂₁ N ₂ O ₄ Cl	64.0	5.1	6.8	8.6	64.0	5.0	6.6	8.5
p-Cl		35	116	C ₂₁ H ₁₉ N ₂ O ₄ Cl	63.2	4.8	7.0	8.9	63.1	4.9	6.9	9.0
p-Cl		37	151	C ₂₁ H ₁₈ N ₂ O ₄ Cl ₂	58.2	4.2	6.5	16.2	58.1	4.4	6.6	16.1
N-acylpyrazoles (8)												
p-CH ₃		30	157	C ₂₂ H ₂₀ N ₂ O ₃	73.3	5.6	7.8	-	73.3	5.7	7.8	-
p-CH ₃		35	159	C ₂₂ H ₁₉ N ₂ O ₃ Cl	66.9	4.8	7.1	9.0	66.7	4.9	7.0	8.9
p-Cl		33	153	C ₂₁ H ₁₇ N ₂ O ₃ Cl	66.2	4.5	10.0	9.3	66.1	4.6	10.1	9.1
p-Cl		40	178	C ₂₁ H ₁₆ N ₂ O ₃ Cl ₂	60.7	3.9	6.8	16.9	60.6	4.1	6.7	16.7

Ethyl 5-substituted isoxazole-3-carboxylates (5):

These esters were prepared by boiling compounds 2 (1 mmol) in ethanol (20 mL) with hydroxylamine hydrochloride (1 mmol) and sodium acetate (1 mmol) in water (2 mL) for 2 hr. Crystallization from dilute ethanol gave colourless needles of the isoxazole ester, yield 45-50% (see Table 5). The methyl isoxazole esters were obtained by carrying the above reaction with hydroxylamine hydrochloride in methanol and in the absence of sodium acetate (see Table 5).

3-Substituted-2-oxyquinoxalines (6):

A mixture of the ethyl hexenoate (2, 1 mmol) and o-phenylenediamine (1 mmol) in ethanol (30 mL) was heated under reflux for 2 hr. The oxyquinoxaline derivative obtained after concentration was filtered and recrystallized from ethanol in orange needles, yield 73-75% (see Table 6).


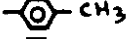
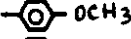






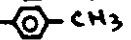
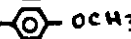


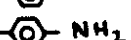
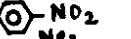
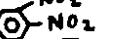


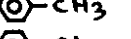





Ethyl 6-aryl-2,4-dioxohexenoate 2-acylhydrazones (7):

An ethanolic solution (50 mL) of the appropriate acylhydrazine (1 mmol) was added to a cold solution of the ethyl hexenoate (2, 1 mmol) in ethanol (50 mL) containing two drops of glacial acetic acid and the reaction mixture left at room-temperature for 24 hr. The orange-yellow solid thus separated was filtered, washed with little ethanol and purified by recrystallization from chloroform-light petroleum (b.p. 40-60°C) in needles, yield 35-38% (see Table 7).

Ethyl 1-acyl-5-substituted pyrazole-3-carboxylates (8):

These acylpyrazoles were prepared by boiling the foregoing acylhydrazones (7, 0.6 g) with ethanol (100 mL) containing one drop HCl for 1 hr. The acylpyrazole esters that separated out from the reaction mixture on concentration, cooling and dilution

Table-8: Microanalytical data of 4-Aryl but-3-en-2-one 2-acylhydrazones (9).

R	R'	Yield %	M.p. °C	Molecular formula	Calculated (%)			Found (%)		
					C	H	N	C	H	N
o-CH ₃	-CH ₂ CN	30	147	C ₁₄ H ₁₅ N ₃ O ₂	65.4	5.8	16.3	65.3	6.0	16.2
"		35	190	C ₁₈ H ₁₈ N ₃ O ₂	73.5	6.1	9.5	73.4	6.3	9.5
"		33	200	C ₁₉ H ₂₀ N ₃ O ₂	74.0	6.5	9.1	74.1	6.3	9.0
"		35	204	C ₁₉ H ₂₀ N ₃ O ₃	70.4	6.2	8.6	70.4	6.1	8.6
"		40	206	C ₁₈ H ₁₇ N ₃ O ₂ Cl	65.8	5.2	8.5	65.7	5.3	8.5
"		40	174	C ₁₈ H ₁₇ N ₃ O ₂ Br	58.1	4.6	7.5	58.0	4.7	7.6
"		40	237	C ₁₈ H ₁₉ N ₃ O ₂	69.9	6.2	13.6	69.9	6.3	13.7
"		35	230	C ₁₈ H ₁₇ N ₃ O ₄	63.7	5.0	12.4	63.6	5.2	12.5
"		37	265	C ₁₈ H ₁₆ N ₃ O ₄	56.3	4.2	14.6	56.1	4.3	14.7
p-CH ₃	-CH ₂ CN	32	194	C ₁₄ H ₁₅ N ₃ O	69.7	6.2	17.4	69.7	6.3	17.2
"		30	174	C ₁₈ H ₁₈ N ₃ O	77.7	6.5	10.1	77.5	6.5	10.0
"		33	198	C ₁₉ H ₂₀ N ₃ O	78.1	6.9	9.6	78.0	6.8	9.7
"		30	200	C ₁₉ H ₂₀ N ₃ O ₂	74.0	6.5	9.1	74.1	6.7	9.0
"		38	210	C ₁₈ H ₁₇ N ₃ OCl	69.1	5.4	9.0	69.0	5.6	8.9
"		38	220	C ₁₈ H ₁₇ N ₃ OBr	60.7	4.8	7.9	60.6	5.0	8.0
"		38	255	C ₁₈ H ₁₉ N ₃ O	73.7	6.5	14.3	73.5	6.6	14.2
p-CH ₃		40	218	C ₁₈ H ₁₇ N ₃ O ₃	66.9	5.3	13.0	66.8	5.5	13.2
"		35	220	C ₁₈ H ₁₆ N ₃ O ₃	58.7	4.4	15.2	58.5	4.4	15.3
"		40	190	C ₁₉ H ₂₀ N ₃ O	78.1	6.9	9.6	78.0	7.0	9.5
p-Cl		35	187	C ₁₇ H ₁₅ N ₃ OCl	68.3	5.0	9.4	68.3	5.2	9.6
"		34	209	C ₁₈ H ₁₇ N ₃ OCl	69.1	5.4	9.0	69.0	5.6	9.1
"		33	170	C ₁₇ H ₁₄ N ₃ OCl ₂	61.3	4.2	8.4	61.2	4.3	8.6
"		35	215	C ₁₇ H ₁₄ N ₃ OBrCl	54.2	3.7	7.4	54.2	3.8	7.4
"		35	203	C ₁₈ H ₁₇ N ₃ O ₂ Cl	65.8	5.2	8.5	65.6	5.3	8.5
"		40	210	C ₁₇ H ₁₄ N ₃ O ₃ Cl	59.4	4.1	12.2	59.4	4.0	12.0
"		40	186	C ₁₈ H ₁₇ N ₃ OCl	69.1	5.4	8.9	69.0	5.5	8.8

with water, was crystallized from dilute ethanol in red-brown needles, yield 30-40% (see Table 7).

4-Aryl-but-3-en-2-ones (1):

To a well stirred solution of p-substituted benzaldehyde (1 mmol) in dimethyl ketone (40 mL) was added drop by drop with a 10% sodium hydroxide solution (2 mL) through a period of 20 min. and stirring was continued for another 2½ hr. The mixture was then acidified with dilute hydrochloric

acid, ether extracted and the ether layer washed several times with water till neutral then dried. After distillation of the ether, the ,-unsaturated ketone (1) was produced as yellow oil, yield 70%.

4-Aryl-but-3-en-2-one-2-acylhydrazones (9):

These derivatives were prepared by boiling the ketone (1, 1 mmol) with the desired acylhydrazine (1 mmol) in ethanol (50 mL) containing two drops

Table-9: Microanalytical data of 4-Arylbut-3-en-2-one-2 arylhydrazones (10).

R	R'	Yield %	M.p. °C	Molecular formula	Calculated (%)			Found (%)		
					C	H	N	C	H	N
o-CH ₃ O		36	205	C ₁₇ H ₁₉ N ₃ O ₃ S	59.1	5.5	12.2	59.0	5.6	12.0
o-CH ₃ O		32	118	C ₁₈ H ₁₈ N ₂ O ₃	69.7	5.8	9.0	69.5	5.9	9.1
o-CH ₃ O		35	176	C ₁₇ H ₁₈ N ₃ O ₃ S	61.8	5.5	8.5	61.7	5.5	8.5
o-CH ₃ O		40	202	C ₁₇ H ₁₇ N ₃ O ₃	65.6	5.5	13.5	65.5	5.7	13.3
o-CH ₃ O		38	240	C ₁₇ H ₁₆ N ₄ O ₃	57.3	4.5	15.7	57.1	4.7	15.8
p-CH ₃		36	179	C ₁₇ H ₁₉ N ₃ O ₃ S	62.0	5.8	12.8	62.1	5.8	12.9
p-CH ₃		40	218	C ₁₇ H ₁₇ N ₃ O ₂	69.2	5.8	14.2	69.1	5.9	14.1
p-CH ₃		38	250	C ₁₇ H ₁₆ N ₄ O ₄	60.0	4.7	16.5	60.0	4.8	16.6
p-Cl		40	62	C ₁₆ H ₁₆ N ₃ O ₃ SCl	54.9	4.6	12.0	54.7	4.7	12.1
p-Cl		36	109	C ₁₇ H ₁₅ N ₂ O ₂ Cl	64.9	4.8	8.9	64.8	4.9	9.0
p-Cl		38	175	C ₁₆ H ₁₄ N ₃ O ₂ Cl	60.9	4.4	13.3	60.7	4.6	13.1
p-Cl		38	198	C ₁₆ H ₁₃ N ₄ O ₄ Cl	53.3	3.6	15.5	53.2	3.8	15.4

Table-10: Microanalytical data of 1-Aryl-3,5-disubstituted-2-pyrazolines (11).

R	R'	Yield %	M.p. °C	Molecular formula	Calculated (%)			Found (%)		
					C	H	N	C	H	N
p-CH ₃ O		28	184	C ₁₇ H ₁₉ N ₃ O ₃ S	59.1	5.5	12.2	59.0	5.6	12.2
p-CH ₃ O		30	205	C ₁₇ H ₁₇ N ₃ O ₃	65.6	5.5	13.5	65.6	5.7	13.4
p-CH ₃ O		28	242	C ₁₇ H ₁₆ N ₄ O ₅	57.3	4.5	15.7	57.1	4.6	15.6
p-CH ₃		30	190	C ₁₇ H ₁₉ N ₃ O ₃ S	62.0	5.8	12.8	61.8	5.9	12.9
p-CH ₃		28	116	C ₁₇ H ₁₇ N ₃ O ₂	69.2	5.8	14.2	69.1	5.8	14.3
p-CH ₃		30	256	C ₁₇ H ₁₆ N ₄ O ₄	60.0	4.7	16.5	60.1	4.5	16.4
p-Cl		30	212	C ₁₆ H ₁₆ N ₃ O ₃ SCl	54.9	4.6	12.0	54.7	4.8	12.2
p-Cl		28	205	C ₁₆ H ₁₄ N ₃ O ₂ Cl	60.9	4.4	13.3	60.7	4.4	13.3
p-Cl		28	245	C ₁₆ H ₁₃ N ₄ O ₄ Cl	53.3	3.6	15.5	53.3	3.6	15.6

Table-11: Microanalytical data of 1-Aryl-4-bromo-3,5-disubstituted pyrazoles (12).

R	R'	Yield (%)	M.p. °C	Molecular formula	Calculated (%)				Found (%)			
					C	H	N	Br	C	H	N	Br
o-CH ₃ O		30	105	C ₁₇ H ₁₃ N ₂ OBr ₃	41.0	2.6	5.6	47.6	41.0	2.8	5.5	47.5
p-Cl		25	106	C ₁₆ H ₁₃ N ₂ O ₂ SClBr	45.1	3.1	9.9	18.6	45.0	3.3	9.8	18.8
p-Cl		28	104	C ₁₆ H ₁₁ N ₃ O ₂ ClBr	49.0	2.8	10.7	20.2	48.9	3.0	10.6	20.1
p-Cl		25	196	C ₁₆ H ₁₁ N ₂ O ₂ SClBr ₂	39.3	2.3	5.7	32.3	39.2	2.5	5.7	32.1

glacial acetic acid for 1 hr. On concentration and cooling the separated hydrazone was filtered off and recrystallized from dilute methanol in needles. Yield 30-40% (see Table 8).

4-Aryl-but-3-en-2-one 2-arylhya-zones (10):

A mixture of compound 1 (1 mmol) and the appropriate arylhydrazine (1

mmol) in ethanol (25 ml) was refluxed for 1 hr on a steam-bath. Concentration and cooling of the reaction mixture furnished the hydrazone that crystallized from methanol in needles, yield 30-40% (see Table 9).

1,5-Diaryl-3-methyl-2-pyrazolines
(11):

The arylhydrazones (10; 1 mmol) was boiled with ethanol (25 mL) containing one drop of hydrochloric acid for 1 hr on a water-bath. The reaction mixture was then concentrated and the precipitated products were recrystallized from methanol in needles, yield 28-30% (see Table 10).

4-Bromo-1,5-diaryl-3-methylpyrazoles
(12):

The foregoing pyrazolines (11; 3 mmol) in water (25 mL) were treated gradually with continuous stirring with 5% bromine water (25 mL) for 20 hr. The brominated pyrazoles which separated out were filtered off, washed successively with water, dried and recrystallized from dilute methanol in needles, yield 25-30% (see Table 11).

References

1. J.B. Wright, E.W. Dulin and J.H. Markillie,
J. Med. Chem., **7**, 102 (1964).
2. G.C. Gerritsen and W.E. Dulin,
Diabetes, **14**, 507 (1965).
3. D.L. Smith, A.A. Forist and W.E. Dulin,
J. Med. Chem., **8**, 350 (1965).
4. D.L. Smith, A.A. Forist and G.C. Gerritsen,
J. Pharmacol. Exp. Ther., **150**, 316 (1965).
5. R. Soliman, H. Mokhtar and E.S. El-Ashry,
Pharmazie, **33**, 184 (1978).
6. H. Mokhtar and R. Soliman,
Pharmazie, **33**, 649 (1978).
7. H. Faid-Allah, H. Mokhtar and R. Soliman,
J. Heterocycl. Chem., **18**, 1561 (1981).
8. H. Mokhtar,
Pharmazie, **3**, 150 (1979).
9. H. Mokhtar and L. Rateb,
Pharmazie, **12**, 782 (1978).
10. R. Soliman, H. Mokhtar and H.F. Mohamed,
J. Pharm. Sci., **72**, 999 (1983).
11. R. Soliman, H. Mokhtar and H.F. Mohamed,
J. Pharm. Sci., **72**, 1004 (1983).
12. R. Soliman and H. Faid-Allah,
J. Pharm. Sci., **70**, 602 (1981).
13. R. Soliman, H. Faid-Allah and S.K. El-Sadany,
J. Pharm. Sci., **70**, 606 (1981).
14. H.M. Mokhtar and J. Wojtanis,
Indian J. Chem., **24B**, 188 (1985).
15. H.M. Mokhtar,
Pakistan J. Sci. Ind. Res., **28**, 85 (1985).
16. H. Faid-Allah and H. Mokhtar,
Indian J. Chem., *In press*.
17. F.G. Valdecases,
Med. Clin. (Barcelona), **4**, 275 (1952).