

SYNTHESIS OF TRISUBSTITUTED PYRAZOLES WITH POSSIBLE ANTIMICROBIAL ACTIVITY

Hassan M. Mokhtar

*Department of Chemistry, Faculty of Science,
University of Alexandria, Alexandria, Egypt*

(Received August 13, 1984; Review Dec. 17, 1984)

Several 2,5-disubstituted oxadiazoles and 1,3,5-trisubstituted pyrazoles have been synthesized. Condensation of 2-aryl-4-formyl triazoles with acylhydrazines afforded the corresponding acylhydrazones, which upon oxidation with iodine-mercuric oxide mixture in dry ether gave the corresponding 2,5-disubstituted oxadiazoles.

Similarly, condensation of α , β -unsaturated ketones with arylhydrazines, afforded the corresponding arylhydrazones. Heating with ethanolic hydrogen chloride gave the corresponding pyrazolines. Oxidation of the pyrazolines with bromine water gave the brominated pyrazole derivatives.

On the other hand, condensation of α , β -unsaturated ketones with ethyl oxalate gave ethyl 2,4-cioxo-6-substituted hex-5-enoate which with arylhydrazines gave the corresponding pyrazole-3-esters.

The structure of the synthesized compounds was affirmed by m.p., microanalysis, i.r., p.m.r. and m.s. spectral analysis.

INTRODUCTION

Many 3,5-disubstituted pyrazoles and their metabolite 5-substituted pyrazole-3-carboxylic acids were found to possess potent hypoglycemic activity [1-5]. In the present paper has been reported the synthesis of a number of tri-substituted pyrazoles in the expectation that they might be of potential anti-microbial value. The prepared pyrazole compounds have either methyl or carboxyl group on position 3, a substituted triazole nucleus on position 5, and aryl, sulphonamido, pyridyl or phthalazinyl group on position 1. It has been also reported that *p*-aminobenzoic acid, a member of vitamin B-complex, is involved in the synthesis of folic acid coenzymes and pteroylglutamic acid [6], a compound having full folic acid activity. Such coenzymes are essential growth factors for microorganisms [7] as well as in the conversion of certain precursors into purines [8]. *p*-Aminobenzoic acid is used as an antirecketsial agent [9]. Furthermore, it has been found that certain acid hydrazides such as *p*-aminosalicylic acid hydrazide [10] and cyanoacetic acid hydrazide [11] have antimicrobial activity. In the present work some acylhydrazones of formylhalogenotriazole and certain α , β -unsaturated carbonyl triazole derivatives were prepared in the hope that they might be of beneficial antituberculous value.

The reaction of 2-*p*-bromophenyl-4-formyltriazole [12] (4) with acylhydrazines afforded the corresponding

acylhydrazones (5). Their i.r. absorption spectra revealed bands in the region of 3280-3130 cm^{-1} indicative of (NH) group, at 1605-1570 cm^{-1} for (C=N) group and at 1670-1620 cm^{-1} due to carbonyl group of the hydrazone part. Oxidation of these hydrazones (5) with iodine-mercuric oxide mixture in dry ether gave the dehydrogenated products (6), viz. 5-aryl-2-[2-*p*-bromophenyltriazol-4-yl] oxadiazoles. Their i.r. spectra showed bands at 1610-1560 cm^{-1} due to the (C=N) group, at 780-725 cm^{-1} indicative of mono-substituted benzene ring but neither carbonyl group nor (NH) group bands were observed in their spectral regions. Furthermore, their p.m.r.(CDCl_3) spectra gave multiplet signals at δ 7.16-8.37 ppm characteristic for conjugated and aromatic ring protons but no signals corresponding to either the (CH) or (OH) protons were observed, proving their disappearance through cyclization to give the product (6). The structure of these oxadiazoles was further confirmed from the mass spectra of compound (6; R=H) (see Table 1). It gave a large molecular ion peak at m/z 367 (Br^{79}) and the base peak appeared at m/z 105 was attributed to the $\text{C}_7\text{H}_5\text{O}^+$ ion, followed by all fragments expected from its structure.

Condensation of the formyltriazole (3) with dimethyl ketone gave the α , β -unsaturated ketone (7) as main products. Its p.m.r. (CDCl_3) spectra gave the methyl protons as singlet at δ 2.18 and multiplet signals at δ 7.02-8.34

ppm due to conjugated and aromatic rings protons, whereas, its uv spectra showed two maxima at 273 and 343 nm and two minima at 248 and 292 nm. Compound (7) was obtained as a by-product from the foregoing reaction and its p.m.r. (CDCl_3) spectra revealed multiplet signals at δ 7.17–8.24 ppm due to conjugated and aromatic ring protons. The reaction of 4-[2-phenyltriazol-4-yl] but-3-en-2-one (7) with arylhydrazines gave the corresponding arylhydrazones (8). Their i.r. spectra showed bands at 3240–3145 cm^{-1} characteristic for (NH) group, at 1610–1580 cm^{-1} for (C=N) group and two bands at 1350–1330 cm^{-1} and 1190–1170 cm^{-1} indicative of $-\text{SO}_2\text{N}$ group. Hydrazones (8) on refluxing with ethanol containing one drop HCl underwent cyclization to the pyrazolines (9). Their i.r. spectra exhibited two bands characteristic for the $-\text{SO}_2\text{N}$ group at 1355–1330 cm^{-1} and 1190–1170 cm^{-1} , bands due to saturated (C–H) bond of the methyl group at 2935–2840 cm^{-1} and at 770–740 cm^{-1} due to mono-substituted benzene ring. Furthermore, their uv spectra revealed two maxima stretching up to 290 and 410 nm and two minima up to 248 and 352 nm. The structure of these pyrazolines was further confirmed from the mass spectra of compound (9; $\text{R}=\text{p}-\text{O}_2\text{N}-\text{C}_6\text{H}_4-$) (see Table 1). It gave a large molecular ion peak at m/z 348, and the base peak attributed to the ion $\text{C}_6\text{H}_5\text{N}^+$ was observed at m/z 91, followed by all the fragments expected from its structure. Oxidation of the pyrazolines (9) with an excess of bromine water led to the formation of the corresponding brominated pyrazole derivatives (10), where bromination takes place in both in the *p*-position of the phenyltriazole ring, the 4-position of the pyrazole nucleus, and the *p*-position of the *N*-phenylpyrazole ring when free. Their p.m.r. (CDCl_3) spectra gave the methyl group protons as singlet at δ 2.33 and the aromatic rings protons as multiplet at 7.13–8.02 ppm, whereas their uv spectra showed two maxima stretching up to 207 and 289 nm and one minima up to 239 nm. The structure of these pyrazoles (10) was further confirmed by measuring the mass spectra of compound (10; $\text{R}=\text{p}-\text{Br}-\text{C}_6\text{H}_4-$) (see Table 1, where it gave a small molecular ion peak at m/z 537. The base peak appeared at m/z 90 and was due to the $\text{C}_6\text{H}_4\text{N}^+$ ion, followed by all expected fragments produced from its structure.

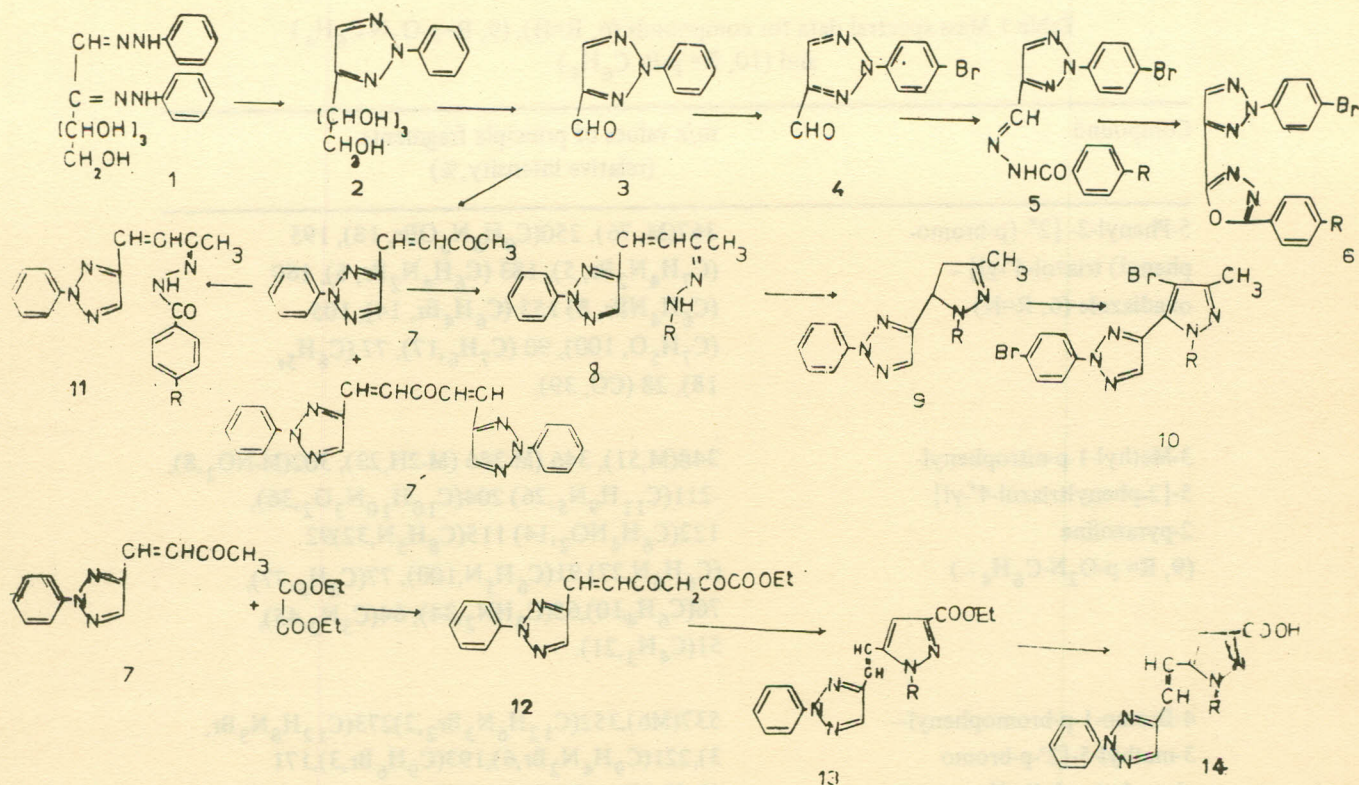
With acylhydrazines, the ketone (7) gave the corresponding acylhydrazones (11) that were yellow coloured. Their i.r. spectra revealed the carbonyl group band of the hydrazone part at 1670–1640 cm^{-1} , bands at 3390–3260 cm^{-1} characteristic for (NH) group, at 1595–1490 cm^{-1} indicative of (C=C, aromatic) and at 1605–1580 cm^{-1} due to (C=N) group. In addition to these absorption bands, the

(NO_2) group bands were observed at 850 and in the region of 1540–1340 cm^{-1} . Furthermore, the p.m.r. (CDCl_3) spectra of these hydrazones (11) gave the (CH_3) group protons as singlet at δ 2.16–2.18, multiple signals at 7.23–8.56 due to conjugated and aromatic rings protons, and the (NH) proton as singlet at δ 8.82 ppm. The uv spectra of hydrazone (11; $\text{R} = 3, 5-(\text{NO}_2)_2-\text{C}_6\text{H}_3-$) showed one maxima at 210 and a shoulder at 226 nm.

The α,β -unsaturated ketone (7) on condensation with ethyl oxalate afforded ethyl 2,4-dioxo-6-[2-phenyltriazol-4-yl] hex-5-enoate (12). Its i.r. spectra gave bands at 1730 cm^{-1} due to the carbonyl ester group, at 1620–1490 cm^{-1} indicative of (C=C, aromatic), at 1260–1025 cm^{-1} for ($-\text{C}-\text{O}-\text{C}-$) of ester group and the (OH) group band appeared in the region of 3500–3400 cm^{-1} . Its p.m.r. (CDCl_3) spectra gave signals at δ 1.35 (triplet, 3H, $-\text{CH}_2\text{CH}_3$); 4.30 (quartet, 2H, $-\text{CH}_2\text{CH}_3$); 6.25, 6.80 (doublet, doublet, 1H, 1H, $-\text{CH}=\text{CH}-$); 6.55 (singlet, 1H, $=\text{CH}-$) and at 7.22–8.25 (multiplet, 7H, OH and aromatic protons) ppm. The signal at δ 6.55 ppm proves the enolic form of ester (12) and this explains its reaction with hydrazines to give the pyrazole-3-esters (13) and not the 5-esters. The ethyl hexenoate (12) on reaction with hydrazine, aryl-4-sulphamyl-, 2-[4-hydrazinobenzene sulphonamido] pyrimidine and 2-pyridylhydrazines as well as hydralazine yielded the corresponding trisubstituted pyrazole esters (13). Formulation of the reaction products as (13) was based on the comparative reactivity of the two carbonyl groups present in compound (12). The C-2 carbonyl group is more reactive than the C-4 carbonyl and consequently preferable attack by nucleophilic reagents. Thus, the nucleophilic attack of the hydrazine (s) then took place on the C-2 carbonyl resulting in the formation of its corresponding mono-hydrazone as intermediate which simultaneously undergoes ring closure with the elimination of a water molecule from the hydroxyl group of the enolized C-4 carbonyl and the iminoproton of the hydrazone residue. The i.r. absorption spectra of esters (13) showed carbonyl group band in the region of 1720–1715 cm^{-1} and two bands at 1355–1330 and 1195–1175 cm^{-1} for the $-\text{SO}_2\text{N}$ group. Furthermore, their uv spectra revealed two maxima stretching up to 226 and 355 and one minima up to 297 nm. Hydrolysis of the foregoing pyrazole esters (13) with ethanolic 2N KOH yielded the corresponding acids (14). Their i.r. spectra gave carbonyl group band at 1720 cm^{-1} and (OH) group absorption band in the region of 3500–3380 cm^{-1} .

EXPERIMENTAL

General-melting points were determined in open glass



capillaries and are uncorrected. IR absorption spectra were recorded with a Unicam SP 1025 recording spectrophotometer using potassium bromide pellets, uv spectra were measured with a Unicam SP 1750 instrument in ethanol and p.m.r. spectra were taken with a Varian HA 100 instrument. Microanalyses were performed in the Faculty of Science, Cairo University and the mass spectra were measured on a Varian M 66 spectrophotometer.

4-Formyl-2-phenyl-1,2,3-triazole (3). A suspension of *D*-arabino-hexose phenylosotriazole (2) (1 g) prepared from (1), in a mixture of water (100ml) and 0.87 M aqueous sodium periodate solution (35 ml) was stirred for 24 hr at room temperature. The deposited crystals were filtered off, washed successively with water and recrystallized from dilute methanol in colourless needles, m.p. and mixed m.p. with authentic sample [12] at 68°C.

2-(*p*-Bromophenyl)-4-formyl-1,2,3-triazole (4). A suspension of 4-formyl-2-phenyltriazole (3; 2g) in water (100 ml) was treated with bromine (1 ml) and stirred for 10 hr at room temperature. The crystals were filtered off, washed successively with water and recrystallized from dilute ethanol in needles, m.p. 106° (lit. [13] m.p. 106°) (yield (80%).

2-(*p*-Bromophenyl)-4-formyltriazole mono-acylhydrazones (5). A mixture of (4; 1 mmol) in ethanol (50 ml) was refluxed with the desired acylhydrazine on a steam bath for

1 hr. A precipitate appeared after 10 min. boiling. The deposited hydrazone was filtered off, and recrystallized from ethanol, yield, 55% (see Table 2).




5-Aryl-2-[2-*p*-bromophenyltriazol-4-yl] oxadiazoles (6). A suspension of the foregoing hydrazones (5; 1 g) in dry ether (100 ml) was treated with a mixture of iodine (0.7 g), yellow mercuric oxide (1 g) and magnesium oxide (0.8 g) and the mixture stirred at room temperature for 24 hr. The ether layer was filtered off, washed with KI solution and then with Na₂S₂O₃ solution to remove the excess iodine, then with water and dried. After the distillation of ether, the separated oxadiazole was recrystallized from ethanol in colourless needles; yield, 30-40% (see Table 3).

4-[2-Phenyltriazol-4-yl] but-3-en-2-one (7). To a well stirred solution of 4-formyl-2-phenyltriazole (3; 1 mmol) in dimethyl ketone (40 ml) was added drop by drop with a 10% sodium hydroxide solution (2 ml) for 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 with water then filtered off to remove the deposited solid (7) and then dried. After distillation of the ether, the α , β -unsaturated ketone (7) was produced as brown oil; yield, 70%. Compound (7) was obtained as a by-product from the foregoing reaction in 10% yield, and was recrystallized from ethanol in yellow

Table 1 Mass spectral data for compounds (6, R=H), (9, R=p-O₂N-C₆H₄) and (10, R= p-Br-C₆H₄)

Compound	m/z values of principle fragments (relative intensity,%)
5-Phenyl-2- [2'-(p-bromo-phenyl) triazol-4'-yl] - oxadiazole (6, R=H)	367(M, 76), 250(C ₉ H ₅ N ₃ OBr, 18), 195 (C ₇ H ₄ N ₂ Br, 5), 183 (C ₆ H ₄ N ₂ Br, 6), 169 (C ₆ H ₄ NBr, 8) 155 (C ₆ H ₄ Br, 14), 105 (C ₇ H ₅ O, 100), 90 (C ₇ H ₆ ,17), 77 (C ₆ H ₅ , 18), 28 (CO, 39).
3-Methyl-1-p-nitrophenyl- 5-[2-phenyltriazol-4'-yl] 2-pyrazoline (9, R= p-O ₂ N-C ₆ H ₄ -)	348(M,51), 346 (M-346 (M-2H,23), 302(M-NO ₂ ,8), -211(C ₁₁ H ₉ N ₅ ,26) 204(C ₁₀ H ₁₀ N ₃ O ₂ ,36), 122(C ₆ H ₄ NO ₂ ,14) 115(C ₈ H ₅ N,32)92 (C ₆ H ₆ N,27) 91(C ₆ H ₅ N,100), 77(C ₆ H ₅ ,77), 76(C ₆ H ₄ ,10),65(C ₃ HN ₂ ,34), 64(C ₃ N ₂ ,45), 51(C ₄ H ₃ ,21).
4-Bromo-1-p-bromophenyl- 3-methyl-5-[2'-p-bromo phenyltriazol-4'-yl] - pyrazole (10,R=p-Br-C ₆ H ₄ -)	537(M6),352(C ₁₂ H ₆ N ₃ Br ₂ ,2)273(C ₁₂ H ₈ N ₃ Br, 3),221(C ₉ H ₄ N ₂ Br,6),193(C ₉ H ₆ Br,3),171 (C ₆ H ₄ NBr,25),157(C ₆ H ₄ Br,41),140(C ₉ H ₄ N ₂ , 10),104(C ₆ H ₄ N ₂ ,6),90(C ₆ H ₄ N,100)76 (C ₆ H ₄ ,40).

Table 2. Microanalytical and spectral data for 2-(p-Bromophenyl)-4-formyltriazole monoacylhydrazones (5)

R	Yield (%)	M.P. (degrees)	Molecular formula	Calculated (%)				Found (%)				γ KBr max (cm ⁻¹)
				C	H	N	Br	C	H	N	Br	
	55	254	C ₁₆ H ₁₂ BrN ₅ O	51.9	3.2	18.9	21.6	51.8	3.5	18.9	21.7	1630
 Cl	60	272	C ₁₆ H ₁₁ BrClN ₅ O	47.5	2.7	17.3	19.8	47.4	3.0	17.3	20.0	1670
 NH ₂	60	274	C ₁₆ H ₁₃ BrN ₆ O ₂	47.9	3.2	21.0	20.0	48.0	3.2	20.8	19.8	1660

needles, m.p. 190°. [Anal. Calc. for C₂₁H₁₆N₆O: C, 68.5; H, 4.4; N, 22.8. Found: C, 68.5; H, 4.5; N, 23.0]. Its oxime was recrystallized from benzene-methanol mixture in brown needles, m.p. 108° [Anal. Calc. for C₂₁H₁₇N₇O: C, 65.8; H, 4.4; N, 25.6. Found: C, 66.0; H, 4.6; N, 25.5].

4-[2-Phenyltriazol-4-yl] but-3-en-2-one 2-arylhydrazones (8). These derivatives were prepared by boiling the

ketone (7; 1 mmol) with the desired arylhydrazine (1 mmol) in ethanol (50 ml) for 1 hr. On concentration and cooling the separated hydrazone was filtered off and recrystallized from dilute ethanol in yellow needles, yield 30-40% (see Table 4).

1-Aryl-3,5-disubstituted-2-pyrazolines (9). These pyrazolines were obtained by refluxing the appropriate arylhydrazones (8; 1 mmol) in ethanol (25 ml) with hydrochloric acid (0.5 ml) for 1 hr. The reaction mixture was then

concentrated and the precipitated products were recrystallized from ethanol in needles; yield, 20-30% (see Table 5).

1-Aryl-4-bromo-3,5-disubstituted pyrazoles (10). The foregoing pyrazolines (9; 3 mmol) in water (25 ml) were treated gradually with continuous stirring with 5% bromine water (25 ml) for 8 hr. The brominated pyrazoles which separated out were filtered off, washed successively with water, dried, and recrystallized from dilute methanol in needles; yield, 25-35% (see Table 6).

4-[2-Phenyltriazol-4-yl] but-3-en-2-one 2-acylhydrazones (11). A solution of the α,β -unsaturated ketone (7; 1 mmol) in ethanol (50 ml) was boiled with the desired acylhydrazine (1 mmol) for 1 hr. on a steam bath. The hydrazones that separated out were filtered off and recrysta-

lized from ethanol in yellow needles; yield, 25-35% (see Table 7).

Ethyl 2,4-dioxo-6-[2-phenyltriazol-4-yl] hex-5-enoate (12). The 1,3-diketo-ester was prepared by condensation of the ketone (7; 0.1 mol) and ethyl oxalate (0.1 mol) in dry ether (200 ml) in the presence of sodium ethoxide (0.1 mol). After keeping the reaction mixture at room temperature for 24 hr, the separated yellow sodium salt was filtered off, washed with ether, dried and then acidified with cooled dilute sulphuric acid. The titled ester was purified by recrystallization from methanol in yellowish brown needles, m.p. 110^o, yield 45% [Anal. Calc. for C₁₆H₁₅O₄, C, 61.3; H, 4.8; N, 13.4 Found: C, 61.3; H, 5.0; N, 1.35].

Table 3. Microanalytical data for 5-Aryl-2-[2-(p-bromophenyl) triazol-4-yl]-oxadiazoles (6)



R	Yield %	M.P. (degrees)	Molecular formula	Calculated (%)				Found (%)			
				C	H	N	Br	C	H	N	Br
	30	166	C ₁₆ H ₁₀ BrN ₅ O	52.2	2.7	19.0	21.7	52.1	3.0	19.1	22.0
	40	169	C ₁₆ H ₉ BrClN ₅ O	47.7	2.2	17.4	19.9	47.5	2.5	17.3	19.7

Table 4. Microanalytical data for 4-(2-Phenyltriazol-4-yl) but-3-en-2-one 2-aryl-hydrazones (8)

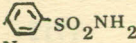

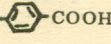
R	Yield %	M.P. (degrees)	Molecular formula	Calculated (5)				Found (%)			
				C	H	N	S	C	H	N	S
	32	143	C ₁₈ H ₁₈ N ₆ O ₂ S	56.5	4.7	22.0	8.4	56.5	4.6	22.1	8.5
	30	81	C ₁₇ H ₁₆ N ₆	67.1	5.3	27.6		67.0	5.5	27.5	
	40	171	C ₁₉ H ₁₇ N ₅ O ₂	65.7	4.9	20.2	65.6	5.0	20.3		

Table 5. Microanalytical data for 1-Aryl-3, 5-disubstituted-2-pyrazolines (9)


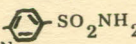

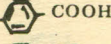

R	Yield %	M.P. (degree)	Molecular formula	Calculated (%)				Found (%)			
				C	H	N	S	C	H	N	S
	25	91	C ₁₈ H ₁₇ N ₅	71.3	5.6	23.1		71.3	5.7	23.1	
	30	192	C ₁₈ H ₁₈ N ₆ O ₂ S	56.5	4.7	22.0	8.4	56.6	4.5	22.1	8.4
	25	172	C ₁₇ H ₁₆ N ₆	67.1	5.3	27.6		67.0	5.2	27.5	
	30	235	C ₁₉ H ₁₇ N ₅ O ₂	65.7	4.9	20.2		65.5	5.0	20.1	
	30	172	C ₁₈ H ₁₆ N ₆ O ₂	62.1	4.6	24.1		62.0	4.5	24.1	

Table 6. Microanalytical data for 1-Aryl-4-bromo-3, 5-disubstituted pyrazoles (10)



R	Yield %	M.P. (degree)	Molecular formula	Calculated (%)				Found (%)			
				C	H	Br	N	C	H	Br	N
	20	183	C ₁₈ H ₁₂ Br ₃ N ₅	40.2	2.2	44.6	13.0	40.2	2.5	44.3	13.1
	25	210	C ₁₈ H ₁₂ Br ₂ N ₆ O ₂	42.9	2.4	31.8	16.7	42.6	2.7	31.4	16.8

Table 7. Microanalytical data for 4-(2-Phenyltriazol-4-yl) But-3-en-2-one acylhydrazones (11)






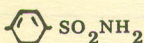
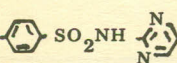

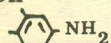
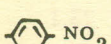
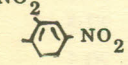

R	Yield %	M.P. (degree)	Molecular formula	Calculated (%)				Found (%)			
				C	H	N	Cl	C	H	N	Cl
-CH ₂ CN	25	151	C ₁₅ H ₁₄ N ₆ O	61.2	4.8	28.6		61.1	5.0	28.7	
	25	133	C ₁₉ H ₁₇ N ₅ O	68.9	5.1	21.2		68.5	5.3	21.5	
	30	224	C ₁₉ H ₁₆ ClN ₅ O	62.4	4.4	19.2	9.7	62.2	4.5	19.5	10.0
	30	163	C ₁₉ H ₁₈ N ₆ O	66.1	5.2	24.3		66.1	5.5	24.5	
	35	204	C ₁₉ H ₁₅ N ₇ O ₅	54.2	3.6	23.3		54.1	3.8	23.4	


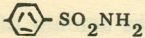

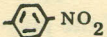
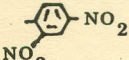
Table 8. Microanalytical and spectral data for ethyl 1-aryl-5-substituted pyrazole-3-carboxylates (13)

R	Yield %	M.P. (degree)	Molecular formula	Calculated (%)				Found (%)				ν KBr max (cm ⁻¹)
				C	H	N	S	C	H	N	S	
H	40	186	C ₁₆ H ₁₅ N ₅ O ₂	62.1	4.9	22.7		62.0	4.7	2.5		1715
	35	92	C ₂₂ H ₁₉ N ₅ O ₂	68.6	4.9	18.2		68.4	5.0	18.4		1715
	40	148	C ₂₂ H ₂₀ N ₆ O ₄ S	56.9	4.3	18.1	6.9	56.6	4.4	18.4	6.8	1715
	40	138	C ₂₆ H ₂₂ N ₈ O ₄ S	57.6	4.1	20.7	5.9	57.3	4.6	20.4		1720
	35	108	C ₂₁ H ₁₈ N ₆ O ₂	65.3	4.7	21.8		65.0	4.9	21.7		1715
	45	144	C ₂₂ H ₂₀ N ₆ O ₃	63.5	4.8	20.2		63.6	4.5	19.9		1720
	45	178	C ₂₂ H ₁₈ N ₆ O ₄	61.4	4.2	19.5		61.6	4.5	19.1		1715
	50	188	C ₂₂ H ₁₇ N ₇ O ₆	55.6	3.6	20.6		55.6	3.5	20.6		1715
	40	208	C ₂₄ H ₂₀ N ₇ O ₂	65.8	4.6	22.4		65.8	4.6	22.6		1720

Ethyl 1-aryl-5-substituted-pyrazole-3-carboxylates (13). These trisubstituted pyrazole esters were obtained by refluxing the ethyl hexenoate (12; 1 mmol) with the appropriate arylhydrazines or hydrazine (1 mmol) in ethanol (50 ml) for 3 hr. On concentration and cooling, the pyrazole esters separated out and were recrystallized from ethanol in needles; yield, 35-50% (see Table 8).

1-Aryl-5-substituted pyrazole-3-carboxylic acids (14). The foregoing esters (13; 0.5 g) was refluxed with ethanolic 2N KOH solution (20 ml) on a steam bath for 3 hr. On concentration, acidification with dilute hydrochloric acid, the solid mass that separated out was filtered off and recrystallized from dilute ethanol in needles, yield 50-65% (see Table 9).

Table 9. Microanalytical and spectral data for 1-aryl-5-substituted pyrazole-3-carboxylic acids (14)

R	Yield %	M.P. (degree)	Molecular formula	Calculated (%)				Found (%)				ν KBr max (cm ⁻¹)
				C	H	N	S	C	H	N	S	
H	50	136	C ₁₄ H ₁₁ N ₅ O ₂	59.8	3.9	24.9		59.7	4.2	24.7		1720
	50	125	C ₂₀ H ₁₅ N ₅ O ₂	67.2	4.2	19.6		67.1	4.5	20.0		1720
	55	256	C ₂₀ H ₁₆ N ₆ O ₄ S	55.1	3.7	19.3	7.3	55.0	4.1	19.1	7.1	1720
	60	136	C ₁₉ H ₁₄ N ₆ O ₂	63.7	3.9	23.5		63.7	4.3	23.9		1720
	65	239	C ₂₀ H ₁₄ N ₆ O ₄	59.7	3.5	20.9		59.8	3.5	21.1		1720
	65	293	C ₂₀ H ₁₃ N ₇ O ₆	53.7	2.9	21.9		53.7	3.3	22.1		1720

REFERENCES

- G.C. Gerritsen and W. E. Dulin, *J. Pharmacol. Exp. Ther.*, **150**, 491-98 (1965).
- G. C. Gerritsen and W. E. Dulin, *Diabetes*, **14**, 507, (1965).
- D. L. Smith, A. A. Forist and W. E. Dulin, *J. Med. Chem.*, **8**, 350-53 (1965).
- D. L. Smith, A. A. Forist and G. C. Gerritsen, *J. Pharmacol. Exp. Ther.*, **150**, 316-21 (1965).
- J. B. Wright, W. E. Dulin and J. H. Markillie, *J. Med. Chem.*, **7**, 102-5 (1964).
- A. Burger, *Medicinal Chemistry*, Wiley-Interscience, New York, (1970) pp. 548-549 and 814-825, 3rd ed.
- R. B. Angier, *J. Am. Chem. Soc.*, **70**, 14 (1948).
- W. Shive, *J. Am. Chem. Soc.*, **69**, 725 (1947).
- O. Gisvold, *Textbook of Organic. Medicinal and Pharmaceutical Chemistry*, 6th ed. (1971), pp. 986-87.
- F.G. Valdecass, *Med. Clin. (Barcelona)*, **4**, 275-79 (1952).
- A. Dimarco, B. Zanchi and V. Zavaglio, *Bull. Soc. Ital. Biol. Sperim.*, **102** (1952), 218; ref. *Chem. Abst* **70**, 35317 (1969).
- H. Mokhtar and R. Soliman, *Carbohydr. Res.*, **90** 144 (1981).
- H.M. Mokhtar, *Carbonhydr. Res.*, **108**, 307-14 (1982).