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# SYNTHESIS AND SPECTRA OF 3,5-DIMETHYLPYRAZOLE-4-CARBOXYLIC ACIDS

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Condensation of ethyl 2-acetylaceto-acetate with hydrazine, arylhydrazines yielded ethyl 3,5dimethylpyrazole-4-carboxylate (III, R = H) and ethyl 1-aryl 3,5-dimethylpyrazole-4-carboxylates (III, R = aryl), which were hydrolyzed to the corresponding acids.

Key words: Synthesis; Spectra; Pyrazoles.

### INTRODUCTION

Electrophilic substitution in the pyrazole ring occurs preferentially in the 4-position [1]. Accordingly, the synthesis of 4-carboxypyrazoles must involve the use of reagents capable of cyclization that possess either the desired carboxyl or substituents which can subsequently lead to it. Among such reagents is ethyl 2-acetylacetoacetate, which yields with hydrazine ethyl 3,5-dimethylpyrazole.4-carboxylate [2].

Peevious studies showed that several substituted 3,5dimethylpyrazoles and their active metabolite 5-methylpyrazole-3-carboxylic acid possessed potent hypoglycemic activities [3-7].

Furthermore, in the light of biological data reported by Soliman and coworkers [8-12] for many 3,5-disubstitute pyrazoles, a possible structure-activity relationship for hypoglycemic activity was observed.

The present study which is a continuation of the previous work [13-18], describes the preparation of a number of 1-aryl-3,5-dimethylpyrazole-4-carboxylic acids in the expectation they might possess antimicrobial activity.

With hydrazine, arylhydrazines the 1,3-diketo-ester (I), yielded the corresponding ethyl 1-H/aryl-3, 5-dimethylpyrazole-4-carboxylates (III, R = H/aryl). Formulation of the reaction products as (III) was based on the reactivity of the two similar carbonyl groups in the 1,3-diketo-ester (I). Thus the attack of the nucleophilic reagent takes place on one of the carbonyl groups resulting in the formation of its corresponding monohydrazone as an intermediate which simultaneously undergoes ring closure with the elimination of a water molecule from the imino-proton of the hydrazone residue and the hydroxyl group of the second enolized carbonyl group. The IR absorption spectra of these demethylpyrazole esters (III) revealed bands in the region of 1710-1730 cm<sup>-1</sup> due to carbonyl of the ester group, at 1580-1605 cm<sup>-1</sup> for (C = N) group, at 1490-1595 cm<sup>-1</sup> indicative of (C = C, aromatic), at 1390-1440 cm<sup>-1</sup> for (C-H) of the methyl group and the (NH) group band of ester (III, R=H) appeared at 3240-3410  $cm^{-1}$ . In addition of these absorption bands, the (NO<sub>2</sub>) group bands was observed at 850 and in the region of 1350-1520 cm<sup>-1</sup>. The structure of these esters (III) was further confirmed by measuring their p.m.r. (CDCl<sub>3</sub>) spectra that gave signals at  $\delta$  3.40 (quartet) and 1.08 (triplet) for the ethyl ester group protons; the two methyl groups protons appeared as two very close singlets in the region of 1.94 proving that they are non-equivalent and the aromatic ring protons as multiplet at 6.10-7.00 ppm. In addition to these signals, in ester (III, R = H) the (NH) group proton signal was observed at a low field ( $\delta = 5.8$ ppm) and this was expected and attributed to the high electronegativity of the N-atom that decreases the electron density on the H-atom of the (NH) group, whereas their electronic absorption spectra were characterised by several maxima stretching up to 360 nm. This was to be expected since the molecule contained a high degree of conjugation between the pyrazole ring, the phenyl ring and the carbonyl of the carbethoxy group. In all the spectra, the position and intensity of the different maxima did not change when the spectra were measured in non-polar solvents such as cyclohexane or in a polar solvent as ethanol. This, together with their high extinction coefficient suggests that these absorption bands are due to  $\pi$  - $\pi^*$  transitions. The weaker  $n-\pi^*$  transitions which are usually characterised by a wavy appearance in non-polar solvents and which become blurred in polar solvents were absent. They probably lie below the  $\pi - \pi^*$  transitions, which due to the high degree of conjugation were shifted

to longer wavelengths and overlap  $n-\pi^*$  transitions which are unaffected by conjugation [19]. These pyrazole esters (III) underwent hydrolysis on treatment with alcoholic potassium hydroxide solution to give the corresponding 1-H/aryl-3,5-diemethylpyrazole--4-carboxylic acids (IV).

Their electronic absorption spectra were similar to those of the pyrazole esters (III) since the ethyl group of the esters has no effect on the uv-spectra. Their IR spectra revealed bands for (C = N) group at 1610 cm<sup>-1</sup>, at 1690-1720 cm<sup>-1</sup> for the carbonyl of the carboxyl group, at 3500 cm<sup>-1</sup> for the (OH) group, at 1500-1600 cm<sup>-1</sup> indicative of (C=C, aromatic), at 1400-1440 cm<sup>-1</sup> for (C-H) of the methyl group and the (NH) group band of acid (IV, R = H) was observed at 3350 cm<sup>-1</sup>. In addition of these absorption bands, the (NO<sub>2</sub>) group bands appeared at 870 and 1350 cm<sup>-1</sup>.

# EXPERIMENTAL

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.

*Ethyl 2-acetylacetoacetate.* This ester was prepared with slight modification to the method reported by Ogata *et al* [20] and Spasov [21] as follows:

To a suspension of sodium powder (0.1 mole) in dry ether (250 ml), ethyl acetoacetate (0.1 mole) was added drop by drop with continuous shaking for a period of 1 hr.

Table 1. Microanalysis and Spectral Data of Ethyl 1-H/aryl-3, 5-dimethylpyrazole-4-carboxylates (III).

]	R	M.p. (o)	Formula	Calcd C	Analy: ./Fou H	State of the local division in	UV absorpt λmax (lo			KBr 'max (cm <sup>-1</sup> )	<sup>1</sup> Η NMR data δ/ppm
11		<u>_</u>				IN				(ст)	
]	Н	98 <sup>x</sup>					238(3.14)			1710(CO); 3300(NH)	3.4(q, 2H, CH <sub>2</sub> ), 1.08(t, 3H, CH <sub>3</sub> ), 1.94-1-98(s, s, 6H,
	$\bigcirc$	68 <sup>xx</sup>					248(4.10),	220sh(	(3.69)		2CH <sub>3</sub> ), 5.8 (s, 1H,NH) 3.42(q,2H,CH <sub>2</sub> ),1.06 (t, 3H, CH <sub>3</sub> ), 1.29 – 1.94 (s, s, 6H, 2CH <sub>3</sub> ), 6.08-7.02 (m, 5H, Ar).
CH₃∙	$\bigcirc$	108	$C_{15}H_{18}N_2O_2$	69.8 69.8		10.9 11.1	249(3.87),	220sh(	(3.54)	1730(CO)	0.000 / .02 (, 011, 12)
Cl ·	$\bigcirc$	173	C <sub>14</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> Çl		5.4	10.1	315(3.66) 245sh (3.93)	255 210	(3.96), (3.76)		3.39(q, 2H, CH <sub>2</sub> ), 1.08 (t, 3H, CH <sub>3</sub> ), 1.94 – 1.96 (s, s, 6H, 2CH <sub>3</sub> ), 6.10-7.00 (m, 4H, Ar).
Br	$\bigcirc$	113	$C_{14}H_{15}N_2O_2Br$	52.0 51.8		8.7 8.7	260(3.91),	220sh	(3.53)	1720(CO)	
I	$\langle \rangle$	-163	$C_{14}H_{15}N_2O_2I$	45.4 45.5	4.1	7.6 7.4	260(4.12),	225sh	(3.72)	1720(CO)	
C1-		90	$C_{14}H_{15}N_2O_2Cl$		5.4	10.1 10.0	250(3.99),	220sh	(3.75)	1720(CO)	
$D_2N$	$\bigcirc$	149xx	XX ·				295(4.09),	227	(3.97)	1720(CO;870 and 1350 (NO <sub>2</sub> )	)
O <sub>2</sub> N	$\leq$	- 155 <sup>xx</sup> 0 <sub>2</sub>	XXX				360(4.16),	227	(4.05)	1720(CO); 870 and 1350(NO <sub>2</sub> )	

X Lit.<sup>2</sup> m.p. 96<sup>°</sup> xx Lit.<sup>22</sup> m.p. 68<sup>°</sup> xxx Lit.<sup>22 23</sup> m.p. 142<sup>°</sup> xxxx Lit.<sup>22,23</sup> m.p. 156-156.5<sup>°</sup>.

R	M.p.	Formula	Analyses Calcd./Found %			UV absorpt	ion data	KBr vmax (cm <sup>-1</sup> )
	(o)					λmax (le	$\log \epsilon$ )	
			C	Н	N			
H	53	$C_6H_8N_2O_2$	51.4	5.7	20.0	248sh(2.23),	237(2.63)	1705(CO); 3350(NH); 3500(OH)
			51.4	5.5	19.9			
1.1	193 <sup>x</sup>					277sh(3.03),	255(3.40)	1720(CO); 3500(OH).
$\langle \rangle$	182	$C_{13}H_{14}N_2O_2$	67.8	6.1	12.2	267sh (3.43),	250(3.63)	1720(C): 3500(OH).
			67.7	6.3	12.1			
CI-	102	$C_{12}H_{11}N_2O_2Cl$	57.4	4.4	11.2	285sh(3.52),	255(3.61)	1705(CO); 3500(OH).
	2		57.7	4.7	10.9			
Br -	115	C12 H11 N2 O2 Br	48.8	3.7	9.5	303sh(3.71),	255(3.86)	1705(CO), 3500(OH).
			48.6	3.9	9.5			
1-(1)-	119	$C_{12}H_{11}N_2O_2I$	42.1	3.2	8.2	317sh(3.73),	262(3.89)	1705(CO), 3500(OH)
			42.3	3.2	8.0	1	N.L. monto	a seal was been and a seal of a
CITY	185	$C_{12}H_{11}N_2O_2Cl$	57.4	4.4	11.2	270 (3.29),	252(3.52)	1705(CO), 3500(OH).
		a seed of the la	57.3	4.2	11.5		demonsteret.	This has been block in the desired
N-	140	$C_{12}H_{11}N_3O_4$	55.2	4.2	16.1	297 (4.03),	222(4.13),	1705(CO); 3500(OH) 870 and
			55.3	4.4		210sh(4.00),		1350 (NO <sub>2</sub> ).
NOY	113	$C_{12}H_{10}N_4O_6$	47.1	3.3		303 (3.96),		1705(CO), 870 and 1350 (NO <sub>2</sub> ).
N	0.	80.F. (25), 80.C. (105	46.9	3.3	18.6	1.00	1919	Selimit, J. Med. (Jugs., 13, 311 (J.

Table 2. Microanalysis and Spectral Data of 1-H/Aryl-3, 5-dimethylpyrazole-4-carboxylic acids (IV).

x Lit.<sup>22</sup> m.p. 194–196<sup>0</sup>

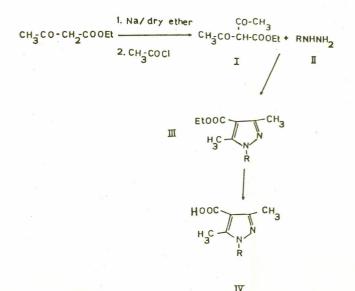
After the addition of ethyl acetoacetate, the reaction was left overnight until all sodium was reacted. To the prepared sodium salt, acetyl chloride (0.1 mole) in dry benzene was added dropwise with continuous shaking for 1 hr. The mixture was refluxed for 10 hr., cooled, treated with water and the benzene-ether layer was separated, whereas the aqueous layer was extracted several times with ether. The combined benzene-ether extracts was treated with cold 10 % sodium hydrogen carbonate solution to remove acidity, then with water and dried. After distillation of the solvents, the pale brown oily residue was subjected to vacuum distillation where ethyl 2-acetylaceto-acetate was collected at  $65-70^{\circ}/17$  mm Hg (yield 45%).

Ethyl 1-H/aryl-3,5-dimethylpyrazole-4-carboxylates (III; R = H/aryl). These compounds were obtained when ethyl 2-acetylacetoacetate (I, 0.1 mole) in ethanol was heated under reflux with 0.1 mole of hydrazine (II; R = H) or with the appropriate arylhydrazine (II; R = aryl) (0.1 mole) for a period of 2-3 hr. The mixture was then concentrated, cooled and the precipitated product filtered and crystallized from light petroleum (b.p. 40-60°) or benzene-petroleum mixture in needles, yield 50-70% (see Table 1).

1-H/aryl-3,5-dimethylpyrazole-4-carboxylic acids (IV; R=H/aryl). The foregoing esters (III; 0.5 g) was reflux-

ed with ethanolic 2N KOH solution (25 ml) on a boiling water bath for 3 hr. On concentration, cooling, acidification with dilute hydrochloric acid, the solid mass that separated out was filtered off and recrystallized from light petroleum (b.p.  $40-60^{\circ}$ ) or benzene-petroleum mixture in needled, yield 50-60% (see Table 2).

#### Scheme



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