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

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Condensation of ethyl 2-acetylacetoacetate with hydrazine, arylhydrazines yielded ethyl 3,5-dimethylpyrazole-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 3,5-dimethylpyrazoles 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 spec-

tra of these demethylpyrazole esters (III) revealed bands in the region of 1710-1730  $\text{cm}^{-1}$  due to carbonyl of the ester group, at 1580-1605  $\text{cm}^{-1}$  for (C = N) group, at 1490-1595  $\text{cm}^{-1}$  indicative of (C = C, aromatic), at 1390-1440  $\text{cm}^{-1}$  for (C-H) of the methyl group and the (NH) group band of ester (III, R=H) appeared at 3240-3410  $\text{cm}^{-1}$ . In addition of these absorption bands, the ( $\text{NO}_2$ ) group bands was observed at 850 and in the region of 1350-1520  $\text{cm}^{-1}$ . The structure of these esters (III) was further confirmed by measuring their p.m.r. ( $\text{CDCl}_3$ ) 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-dimethylpyrazole-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  $1610\text{ cm}^{-1}$ , at  $1690-1720\text{ cm}^{-1}$  for the carbonyl of the carboxyl group, at  $3500\text{ cm}^{-1}$  for the (OH) group, at  $1500-1600\text{ cm}^{-1}$  indicative of (C=C, aromatic), at  $1400-1440\text{ cm}^{-1}$  for (C-H) of the methyl group and the (NH) group band of acid (IV, R = H) was observed at  $3350\text{ cm}^{-1}$ . In addition of these absorption bands, the ( $\text{NO}_2$ ) group bands appeared at  $870$  and  $1350\text{ cm}^{-1}$ .









## 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	Analyses			UV absorption data		KBr $\nu_{\text{max}}$ ( $\text{cm}^{-1}$ )	$^1\text{H NMR}$ data $\delta/\text{ppm}$
			Calcd./Found	C	H	N	$\lambda_{\text{max}}$ (log $\epsilon$ )		
H	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, 2CH <sub>3</sub> ), 5.8 (s, 1H, NH)
	68 <sup>xx</sup>					248(4.10),	220sh(3.69)	1720(CO)	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).
CH <sub>3</sub> - 	108	C <sub>15</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	69.8 69.8	7.0 6.8	10.9 11.1	249(3.87),	220sh(3.54)	1730(CO)	
Cl- 	173	C <sub>14</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> Cl	60.3 60.5	5.4 5.2	10.1 10.4	315(3.66) 245sh (3.93)	255 210	(3.96), 1730(CO) (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- 	113	C <sub>14</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> Br	52.0 51.8	4.6 4.4	8.7 8.7	260(3.91),	220sh (3.53)	1720(CO)	
I- 	163	C <sub>14</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> I	45.4 45.5	4.1 4.2	7.6 7.4	260(4.12),	225sh (3.72)	1720(CO)	
Cl- 	90	C <sub>14</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> Cl	60.3 60.5	5.4 5.5	10.1 10.0	250(3.99),	220sh (3.75)	1720(CO)	
O <sub>2</sub> N- 	149 <sup>xxx</sup>					295(4.09),	227 (3.97)	1720(CO); 870 and 1350 (NO <sub>2</sub> )	
O <sub>2</sub> N-  NO <sub>2</sub>	155 <sup>xxxx</sup>					360(4.16),	227 (4.05)	1720(CO); 870 and 1350(NO <sub>2</sub> )	

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



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