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SYNTHESIS AND MAO ACTIVITY OF 3-SUBSTITUTED-5-(5'-ARYL-1',3',4',- OXADIAZOL-2',YL)-1,2-DIMETHYL-PYRROLES

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Methylation of 3-substituted-2-methylpyrrole-5- carboxaldehyde gave the corresponding methylated derivative, which condensed with acylhydrazines to afford the corresponding hydrazones. Oxidative cyclisation of the prepared acylhydrazones furnished 3-substituted-5- (5'-aryl-1',3',4'-oxadiazol-2'-yl), -1,2-dimethyl-pyrroles. These compounds were evaluated for their monoamine oxidase (MAO) activity (in vitro). Some of them showed activating effect while others have inhibitory action on MAO.

Key words: 3-substituted-5-(5'-aryl-1',3',4'-oxadiazol-2-yl)-1,2-dimethyl-pyrroles, MAO activity.

Introduction

It has been shown that oxadiazoles possess central nervous system (CNS) properties [1-3] and that the 1,3,4-oxadiazoles have a large number of uses in drug synthesis [4,5]. Monoamine oxidase plays an important role in brain function catalyzing the deamation of the corresponding aldehyde, H_2O_2 and amonia [6] with the result that the enzyme plays different physiological roles in the regulation of several neuroendocrine secretions and some emotional behaviour [7,8].

So, in this work we undertook the synthesis of new 1,3,4-oxadiazoles which may have different CNS effects.

Experimental

The compounds were synthesized following the route given in the Scheme I, and were routinely checked for homogeneity by TLC on silica gel G using the following solvent systems"

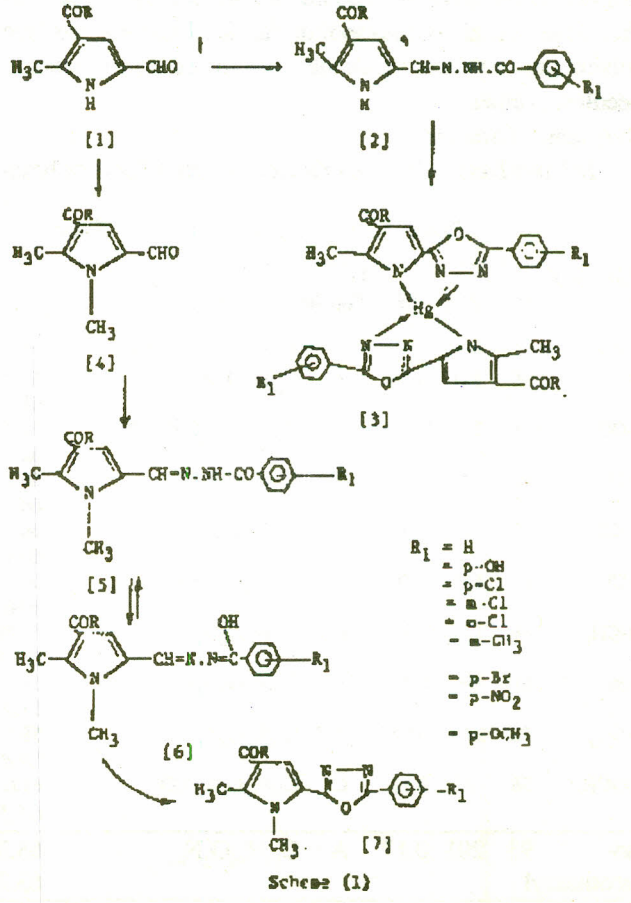
A:	$CHCl_3$	:	CH_3OH	(15:1)
B:	ethyl acetate	:	n-Hexane	(2 :1)
C:	ethyl acetate:		n-Hexane	(1 :1)

Their IR and UV spectra were recorded on Unicam SP, 1025 and Unicam SP, 2000; infrared spectrophotometers and Unicam SP 1750 ultraviolet spectrophotometer respectively. NMR spectra were recorded on a Varian EM 390, 90 MHZ NMR spectrometer using tetramethylsilane as internal standard. Melting points were determined on a Kofler block and are uncorrected, Microanalysis were performed at the Faculty of Science, Cairo University, Cairo, Egypt. An LKB Ultraspec II spectrophotometer was used for MAO assay,

3-Substituted-2-methyl-pyrrole-5-carboxaldehyde (1). The method of Garcia Gonzalez *et.al.* [9] was used for synthesis of 3-ethoxycarbonyl and 3-acetyl derivatives.

3-Substituted-1,2-dimethyl-pyrrole-5-carboxaldehyde (4). The method of El Kholy *et. al.* [10] for methylation was used for the preparation of (4) from (1).

For 3-acetyl derivative, yield 61%, m.p. 137°, R_f 0.93 in solvent A, IR (KBr) 1675 (CHO)1685 ($COCH_3$) cm^{-1}, λ^{EtOH}_{Max} 232 and 292 nm (log 4.99 and 4.98), ^{1}H-NMR (acetone-d_6), 2.43 (3H,s, CH_3), 2.62 (3H,s,($COCH_3$), 3.85 (3H,s, N-CH_3), 7.25 (1H,s,CH) and 9.4 (1H,s,CHO) ppm; found C,



Scheme (1)

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65.45; H, 6.70;N, 8.48 calc. for $C_9H_{11}NO_2$, C,65.80, H, 6.60, N,8.50%, For the 3-ethoxycarbonyl derivative, yield 90%, m.p. 55° , R_f 0.62 in solvent A, IR (KBr) 1660 (CHO), 1690 (CO-ester)cm^{-1} λ^{EtOH}_{Max} 218 and 288 nm (log 5.47 and 5.68), ^{1}H-NMR ($CDCl_3$) 1.2 (3H,t,CH_3-ester), 2.53 (3H,s,CH_3) 3.85 (3H,s,N-CH3), 4.2(2H,q, CH_2-ester), 7.24 (1H,s,CH) and 9,38 (1H,s, CHO ppm. found C,61.40; H,6.60; N,7.10%, calc. for $C_{10}H_{13}NO_3$, C, 61.54, H, 6.67.N,7.18%.

3-Substituted-1,2-dimethyl Pyrrole-5-carboxaldehyde acylhydrazones; (5). A solution of 3-substituted aldehydes (4), each separately (2 gm, 0.01 mole) in ethanol, containing acetic acid (0.1ml), was treated with an equivalent amount of acylhydrazine in ethanol (10 ml). The reaction mixture was refluxed for one hour; after cooling the acylhydrazone derivative that separated out was filtered off, washed with a little ethanol, dried, and crystallized from ethanol (Tables 1 and 2).

3-Substituted-5-(5'-aryl-1',3',4'-oxadiazol-2'-yl)1,2-dimethylpyrrole (7). Solutions of the dry acylhydrazones (2.0gm, 0.01 mole) in dry ether (50ml) were stirred with yellow mercuric oxide (3.0 gm), magnesium oxide (0.4 gm) and iodine (1.5 gm) at room temperature for 48 hours under anhydrous conditions. The reaction mixture was filtered and the etherial layer washed with potassium iodide solution (50 ml). sodium thiosulphate (50 ml) and water respectively and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a yellow syrup that crystallised from ethanol in needles, (Tables 3-6).

Biochemical Studies.

In Vitro Determination of MAO activity. Chickens brain (9.7 gm) was homogenized [11] using potter homogenizer with ice-cold (0.1 M) sodium phosphate buffer pH 7.4 and sucrose solution (0.3 M). The mitochondrial fraction was isolated by differential centrifugation and treated with the sodium phosphate buffer (1 gm tissue/ml buffer) to give a homogeneous enzyme preparation.

MAO activities was measured [12] by recording the increase in absorbance at 250 nm which occurs when benzylamine as substrate is oxidized to benzaldehyde as following: 2.8 ml of benzylamine solution (0.37 x 10^{-3} M) in sodium phosphate buffer (0.1 M,pH 7.4) was added to the enzyme preparation (0.2 ml), and incubated at 38° for 10-15 min. A blank without the benzylamine was used. Each reaction mixture was centrifuged and measured at 250 nm.

Similar experiments were attempted with the prepared compounds (each, 1 x 10^{-3} M in propylene glycol) whereby (0.2 ml) of each compound separately was added to 2.8 ml buffer and (0.2 ml) of enzyme preparation. Repeated assays were carried out using 2.8 ml of benzylamine in the buffer and the residual MAO activity measured, (Table 7,8). All determination were taken as the mean of duplicate measurements.

The type of inhibition of the examined compounds was characterized when I/V was plotted against 1/[S], (Lineweaver-Burk plots) using different concentrations of benzylamine substrate in sodium phosphate buffer [(0.12, 0.25, 0.37, 0.75, 1) x 10^{-3}M], (Table 9).

Results and Discussion

It has been shown that the oxidative cyclization of the acylhydrazone derivative of a 4-substituted-2-methylpyrrole-

Table 1. Analytical Data for 3-acetyl-5-formyl-1, 2-dimethyl-pyrrole-5-acylhydrazones.

R_1	Yield %	M.P. (°C)	TLC Rf	TLC Solvent	Formula	Anal. Calc./found(%) C	H	N	X	KBr max. cm^{-1} C=N	CONH	COCH3	N-H
H	96	221	0.73	A	$C_{16}H_{17}O_2N_3$	67.8	6.0	14.8	—	1630	1660	1685	3220-3250
						68.0	5.7	14.5	—				
p-OH	58	254	0.15	B	$C_{16}H_{17}O_3N_3.1/2H_2O$	62.3	6.17	13.6	—	1600	1625	1645	3235-3400
						62.4	6.30	14.0	—				
p-Cl	80	97	0.58	B	$C_{16}H_{16}O_2N_3Cl$	60.5	5.0	13.2	11.2	1630	1665	1675	3440-3510
						60.6	4.9	13.2	11.3				
m-Cl	97	86	0.44	C	$C_{16}H_{16}O_2N_3Cl$	60.5	5.0	13.2	11.2	1625	1645	1670	3390-3500
						60.3	5.0	13.2	11.6				
o-Cl	97	155	0.44	C	$C_{16}H_{16}O_2N_3Cl$	60.5	5.0	13.2	11.2	1610	1665	1685	3410-3540
						60.6	5.2	13.0	11.6				
m-CH_3	88	102	0.29	C	$C_{17}H_{19}O_2N_3$	68.69	6.39	14.14	—	1620	1635	1680	3400-3430
						68.80	6.40	14.0	—				
p-Br	61	94	0.4	A	$C_{16}H_{16}O_2N_3Br$	53.0	4.4	11.6	22.1	1620	1640	1665	3430-3480
						53.0	4.6	11.2	22.0				
p-NO_2	78	240	0.3	A	$C_{16}H_{16}O_4N_4$	58.54	4.88	17.07	—	1620	1635	1670	3340
						58.20	4.80	17.50	—				
p-OCH_3	58	87	0.11	C	$C_{17}H_{19}O_3N_3H_2O$	61.6	5.7	12.7	—	1610	1635	1660	3440-3500
						61.5	6.2	12.4	—				
iso-nicotinuoyl	93	201	0.17	A	$C_{15}H_{16}O_2N_4$	63.38	5.63	19.72	—				
						63.20	5.60	19.70	—				

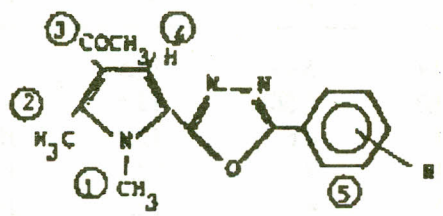
5-carbaldehyde with mercuric oxide afforded bis-methyl-5-(5'-aryl-1',3',4'-oxadiazol-2'-yl)-2-methylpyrroles as mercuric complex (3) [13].

To avoid this complexation, methylation of the 3-substituted aldehyde (1) afforded the methylated derivative (4). The ^{1}H-NMR spectra of these aldehydes (4) were consistent

TABLE 2. ANALYTICAL DATA FOR 3-ETHOXYCARBONYL-5-FORMYL-1, 2-DIMETHYL-PYRROLE-5ACYLHYDRAZONES.

RI	Yield %	M.P. (°C)	TLC Rf	TLC Sol-vent	Formula	Anal. Calc./found(%) C	H	N	X	KBr ν_{max} cm^{-1} C=N	CONH	COCH3	N-H
H	62	178	0.7	A	$C_{17}H_{19}O_3N_3$	65.17	6.07	13.42	—	1635	1670	1720	3500-3540
						64.90	6.10	13.40	—				
p-OH	72	237	0.49	B	$C_{17}H_{19}O_4N_3$	62.01	5.78	12.77	—	1625	1660	1690	2960-3200
						61.70	5.40	12.70	—				
p-Cl	78	180	0.54	C	$C_{17}H_{18}O_3N_3Cl$	58.71	5.18	12.60	10.2	1630	1675	1710	3450-3520
						58.31	5.0	12.09	10.2				
m-Cl	67	78	0.58	C	$C_{17}H_{18}O_3N_3Cl$	58.71	5.18	12.60	10.2	1625	1645	1715	3445-3465
						58.40	5.20	12.2	10.0				
0-Cl	70	103	0.62	C	$C_{17}H_{18}O_3N_3Cl$	58.71	5.18	12.60	10.2	1630	1675	1725	3200-3240
						58.40	5.20	12.2	10.0				
p-CH_3	35	79	0.44	C	$C_{18}H_{21}O_3N_3.H_2O$	62.61	7.03	12.17	—	1625	1645	1710	3450
						62.30	6.9	12.50	—				
m-CH_3	49	145	0.40	C	$C_{18}H_{21}O_3N_3$	65.06	6.4	12.84	—	1620	1665	1720	3210
						65.06	6.4	12.84	—				
p-Br	86	162	0.48	C	$C_{17}H_{18}O_3N_3Br$	52.4	4.59	10.71	20.41	1630	1670	1710	3440-3510
						51.80	4.50	10.70	20.2				
p-NO_2	48	125	0.47	C	$C_{17}H_{18}O_5N_4.1/2H_2O$	55.74	5.2	15.3	—	1635	1675	1710	3500-3520
						55.40	5.0	15.5	—				
p-OCH_3	41	152	0.56	B	$C_{18}H_{21}O_4N_3$	62.97	6.12	12.24	—	1635	1675	1690	3370
						62.70	5.90	12.50					
iso-nicotinuoyl	87	143	0.62	B	$C_{16}H_{18}O_3N_4.H_2O$	57.81	6.02	16.09					
						57.90	5.70	17.0	—				

TABLE 3. THE INFRARED AND $_1$H-NMR SPECTRA OF 3-ACETYL-5-(5'-ARYL-1', 3', 4'-OXADIAZOL-2'-YL)-1, 2-DIMETHYL-PYRROLE:



R	Sol-vent	ppm H-1	H-2	H-3	H-4	H-5	KBr ν cm^{-1} max. C=N	COOEt
H	D	3.95	2.41	2.58	7.12	7.41-8.0	1610	1675
p-OH	–	–	–	–	–	–	1625	1670
p-Cl	D	4.10	2.59	2.98	7.18	7.40-7.95	1620	1670
m-Cl	–	–	–	–	–	–	1625	1670
o-Cl	–	–	–	–	–	–	1620	1675
m-CH_3	E	3.88	2.35	2.51	7.30	7.28-7.9	1625	1665
p-Br	–	–	–	–	–	–	1625	1660
p-NO_2	–	–	–	–	–	–	1625	1710
p-OCH_3	E	3.88	2.38	2.51	7.35	7.09-7.35	1625	1685

Notes: 1) In case of m-tolyl, and p-methoxypheny, the methyl protons appeared at 2.53, and 3.8 ppm respectively.

2) D = Chloroform (d_1), E = Dimethylsulfoxide (d_6).

TABLE 4. THE INFRARED AND 1H-NMR SPECTRA OF 3-ETHOXYCARBONYL-5-(5'-ARYL-1', 3', 4'-OXADIAZOL-2'-YL)-1, 2-DIMETHYL-PYRROLE:

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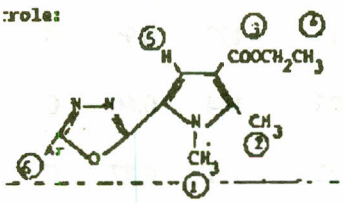

Ar	ppm H-1	H-2	H-3	H-4	H-5	H-6	KBr ν cm^{-1} max. C=N	COOEt
C_6H_5	3.95	2.75	4.24	1.35	7.25	7.42-7.98	1615	1720
m-C_6H_4Cl	3.95	2.58	4.23	1.35	7.25	7.38-7.90	1632	1725
o-C_6H_4Cl	4.00	2.60	4.27	1.35	7.30	7.50-7.95	1635	1720
p-$C_6H_4CH_3$	4.03	2.48	4.30	1.45	7.25	7.35-7.95	1625	1710
m-$C_6H_4CH_3$	3.95	2.40	4.25	1.37	7.23	7.30-7.80	1630	1712
p-C_6H_4Br	3.95	2.53	4.20	1.28	7.20	7.53-7.86	1625	1725
p-$C_6H_4NO_2$	4.01	2.63	4.32	1.40	7.32	8.00-8.25	1625	1720
p-$C_6H_4OCH_3$	3.97	2.59	4.27	1.38	7.20	6.92-7.95	1630	1720
p-C_5H_4N	3.90	2.53	4.21	1.30	7.22	7.90-8.72	1615	1715

Notes: 1) In case of p-tolyl, m-tolyl, and p-methoxypheny, the methyl protons appeared at 2.65, 2.55 and 3.82 ppm respectively.

Table 5. Analytical Data for 3-Acetyl-5-(5'-aryl-1', 3', 4'-oxadiazol-2'-yl)1, 2-Dimethyl-pyrroles.

RI	Yield %	M.P. (°C)	TLC R_f	TLC Solvent	Formula	Anal. Calc./found (%) C	H	N	X
H	20	158	0.73	B	$C_{16}H_{15}O_2N_3$	68.33	5.3	14.95	–
						68.30	5.0	14.90	–
p-OH	21	122	0.63	B	$C_{16}H_{15}O_3N_3$	64.65	5.05	14.14	–
						65.0	5.20	14.10	–
p-Cl	25	181	0.87	B	$C_{16}H_{14}O_2N_3Cl$	60.9	4.4	13.3	11.3
						60.8	4.6	13.5	11.6
m-Cl	40	96	0.88	C	$C_{16}H_{14}O_2N_3Cl$	60.9	4.4	13.3	11.3
						60.6	4.3	13.3	11.7
o-Cl	20	197	0.85	C	$C_{16}H_{14}O_2N_3Cl$	60.9	4.4	13.3	11.3
						60.8	4.6	13.3	11.6
m-CH_3	30	110	0.78	C	$C_{17}H_{17}O_2N_3$	69.15	5.76	14.24	–
						69.0	5.35	14.50	–
p-Br	20	115	0.53	A	$C_{16}H_{14}O_2N_3Br$	53.3	3.9	11.7	22.2
						53.6	3.9	11.5	22.0
p-NO_2	28	193	0.34	A	$C_{16}H_{14}O_4N_4$	58.9	4.49	17.18	–
						58.0	4.10	17.40	–
p-OCH_3	13	170	0.57	C	$C_{17}H_{17}O_3N_3.2H_2O$	58.8	6.05	12.1	–
						58.7	6.30	12.2	–

Table 6. Analytical Data of 3-Ethoxycarbonyl-5-(5'-aryl-1', 3' 4'-oxadiazol-2'-yl)1, 2-Dimethyl-pyrroles.

R_1	Yield %	M.P. (°C)	TLC R_f	TLC Solvent	Formula	Anal. Calc./found (%) C	H	N	X
H	13	172	0.96	B	$C_{17}H_{17}O_3N_3$	65.59	5.47	13.50	–
						65.80	5.50	13.5	–
p-Cl	23	144	0.60	C	$C_{17}H_{16}O_3N_3Cl$	59.1	4.6	12.2	10.3
						58.9	4.3	12.1	10.6
m-Cl	22	111	0.87	C	$C_{17}H_{16}O_3N_3Cl$	59.1	4.6	12.2	10.3
						59.0	4.3	12.2	10.6
o-Cl	15	94	0.84	C	$C_{17}H_{16}O_3N_3Cl$	59.1	4.6	12.2	10.3
						59.0	4.6	12.1	10.3
p-CH_3	20	118	0.83	C	$C_{18}H_{19}O_3N_3$	66.46	5.85	12.92	–
						66.30	5.80	12.90	–
m-CH_3	13	90	0.93	C	$C_{18}H_{19}O_3N_3$	66.46	5.85	12.92	–
						66.40	6.0	12.90	–
p-Br	35	140	0.75	C	$C_{17}H_{16}O_3N_3Br.3H_2O$	45.9	5.0	9.5	18.0
						45.7	5.0	9.7	18.1
p-NO_2	20	185	0.83	C	$C_{17}H_{16}O_5N_4$	57.30	4.49	15.73	–
						57.40	4.80	16.0	–
p-OCH_3	36	125	0.90	B	$C_{18}H_{19}O_4N_3$	63.34	5.57	12.32	–
						63.0	5.30	12.50	–
3-p-C_5H_4N	26	156	0.86	B	$C_{16}H_{16}O_3N_4$	61.54	5.13	17.95	–
						61.40	5.50	18.10	–

with the structure, thus no (N-H) protons were observed but instead a new N-CH_3 singlet appeared at about 3.9 ppm, in addition to the other signals in the molecule. The methylated aldehydes (4) reacted with acylhydrazines in acidic medium to give the acylhydrazones (5). The ^{1}H-NMR spectrum of the benzoylhydrazone (Scheme I, R = OEt,R_1 = H) showed signals at 1.25 (3H,t,J = 6Hz, CH_3-ester), 2.43. (3H,s,-CH_3) 3.72 (3H,s,N-CH_3) ,4.15 (2H,q,J = 6Hz, CH_2-ester),6.6 (1H,s,CH), 7.25 (3H,t,J = 6Hz, Ar-H), 7.8 (2H,d,J = 6Hz, Ar-H), 8.12 (1H,s, CH = N) and 11.4 ppm (1H,s, NHCO), (Tables 1 and 2).

TABLE 7. EFFECT OF E-ETHOXYCARBONYL-5-(5-ARYL-1', 3', 4'-OXADIAZAL-2'-YL)-1, 2-DIMETHYLPYRROLES ON MAO ACTIVITY.

R_1	Absorbance at 250 mm	Effect on MAO
Control	0.418	–
p-NO_2	0.117	inh.
m-CH_3	0.292	inh.
p-Br	0.406	inh.
p-Cl	0.584	act.
p-OH	0.700	act.
m-Cl	0.773	act.
p-CH_3	0.810	act.
H	0.946	act.
p-OCH_3	1.156	act.

inh.: inhibitor act.: activator

TABLE 8. EFFECT OF 3-ACETYL-5-(5-ARYL-1', 3', 4'-OXADIAOAL-2'-YL)-1, 2-DIMETHYLPYRROLES ON MAO ACTIVITY.

R_1	Absorbance at 250 mm	Effect on MAO
control	0.173	–
m-CH_3	0.227	act.
O-Cl	0.335	act.
p-CH_3	0.342	act.
m-Cl	0.370	act.
p-OCH_3	0.373	act.
isonicotinuoyl	0.427	act.
p-Cl	0.461	act.
p-OH	0.632	act.

act.: activator

TABLE 9. COMPARISON OF MAXIMUM VELOCITY OF REACTION AND APPARENT MICHAELIS CONSTANTS FOR VARIOUS TYPES OF 3-ETHOXYCARBONYL-(5'-ARYL-1', 3', 4'-OXADIAZOL-2'-YL)-1, 2-DIMETHYLPYRROLE.

R_1	Maximum vekicutt	Michaelis constant	Slope	Ki	Typeof inh.
p-No_2	1.869	1.66	1.869	$1.95x10^{-3}$	non-comp.
m-CH_3	1.129	0.323	0.286	$1.34x10^{-3}$	non-comp.
p-Br.	1.11	0.571	0.514	$1.73x10^{-3}$	un-comp.

oxidative cyclization of the acylhydrazones (5) gave through the enol form [6] the corresponding oxadiazole derivatives [7] ^{1}H-NMR spectra showed in all cases the disappearance of both the imino proton of the hydrazone residue as well as the formyl proton at (C-2) of the pyrrole ring, (Tables 4-6)

Although, it was reported [14] previously that oxadiazoles exhibited CNS depressent effect, we noticed that all the prepared compounds when assessed individually with MAO activity showed different effects in which all the -3-acetyl-5-(5'-aryl-1',3',4' oxadiazole-2'-yl)-1,2-dimethyl pyrroles activate the MAO, but with different values depending on the type and position of substitution, and accelerate the step of enzyme-substrate complex, producing more benzaldehyde in decreasing order as the following: p-OH,p-Cl, isonicotinoyl, p-OCH_3,m-Cl, p-CH_3 o-Cl, and m-CH_3.

Also, the 3-ethoxycarbonyl-5-(5'-aryl-1',3',4'-oxadiazol-2'-yl) 1,2-dimethylpyrroles appeared to activate MAO except for the p-NO_2, m-CH_3, and p-Br substituted derivaties, which showed potent MAO inhibitory activity. It was believed that this occur via the preliminary formation of an intermediate Michaelis-like reversible complex between the enzyme and the inhibitor.

In order to identify the type of inhibition of each compound (p-NO_2, m-CH_3, p-Br of the 3-ethoxycarbonyl-5-(5'-aryl-1',3',4'-oxadiazol-2'-yl) we plotted 1/v against 1/s, where v is the velocity of each enzymatic reaction equivalent to the resulted benzaldehyde from each different concentration (S) of benzylamine (Substrate) in case of absence and presence of each inhibitor.

The obtained curves indicated that p-NO_2 and m-CH_3 substituted compounds were non-competitive reversible inhibitors to monoamine oxidase enzyme, which means that the combination of inhibitor with the examined enzyme will occur at some points on the surface of the enzyme essential for activity, but not at the main active center which is attached by the substrate (benzylamine) only.

Furthermore 3-ethoxycarbonyl-5-(5'-p-nitrophenyl-1',3',4'-oxadiazol-2'-yl)1,2-dimethyl-pyrrole was the better inhibitor of the examined compounds, (Table 7) probably due to its high electron attracting property.

However, 3-ethoxycarbonyl-5- (5'-p-bromophenyl, 1',3',4'-oxadiazol-2'-yl)1,2-dimetholpyrrole showed an uncompetitive inhibition to MAO which means that this compound attacked the enzyme-substrate complex. This result was also obtained by plotting 1/v against 1/s in presence and

absence of the examined compound as mentioned before, (Table 9).

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