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Reaction of 2,5-Disubstituted-1,3,4-oxadiazoles

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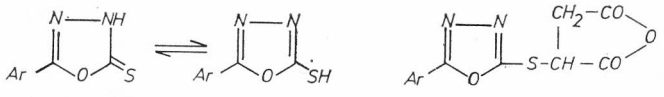
Some 5-aryl-2-mercapto-1,3,4-oxadiazole (*I*) reacted with maleic anhydride, maleic acid and *p*-benzoquinone affording 2-(5-aryl-1,3,4-oxadiazol-2-ylthio)succinic anhydrides (*II*), 2-(5-aryl-1,3,4-oxadiazol-2-ylthio)succinic acids (*III*) and 2-(2,5-dihydroxyphenylthio)-5-aryl-1,3,4-oxadiazoles (*IV*), respectively. Treatment of 2-methylthio-5-phenyl-1,3-oxadiazole (*V*) with amines gives 2-[(alkyl or aryl)-amino]-5-phenyl-1,3,4-oxadiazoles (*VI*). Compound *VIe* condensed with aromatic aldehydes to give 2-(4-cinnamoylanilino)-5-phenyl-1,3,4-oxadiazoles (*VII*) which on bromination afforded the dibromo derivative *VIII* and on treatment with hydroxylamine afforded 2-[4-(5-aryl-2-isoxazolin-3-yl)anilino]-5-phenyl-1,3,4-oxadiazoles (*IX*). Reacting *VII* with hydrazine hydrate gave 2-[4-(5-aryl-2-pyrazolin-3-yl)anilino]-5-phenyl-1,3,4-oxadiazoles (*X*), while on treatement *VII* with acetylacetone and ethylacetoacetate afforded 2-[4-(4-acetyl or carbethoxy-5-phenyl-1-cyclohexen-3-one-1-yl)anilino]-5-phenyl-1,3,4-oxadiazoles (*XIIa, b*), respectively.

INTRODUCTION

For some time we have been occupied with the chemistry of 1,3,4-oxadiazoles[1–4] owing to their prominent use as pharmacological agents and also as intermediates in the pharmaceutical industry.[5–10] In the present investigation the behaviour of certain 2,5-disubstituted-1,3,4-oxadiazoles towards a number of reagents has been studied. The biological activity screenings will be published elsewhere.

RESULTS AND DISCUSSION

5-Aryl-2-mercapto-1,3,4-oxadiazole (*I*)[1–3] reacted with maleic anhydride in anhydrous xylene at 140 °C to give 2-(5-aryl-1,3,4-oxadiazol-2-ylthio)succinic anhydrides (*IIa-c*).

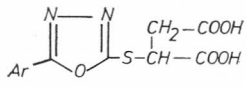


I *II*

I, II, a, Ar = C_6H_5; *b,* Ar = $C_6H_4CH_3$-(*p*-); *c,* Ar = C_6H_4Cl-(*p*-)

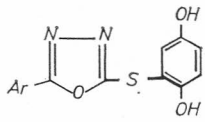
Compounds II were also obtained by the fusion of I with maleic anhydride at 120°. IIa and IIb could be hydrolysed to 2-(5-aryl-1,3,4-oxadiazol-2-ylthio)suc-

cinic acids (IIIa, b), respectively. Also IIIa and III b were obtained by the reaction of Ia and Ib with maleic acid in anhydrous xylene at 140°.



III

a, Ar = C_6H_5
b, Ar = $C_6H_4CH_3$-(*p*-)



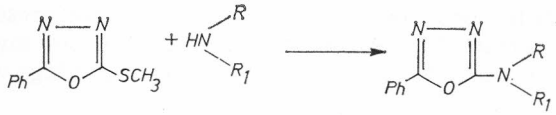
IV

a, Ar = C_6H_5
b, Ar = $C_6H_4CH_3$-(*p*-)

The structural proofs for *II* and *III* use spectroscopic data and elemental analyses. The IR spectrum of *IIa* showed a band at 1785 cm^{-1} for the C=O. Compound *IIIa* exhibited CO absorption bands at 1705 cm^{-1} and 3000 cm^{-1}. The ^1H NMR spectrum of *IIIa* showed the CH_2 protons (2H) as a doublet at 3.2 ppm, the CH proton (1H) as a triplet at 4.8 ppm, the aromatic protons as a multiplet at 7.5—8.1 ppm and the two OH protons as a singlet at 10.7 ppm. The MS of *IIIa* exhibited peaks at m/e 294 (M^+), 276 (M^+—H_2O), 249 (M^+—COOH) and 176 (M^+—succinic acid).

Compounds *Ia* and *Ib* reacted with *p*-benzoquinone in anhydrous xylene 140 °C to give 2-(2,5-dihydroxyphenylthio)-5-aryl-1,3,4-oxadiazoles, *IVa* and *IVb*, respectively. The structure of IV was supported by IR, ^1H NMR and MS and elemental analyses. In the IR spectrum of *IVa* the OH band appeared at 3315 cm^{-1}. Its ^1H NMR spectrum showed the two OH protons as a singlet at 10.7 ppm .The MS of *IVa* and *IVb* exhibited peaks at m/e 286 and 300 (M^+), respectively. M^+—OH and M^+—2OH were observed in both the spectra of *IVa* and *IVb*.

2-Methylthio-5-phenyl-1,3,4-oxadiazole (*V*) (prepared acording to known methods,[11,12] reacted with different amines giving 2-[(alkyl or aryl)amino]-5--phenyl-1,3,4-oxadiazoles (*VI*).[13]



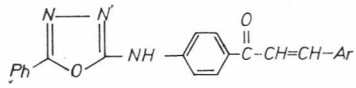
V *VI*

VI; *a*, R = H; $R_1 = C_2H_5$ *b*, R = H; $R_1 = C_6H_5$
c, $R = C_2H_5$; $R_1 = C_2H_5$ *d*, R = H; $R_1 = NHC_6H_5$
e, R = H; $R_1 = C_6H_4COCH_3$-(*p*-)

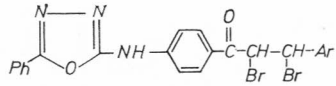
The structure of *VI* was confirmed by spectral data and elemental analyses. The IR spectrum of *VIa* showed the absorption bands of the NH at 3310 cm^{-1} and that for the C=N at 1645 cm^{-1}. In the IR spectrum of *VIe* the C=O group absorption appeared at 1675 cm^{-1} and the NH group at 3320 cm^{-1}. The MS of *VIa* and *VIe* showed molecular ion peaks at m/e 189 and 279, respectively. In MS of *VIa*, peaks at m/e 160 M^+—C_2H_5), 112 (M^+—C_6H_5) could be assigned. In MS of *VIe*, peaks at m/e 264 (M^+—CH_3), 236 (M^+—$COCH_3$), and 159 (M^+——$C_6H_5COCH_3$) were observed.

2-(4-Acetophenylamino)-5-phenyl-1,3,4-oxadiazole (*VIe*) condensed with some aromatic aldehydes in ethanolic potassium hydroxide to give 2-(4-cin-

namoylanilino)-5-phenyl-1,3,4-oxadiazoles (*VII*). Reaction of *VIIa* and *VIIb* with bromine in chloroform at 25 °C afforded 2-[4-(1,2-dibromocinnamoyl)anilino]-5-phenyl-1,3,4-oxadizaoles (*VIIIa, b*), respectively.



VII

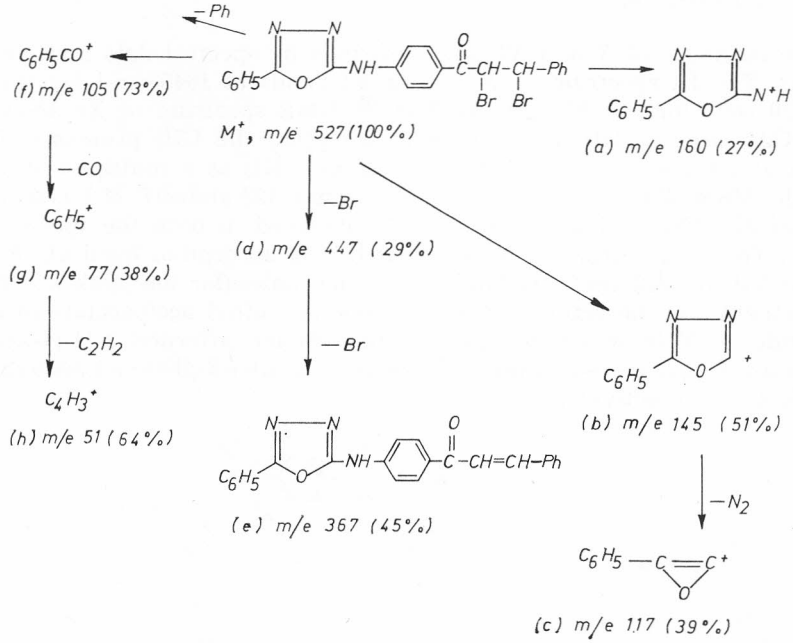


VIII

a, Ar = C_6H_5
b, Ar = C_6H_4OH-(*p*-)
c, Ar = C_6H_4Cl-(*p*-)
d, Ar = $C_6H_4NO_2$-(*p*-)
e, Ar = C_6H_4Br-(*p*-)

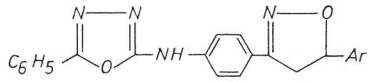
a, Ar = C_6H_5
b, Ar = C_6H_4Cl-(*p*-)

The IR spectra of *VIIa* and *VIIIa* showed the C=O absorption bands at 1650 cm^{-1} and 1660 cm^{-1} and the NH bands at 3200 cm^{-1} and 3300 cm^{-1}, respectively. The MS of *VIIa* showed the molecular ion peak (M^+) at m/e 367. The MS of *VIIIa* ($C_{23}H_{17}Br_2N_3O_2$) is additional evidence for the assigned structure. It reveals the presence of these peaks at m/e 527, m/e 529, and m/e 531, of relative abundance 1 : 2 : 1 characteristic of the presence of two bromine atoms. The fragmentation of M^+ 527 (100%) involves fission in the molecule and depicts ion (a) at m/e 160 (27%) and cleavage at the C—NH bond to furnish ion (*b*) at m/e 145 (51%) which looses N_2 to give ion (*c*) at m/e 117 (39%). Also, the fragmentation of the parent M^+ at m/e 527 involves debromination to furnish species (*d*) at m/e 447 (29%) and species (*e*) at m/e 367 (45%). In addition, ion (*f*) at m/e 105 (73%) could be assigned and suffers loss of CO to give ion (*g*) at m/e 77 (38%) which looses acetylene to give ion (*h*) at m/e 51 (64%) Another ion (*i*) (M^+—Ph) at m/e 450 (29%) was also observed (Scheme 1).



Scheme 1

Compounds *VIIa* and *VIIc* reacted with hydroxylamine to give 2-[4-(5--aryl-2-isoxazolin-3-yl)anilino]-5-phenyl-1,3,4-oxadiazoles (*IXa* and *IXb*), respectively.

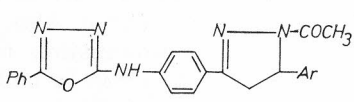


IX

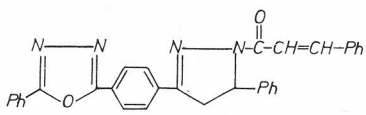
a, Ar = C_6H_5; *b*, Ar = C_6H_4Cl-(*p*-)

The ^1H NMR spectrum of *IXa* showed the CH proton (1H) of the oxazole ring as a triplet at 4.8 ppm, the CH_2 protons (2H) as a doublet at 3.7 ppm, the NH proton (1H) as a singlet at 4.4 ppm and the aromatic protons (13H) as a multiplet at 6.9—8.2 ppm. The MS of *IXa* showed peaks at m/e 382 (M^+), 305 (M^+—C_6H_5) and 277 (M^+—C_6H_5CO).

Compounds *VIIa, e, d* reacted with hydrazine hydrate in acetic acid to give 2-[4-(5-aryl-2-pyrazolin-3-yl)anilino]-5-phenyl-1,3,4-oxadiazoles (*Xa-c*).[13] Condensation of *Xa* with benzaldehyde in boiling ethanolic potassium hydroxide afforded 2-[4-(1-cinnamoyl-5-phenyl-2-pyrazolin-3-yl)anilino]-5-phenyl-1,3,4--oxadiazole (*XI*).



X

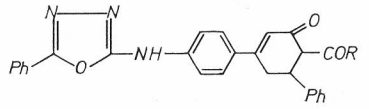


XI

Xa, Ar = C_6H_5; *Xb*, Ar = C_6H_4Cl-(*p*-)
Xc, Ar = $C_6H_4NO_2$-(*p*-)

The structure of *X* and *XI* was confirmed by spectral data and elemental analyses. The IR spectrum of *Xa* exhibited bands at 1645 cm^{-1} for the CON, and 3270 cm^{-1} for the NH groups. The ^1H NMR spectrum of *Xa* showed the NC*H*—C_6H_5 proton (1H) as a triplet at 2.9 ppm, the CH_2 protons (2H) as a doublet at 3.4 ppm and the aromatic protons (14H) as a multiplet at 7.1—8.2 ppm. The MS of *Xa* and *Xb* showed peaks at m/e 423 and 457 (M^+), respectively. Peaks at M^+—CH_3 and M^+—$COCH_3$ were observed in both the spectra of *Xa* and *Xb*. The IR spectrum of *XI* showed the CO absorption band at 1680 cm^{-1} and the NH at 3210 cm^{-1}. Its MS showed the molecular ion peak at 512 (M^+).

Furthermore, the action of acetylacetone and ethyl acetoacetate in sodium methoxide on *VIIa* was investigated. The reaction afforded 2-[4-(4-acetyl or carbethoxy-5-phenyl-1-cyclohexen-3-one-1-yl)]anilino-5-phenyl-1,3,4-oxadiazoles (*XIIa, b*)[13], respectively.



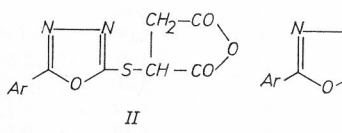
XII

a, R = CH_3
b, R = OC_2H_5
c, R = OH

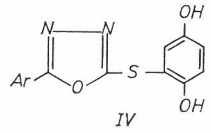
The structure of *XII* is inferred apart from IR, MS and elemental analyses from the hydrolysis of *XIIb* with sodium hydroxide yielding 2-[4-(4-carboxyl-5-phenyl-1-cyclohexen-3-one-1-yl)anilino]-5-phenyl-1,3,4-oxadiazole (*XIIc*). The IR spectra of *XIIa* and *XIIb* showed absorption bands at 1655 and 1650 cm^{-1} (CO), at 1675 cm^{-1} ($COCH_3$) and 1770 cm^{-1} ($COOC_2H_5$), and the NH band at 3290 cm^{-1} and 3280 cm^{-1}, respectively. The MS of *XIIb* exhibited peaks at m/e 466 (M^+), 421 (M^+—OC_2H_5), 393 (M^+—$COOC_2H_5$) and 361 (M^+—C_6H_5CO). The IR spectrum of *XIIc* showed the absorption bands of the C=O at 1655 cm^{-1} and the COOH at 1710 cm^{-1} and 3000 cm^{-1}.

TABLE I

Experimental and Analytical Data of the Products II—XII



II



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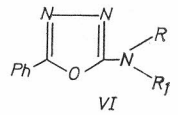
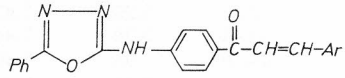
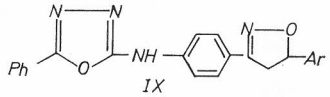


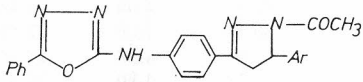
VI



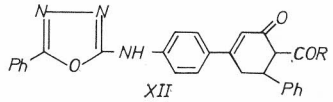
VII



IX



X



XII

Product	M. p. (°C)	Solvent*	Yield (%)	Analyses Calcd./Found (%)			
				C	H	N	S
IIa	161	E	72	52.17 52.00	2.90 3.11	10.14 10.21	11.59 11.78
IIb	154	E	69	53.79 53.68	3.45 3.41	9.66 9.50	11.03 10.89
IIc	141	M	75	46.45 46.40	2.26 2.21	9.03 8.91	10.32 10.21
IIIa	130	P	72	48.98 49.30	3.40 3.31	9.52 8.99	10.88 10.75
IIIb	124	P	67	50.65 50.50	3.89 3.81	9.09 8.89	10.39 10.82
IVa	143	E	66	58.74 58.83	3.50 3.41	9.79 9.64	11.19 11.03
IVb	167	M	70	60.00 60.21	4.00 3.91	9.33 9.25	10.66 10.49
VIa	71	D	78	63.49 63.37	5.82 5.81	22.22 22.00	— —
VIb	153	D	81	70.88 71.00	4.64 4.41	17.72 17.53	— —

Product	M. p. (°C)	Solvent*	Yield (%)	Analyses Calcd./Found (%)			
				C	H	N	S
VIc	103	E	74	66.35	6.91	19.35	—
				66.18	6.84	19.24	—
VId	173	M	83	66.66	4.76	22.22	—
				66.44	4.70	22.04	—
VIe	195	D	71	68.81	4.66	15.05	—
				69.00	4.49	15.00	—
VIIa	201	D	57	75.20	4.63	11.44	—
				75.13	4.70	11.25	—
VIIb	209	M	63	72.06	4.43	10.97	—
				72.19	4.32	10.85	—
VIIc	198	E	69	68.82	3.99	10.47	8.72
				68.65	4.00	10.39	8.68
VIId	220	E	80	66.99	3.88	13.59	—
				67.14	3.80	13.65	—
VIIe	233	P	78	61.88	3.59	9.41	17.93
				61.80	3.39	9.24	17.58
VIIIa	179	E	64	52.37	3.23	7.97	30.36
				52.44	3.20	7.84	30.71
VIIIb	192	B	59	49.19	2.85	7.49	28.52
				49.15	2.81	7.39	28.90
IXa	164	E	57	72.25	4.71	14.66	—
				72.11	4.53	14.48	—
IXb	178	E	61	66.35	4.09	13.46	8.52
				66.10	4.00	13.29	8.39
Xa	210	M	64	70.92	4.96	16.55	—
				71.14	4.90	16.39	—
Xb	217	E	63	65.65	4.38	15.32	7.66
				65.50	4.21	15.11	7.31
Xc	250	M	59	64.10	4.27	17.95	—
				64.21	4.18	18.12	—
XI	293	P	73	72.66	4.30	13.67	—
				72.71	4.21	13.52	—
XIIIa	210	P	75	74.83	5.12	9.35	—
				74.70	5.00	9.21	—
XIIb	161	M	80	72.65	5.22	8.77	—
				72.50	5.09	8.68	—
XIIc	204	M	91	71.84	4.66	9.31	—
				71.92	4.51	9.54	—

* B = Benzene; D = Dioxane; E = Ethanol; M = Methanol; P = Petroleum ether (60—80 °C).

EXPERIMENTAL*

IR (KBr) spectra were recorded using a Unicam S. P. 1200 spectrophotometer. ^{1}H NMR ($CDCl_3$) spectra were recorded at 60 MHZ on a Varian EM-560 spectrometer using TMS as the internal reference standard. Chemical shifts are expressed as δ values. MS were recorded on a Micromass 7070F mass spectrometer operating at 70 eV using a direct inlet. Elementary analyses were carried out by the Microanalytical Laboratory of the NRC, Cairo, A.R.E. All melting points are uncorrected.

Starting materials: The starting compounds were prepared by known methods. *Ia-Ic*,[1-3,14,15] *V*[11,12]

* The new compounds are under preliminary biological investigation at present.

Action of Maleic Anhydride on Ia-c

Method a: Compounds *I* (0.01 mol) in 10 ml anhydrous xylene and maleic anhydride (0.01 mol) were refluxed for 5 hrs. The mixture was evaporated to dryness to yield the solid *IIa-c.*

Method b: Compounds I (0.01 mol) and maleic anhydride (0.015 mol) were fused for 2 hrs at 120 °C under N_2. The fused mass after cooling was extracted with benzene, the solvent was evaporated to dryness and the residual solid was recristallised to give *IIa-c.*

Preparation of 2-(5-Aryl-1,3,4-oxadiazolyl-2-ylthio)succinic Acids (IIIa, b)

Method a: Compounds *I* (0.01 mol) in 10 ml anhydrous xylene and maleic acid (0.01 mol) were refluxed for 5 hrs. The mixture was evaporated to dryness to yield the solids *IIIa, b.*

Method b: Hydrolysis of IIa and IIb. A suspension of *IIa, b* (1 g) in 20 ml of water was refluxed for 3 hrs. The precipitate was filtered off and crystallised to give *IIIa, b.*

Action of p-Benzoquinone on Ia and Ib

Compounds *I* (0.01 mol) in 10 ml anhydrous xylene and p-benzoquinone (0.01 mol) were refluxed for 9 hrs. The solevnt was distilled under reduced pressure and the residual solid was crystallised to give *IV.*

Action of Amines on V

A mixture of *V* (0.01 mol) and the appropriate amine (0.01 mol) in 20 ml ethanol was refluxed for 3 hrs. The solvent was evaporated to dryness and the residual solid was crystallised to give *VIa-d.* Compound *VIe* was prepared by heating a mixture of *V* (0.01 mol) with *p*-aminoacetophenone (0.01 mol) at 170 °C for 1 hr. The reaction product was cooled to room temperature and crystallised to give *VIe.*

Action of Aldehydes on VIe

The aromatic aldehyde (0.012 mol) was added dropwise to a solution of *VIe* (0.01 mol) in 20 ml ethanolic potassium hydroxide (5%). The mixture was refluxed for 4 hrs and then concentrated and cooled. The solid that separated was filtered off and crystallised to give *VII.*

Bromination of VIIa and VIIb

Bromine (0.01 mol) was added dropwise with stirring to a solution of each of *VIIa* and *VIIb* (0.01 mol) in 20 ml chloroform at 25 °C for 1 hr. The mixture was left overnight, concentrated and filtered off to give *VIIIa, b.*

Action of hydroxylamine on VIIa and VIIb

A mixture of *VIIa, b* (0.01 mol), hydroxylamine hydrochloride (0.01 mol) and sodium hydroxide (0.1 g) in 20 ml ethanol was refluxed for 3 hrs. The mixture was poured into cold water and the solid formed was collected and crystallised to give *IXa, b.*

Action of Hydrazine Hydrate on VIIa, c, d

Compounds *VII* (0.01 mol) in 10 ml acetic acid and hydrazine hydrate (0.5 g, 98%, 0.01 mol) were refluxed for 4 hrs, cooled and then poured into water. The solid formed was crystallised and identified as *Xa-c.*

Action of Benzaldehyde on Xa

Benzaldehyde (0.012 mol) was added dropwise to a solution of *Xa* (0.01 mol) in 10 ml ethanolic potassium hydroxide (5%). The mixture was refluxed for 5 hrs, then concentrated and cooled. The residual solid was crystallised to give *XI.*

Action of Acetilacetone and Ethyl Acetoacetate on VIIa

Compound *VIIa* (0.01 mol) in sodium methoxide (prepared from 0.5 g sodium metal in 10 ml methanol) and acetylacetone or ethyl acetoacetate (0.01 mol) were refluxed for 6 hrs. The mixture was cooled and poured into water. The residual solid was crystallised to give *XIIa, b* respectively.

Hydrolysis of XIIb

Compound *XIIb* (0.01 mol) was refluxed in methanolic sodium hydroxide (20 ml, 7%) for 3 hrs. On acidification a solid was precipitated and identified as *XIIc*.

REFERENCES

1. A. A. El-Barbary, M. Anwar, A. A. Ghattas, and A. F. Hashem, *Rev. Roum. Chim.* **26** (1981) 449.
2. M. Anwar, A. A. El-Barbary, A. A. Ghattas, and A. F. Hashem, *Polish J. Chem.* **55** (1981) 599.
3. A. A. El-Barbary and H. Hammouda, *Arch. Pharm.* **317** (1984) 547.
4. A. A. El-Barbary and M. El-Borai, *Polish J. Chem.* In Press.
5. J. J. Goodman, M. Matrishim, R. W. Young, and J. R. McCormick, *J. Bacteriol.* **78** (1959) 492.
6. A. E. Wilder-Smith, *Hungarian Patent* 159,568 (1963), *C. A.* **61** (1964) 3118.
7. T. R. Vakula and V. R. Srinivasan, *Ind. J. Chem.* **7** (1969) 583.
8. A. A. Abou Ouf, M. M. El-Kerdawy, A. M. Farghaly, and L. M. Gad, *Egypt. J. Pharm. Sci.* **21** (1980) 189.
9. B. Abd El-Fattah, *Egypt. J. Pharm. Sci.* **22** (1981) 193.
10. O. M. El-Badry and B. Abd El-Fattah, *Egypt. J. Pharm. Sci.* **22** (1981) 199.
11. J. H. Boyer, in *Heterocyclic Compounds* (R. C. Elderfield, ed.), Vol. **7**, Wiley, New York, p. 525 (1961); L. G. Behr, in *Five and Six-membered Compounds with Nitrogen and Oxygen*, Vol. **17** of *The chemistry of Heterocyclic Compounds*, (R. H. Wiley, ed.), (Interscience) (1962) p. 268.
12. M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Japan* **33** (1960) 1394.
13. N. M. Yousif, Doctoral Thesis, University of Cairo (1981).
14. E. Hoggarth, *J. Chem. Soc.* (1952) 4811.
15. R. W. Young and K. H. Wood, *J. Amer. Chem. Soc.* **77** (1955) 4400.

SAŽETAK

Reakcija 2,5-disupstituiranih-1,3,4-oksadizola

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Reakcijom 5-aril-2-merkapto-1,3,4-oksadiazola (*I*) s anhidridom maleinske kiseline, maleinskom kiselinom i *p*-benzokinonom pripravljeni su 2-(5-aril-1,3,4-oksadiazol-2-iltio) sukcinanhidridi (*II*), kiseline (*III*) kao i 2-(2,5-dihidroksifeniltio)-5-aril-1,3,4-oksadiazoli (*IV*). Reakcijom 2-metiltio-5-fenil-1,3,4-oksadiazola (*V*) s aminima dobiveni su 2-[(alkil i aril)-amino]-5-fenil-1,3,4-oksadiazoli. Kondenzacija s aromatskim aldehidima *VIe* daje 2-(4-cinamoilanilino)-5-fenil-1,3,4-oksadiazole (*VII*) koji bromiranjem prelaze u dibromderivate *VIII* i zatim s hidroksilaminom u 2-[4-(5-aril-2-izoksazolin-3-il)anilino]-5-fenil-1,3,4-oksadiazole (*IX*). Reakcijom *VII* s hidrazin-hidratom dobiven je 2-[4-(5-aril-2-pirazolin-3-il)anilino]-5-fenil-1,3,4-oksadiazoli (*X*) dok reakcijom s acetilacetonom i etilacetatom *VII* daje 2-[4-(4-acetil ili karbetoksi-5-fenil-1-cikloheksen-3-on-1-il)anilino]-5-fenil-1,3,4-oksadiazole.