SYNTHESIS OF INDOLE DERIVATIVES AS POTENTIAL BIODYNAMIC AGENTS: PART II: 1,5-DISUBSTITUTED 3-(5-ARYL-1,3,4-OXADIAZOLYL-2-) IMINOINDOLIN-2-ONES AS POSSIBLE ANTIBACTERIAL AND CNS ACTIVE AGENTS

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ABSTRACT

A series 1,5-disubstituted -(5-aryl-1,3,4- oxadiazolyl-2) iminoindolin-2-ones (**3a-r**) have been synthesised and evaluated for their antibacterial action against *E. subtilis*, *X. citri*, *X. oryzae*, *X. malvacearum*, and CNS activities.

INTRODUCTION

SEVERAL isatin analogues have been reported to possess antibacterial[1,2], cysticidal[3], hypotensive[4] and CNS[5-7] activities. Further, many oxadiazole derivatives have also been found to exhibit antibacterial[8], antiinflammatory[9] and CNS activities[10]. These observations led us to the synthesis of some new 1,5-disubstituted-3-(5-aryl-1,3,4-oxadiazol-2-yl) imino indolin-2-one (**3 a-r**), in order to test their antibacterial and CNS activities. The results are reported in this communication.

1,5-Disubstituted-3-(5-aryl-1,3,4-oxadiazol-2-yl) imino indolin-2-ones(**3 a-r**) were obtained by treating the appropriate isatins (**1 a-f**)[11-13] with 2-amino-5-aryl-1,3,4-oxadiazoles[14] in absolute ethanol containing a few drops of gl. acetic acid. All these compounds were characterised by their elemental analysis and IR spectral data. 1-Methyl-3-(5 phenyl-1, 3,4-oxadiazol-2-yl)-imino indolin-2-one (**3d**) was prepared alternatively by the treatment of 3-(5-phenyl oxadiazol-2-yl) imino indolin-2-one (**3 a**) with dimethylsulphate, in methanol.

TABLE 1

1,5-Disubstituted-3-(5-Aryl-1,3,4-oxadiazol-2-yl) imino-indolin-2-ones (3) *and their antibacterial activities*

Compound No.	R	R^1	R^2	Yield (%)	M.P.°C	Mean area of inhibition after 24 hr. *E. coli*	*B. subtilis*	*X. citri*	*X. oryzae*	*X. malvacearum*
3a	H	H	H	85	198	+	+	+ +	+	+ +
3b	H	H	o-Cl	75	246		a			
3c	H	H	p-Cl	80	182	+ +	+	+ +	+	+ +
3d	H	CH_3	H	70	202	—	—	+	+	—
3e	H	CH_3	o-Cl	60	225		a			
3f	H	CH_3	p-Cl	80	232	+	+	+ +	+	+
3g	Cl	H	H	78	235d	+	+ +	+	+	+ +
3h	Cl	H	o-Cl	54	188		a			
3i	Cl	H	p-Cl	66	220	+ +	+ + +	+	+	+ +
3j	Cl	CH_3	H	75	180d		a			
3k	Cl	CH_3	o-Cl	62	223-4	—		—	+ +	+
3l	Cl	CH_3	p-Cl	80	205d		a			
3m	CH_3	H	H	70	164-5	—	+	+	—	+ +
3n	CH_3	H	o-Cl	67	190-1	+ +	+ + +	+ +	+	+
3o	CH_3	H	p-Cl	61	180		1			
3p	CH_3CH_3		H	81	217-8	+ + +	+	—	+ +	+
3q	CH_3CH_3		o-Cl	86	210		a			
3r	CH_3CH_3		p-Cl	76	171	+ +	+	+ + +	—	+

Micro analytical values for C, H and N are within ± 0.4% of the calculated values.

Inhibition zone (—) = no inhibition, (+) = zone size 6-8 mm; (+ +) = zone size 8-10 mm, (+ + +) = zone size > 10 mm. *a* indicates not done.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. I.R. spectra were taken on Perkin Elmer-137 spectrophotometer in KBr and ν_{max} have been were recorded in cm^{-1}. TLC was performed on this silica gel layers and spots were visualised by exposing the dried plates to I_2 vapours.

1,5-Disubstituted-3-(5-aryl-1,3,4-oxadiazol-2-yl) imino indolin-2-ones (3 **a-r**)

In a typical reaction, to a solution of **2** (0.01 mol) in ethanol (30 ml) was added an ethanolic soln of **1** (0.01 mol) and the resulting mixture was refluxed after adding one drop of gl. acetic acid for about 6–8 hr. The separated solid was filtered, washed with cold ethanol and recrystallised from the same solvent (table 1). IR-(**3 a-r**) 3050, (aromatic C-H), ~ 1730 (cyclic N-C = O), 1630 (C = N). Additional peaks at ~ 3250 and ~ 1560 (for N-H stretch and bending, respectively) were observed in **3 a-c, g-i** and **m-o** and at ~2900 (for C-H stretch aliphatic) in **3 d-f, j-l & p-r.**

1-Methyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl) imino indolin-2-one (**3 d**) (By methylation of **3 a**)

To a suspension of **3 a** (0.10 mol) in ethanol (30 ml), ethanolic KOH (10 ml; 10%) was added portionwise during 20 min. with shaking. To this dark purple suspension, dimethyl sulphate (0.02 mol) was added and the mixture was then filtered and ethanol was removed from the filtrate by distillation *in vacuo*. The residue was treated with hot water. The mixture heated to give a clear solution. On cooling crystals of **3 d** separated, m.p. 202–4° (mixed m.p. 200–4° C).

BIOLOGICAL ACTIVITY

Antibacterial activity

The method of agar diffusion[15] technique was employed for determining antibacterial spectra of all the compounds. The test organisms included *E. coli, B. subtilis, X. citri, X. oryzae* and *X. malvacearum.* Most of the compounds showed good activity against all the five microorganisms. Compound no. **3 p** appears to produce maximum inhibitory zone (> 10 mm) against *E. coli* whereas compound nos. **3 i & n** produced maximum inhibitory zones (> 10 mm) against *B. subtilis* and compound **3 r** produced the same effect against *X. citri.* The antibacterial activities of other compounds are given in table 1.

Acute toxicity test

The approximate lethal dose, in 50% of tested animals ($AlD_{\bar{50}}$) was determined by the method of Wiel[16]. The compounds given intraperitoneally to albino mice of either sex and by the mortality rate after 24 hr of drug administration, at different doses, the ALD_{50} values were calculated. The compounds are non toxic and the ALD_{50} value are quite high.

Gross CNS activities

The compounds were given intraperitoneally to a group of four mice, weighing between 20–25 g, at the dose levels were of 464, 1000, 215 mg/kg. At these doses, the behavioural changes in gross CNS effects were noted *i.e.* effects on SMA and reactivity of animal to sound and touch, rate of breathing, righting reflexes, posture and on related behaviours. At 1/5 of $ALD_{\bar{50}}$, apart from the gross CNS observations, MES protection[17] Rota-rod test[18] anti-reserpine activity and the effect on body temperature were also observed. Anti-reserpine activity, was done by the known method.

The results of pharmacological observations are noted in table 2.

Monoamine oxidase inhibitory activity

MAO inhibitory activity (compound nos. **3 a,c,f** and **1**) was determined *in vitro* on isolated brain homogenate of Albino rat at the concentration at 1×10^{-3} M of the respective compounds. The method of Tabor *et al* was followed[20].

All the test compounds were found to produce strong CNS depressant properties and muscle relaxant effects as they relaxed body and limbs. Compound no. **3 f** produced the strongest CNS depressant effects. It strongly decreased the SMA and reactivity and the rate of breathing. It also induced the loss of righting reflexes for 5′ to > 3 hr in mice. Further, it showed 30% activity in antireserpine test and 80% activity in Rota-rod test. Other two potent compounds of the series were **3 a** and **3 c**. Compound no. **3 a** exhibited 30% protection of MES, while **3 c** induced catalepsy for 30 minutes and showed 40% activity in MES protection test.

Four compounds of this series (compounds nos. **3 a, c,f** & **1**), found to be stronger CNS depressants, were investigated for their MAO inhibition to ascertain their effects on this adrenergic enzyme. All of these compounds were found to be strong MAO inhibitors at the concentration of 1×10^{-3} M. This shows that the compounds were proadrenergic and could increase the concentration of adrenergic neurotransmitters in the CNS.

The effects of substituents on the basic nucleus of the title compounds do not seem to be very clear but visualising table 2, it is clear that the *p*-Cl substitution on phenyl ring at position-5 of 1,3,4-oxadiazole ring induced relatively strong CNS depressant properties in the compounds.

TABLE 2

Central nervous system activity of the 1,5'disubstituted-3-(5-aryl-1,3,4-oxadiazol-2yl) imino indolin-2-ones(3)

Compd. No.	SMA & Reactivity	Respiration	Loss of RR	Body & limbs	Other effects	ALD^{50}	SMA	Antireserpine	MES Protection	Rota Rod test	Body Temp. (°C)	% MAO inhibition at 10^{-3} M cm of compounds
3a	↓↓	↓	(+)	(R)	i.p.t. (+)	681	↓	—	30	—	1.4 ↓	65.35 ± 0.7
3b	↓↓	↓	(—)	(R)	Cat (+) 30°	1000	↓	—	40	—	0.1 ↓	74 51 ± 0.5
3d	↓↓	↓↓	(+)	(R)		261	↓	—	—	—	1.7 ↓	
3f	↓↓	↓↓	(5′ > 3 hr) (5′ - > 3 hr)	(R)	—	681	↓	30%	—	80	1.2 ↓	68.25 ± 0.2
3g	↓↓	↓↓	(+) (5′ - > 3 hr)	(R)	—	562	↓	—	—	—	1.5 ↓	
3i	↓↓5′	↓5′	(—)	(R)	Ataxia (5′)	1000	↓	—	—	—	2 ↓	
3j	↓↓5′	↓5′	(+) (10′ - 1 hr)	(R)	—	1000	↓	—	—	—	1.6 ↓	
3l	↓↓5′	↓5′	( ) (7′ - 1 hr)	(R)	—	> 1000	↓	—	—	—	—	85.15 ± 0.9
3m	↓↓5′	↓5′	(+) (5′ 1 hr)	(R)	—	178	↓	—	—	—	1.8 ↓	
3o	↓↓5′	↓5′	—	(R)	—	> 1000	↓	—	—	—	1 ↓	
3p	↓↓	↓	(+) (30′ - 90′)	(R)		681	↓	—	—	—	3.2 ↓	
3r	↓↓	↓	—	(R)	—	681	↓	—	—	—	0.2 ↓	

* The second dose was 215 mg/kg ip instead of 1000 mg/kg ip the third dose (100 mg/kg ip) was also used for these compounds (↓) = decreased, (—) = nil, R = Relaxed, i.p.t. = inclined plane test, Cat. = Catalepsy.

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FROM THE JOSHI EFFECT TO OPTO-GALVANIC SPECTROSCOPY*

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SPECTROSCOPISTS have used the discharge tube of various designs to obtain the spectrum of gases and vapours from the earliest times. They were, however, not interested in the small potential/current changes accompanying spectral transitions in the gas under discharge. Other physicists were interested in measuring just these potential and/or current changes occurring in the discharge when exposed to external radiation. They did not study the spectral transitions induced by external radiation[1-9].

The Penning effect refers to an increase in the threshold potential of argon-neon mixtures when irradiated by neon light. This has been elegantly explained as due to the destruction by neon light of the neon metastables initiating secondary ionization by collision[8,10]. Neon has an important excited *metastable* state, Ne^{*m} ($^3P_2$ or $1s_5$)†, of energy 16.62 eV and of radiative lifetime to ground state of the order of seconds. This species plays an important role in secondary ionization by collision, as:

$$Ne^{*m} + Ar \rightarrow Ne + Ar^+ + e^-$$

$^3P_2$ (16.62 eV) $^1S_0$ (0 eV) (15.8 eV)

Similarly with atoms of the cathode material, *M*,

$$Ne^{*m} + M \rightarrow Ne + M^+$$

However, when irradiated with intense light from *another neon discharge* column, the high energy metastable species get depopulated[8,10]

$$Ne^{*m} + h\nu \rightarrow Ne^{**}$$

$^1S_5$ (16.62 eV) (neon discharge) 2p 10...1 (18.38...18.97 eV)

$$Ne^{**} \rightarrow Ne + \text{energy}$$

$^1S_0$ (0 eV) (diversely lost)

This inhibits the collisional ionization processes and hence the threshold for the Ne + Ar mixture under irradiation by neon light (V_L) rises above the value in dark (V_D), *i.e.*, $V_L > V_D$, which is the Penning effect[8,10].

The Joshi effect, on the other hand, is a more widely occurrent phenomenon where the current in a gas, under discharge, under constant applied potential, is suppressed under certain conditions on irradiation by external light of all frequencies, from x-rays to red light, the difference Δi ($= i_{light} - i_{dark}$) being the *Joshi effect*. The relative Joshi effect $\Delta i/i_D$ has been found to be as close as 100% in some cases. The current suppression is almost instantaneous, reversible and apparently independent of the nature of the gas[9,11-14]. The Joshi effect was discovered in 1939.

† *LS* coupling and Paschen notation

* Summary of the talk given before the Fire Research Section of the National Bureau of Standards, Washington, D.C., on 1st September 1981.