SYNTHESIS AND CNS ACTIVITY OF SOME 2-ARYL/ALKYL-3-[-N-PHENYL, N-(DIHYDROXY PHENYL-METHYL)-AMINO]-6,8-DISUBSTITUTED-QUINAZOLIN-4(3H)-ONES

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ABSTRACT

Eight 2-aryl,alkyl-3-(N-phenyl amino)-6,8-disubstituted-quinazolinones(I) have been synthesised by the condensation of phenyl hydrazine with the corresponding benzoxazinones. The Mannich type reaction of the aforesaid (I) with catechol and resorcinol, utilizing their active hydrogen at position-4- and -3 respectively, gave sixteen new title compounds (II). The structures of these compounds have been confirmed by the elemental analysis and the IR spectra. The compounds are non-toxic and CNS depressants. Two compounds have induced the writhing also.

QUINAZOLIN-4(3H)-ONES have been reported to possess the Central Nervous System (CNS) depressant[1–3], anticonvulsant[4] and muscle relaxant properties[5]. Catecholamines and other catechol derivatives are also known to be active against Parkinsonism[6–8]. Catechol and resorcinol have been found to be good decarboxylase inhibitors by Werle and Koch[9]. Catecholamines have been identified as one of the adrenergic chemical neurotransmitters, the key substances related to nervous system[10]. Lastly, hydrazines and hydrazides have variously been described CNS active, mono amine-oxidase and decarboxylase inhibitors[11,12] etc. Many hydrazides of catechol derivatives have been ascertained to be the best medicines[13,14] for the diseases of the extra-pyramidal system of the brain[3] due to their combination of dopaminergic and MAO and decarboxylase inhibitor activities.

The authors synthesised a few quinazolonyl hydrazides(I) by the reaction of cyclic ester grouping in benzoxazinone with phenyl hydrazine. The Mannich type condensation of these compounds with catechol and resorcinol, utilizing their active hydrogens at positions 4 and 3 respectively, gave the title compounds (II). This paper describes the synthesis of these compounds and the action of some of them on the CNS.

5-Bromo and 3,5-dibromo anthranilic acids were prepared by the method of Wheeler and Oats[15]. *5-Iodo anthranilic acid* was prepared using the method of Klemme and Hunter[16].

2-Phenyl-6,8-disubstituted-benzoxazinones have been synthesised as per the method of Tiwari and Pandey[17], while *2-methyl-6,8-disubstituted benzoxazinones* have been synthesised as per the method of Bogert and Seil[18].

2-Phenyl-3-phenylamino-quinazolin 4(3H)-one(I) was synthesised by refluxing 2-phenyl benzoxazinone (0·01 mole) and phenyl hydrazine (0·015 mole) in pyridine (20 ml) on a sand bath for 5–6 h with occasional shaking. The reaction mixture was cooled at room temperature and poured into an ice/water mixture (2 : 1, W/V; 300 g) and left overnight. The solid separated was filtered and recrystallised with alcohol. Yield = 60%; m.p. = 158-59° C. For $C_{20}H_{15}N_3O$; N = 13·49% (13·41%), C = 76·21% (76·67%), H = 4·67%, (4·73%); IR(KBr) = 3240 cm^{-1}, 1670 cm^{-1}, etc.

Similarly others (I) were also synthesised. Their relevant data are given in Table I.

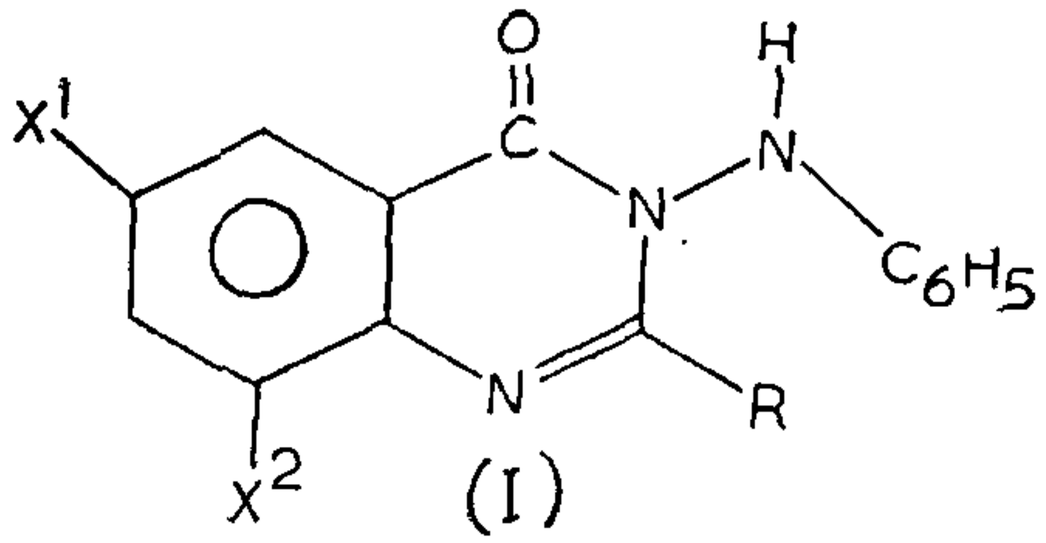
2-Phenyl-3-[-N-phenyl, N(3′, 4′-dihydroxyphenyl-methyl)-amino]-6,8-disubstituted-quinazolin-4(3H)-ones(II) —2-Phenyl-3-phenylamino-quinazolin-4(3H)-one (0·01 mole) and catechol (0·015 mole) were taken in alcohol (50 ml) in a flask and formaldehyde (1 ml) was added to it and refluxed for about 4–5 h, cooled overnight. It was poured into cold water to get the precipitate of the final product, recrystallised twice with ethanol/water. Yield = 50%, m.p. = 196–97° C. For $C_{27}H_{22}N_3O_3$; N = 9·23% (9·63%); C = 73·82% (74·31%); H = 5·12% (5·04%). IR(KBr) = 3470 cm^{-1}, 1600 cm^{-1}, 1320 cm^{-1}, etc.

Others (II) were also synthesised similarly, using appropriate (I) and dihydroxy phenol. Their relevant data are given in Table II.

In the scarcity of solvent in reaction mixture, the catechol and resorcinol gave a polymer instead of the required products (II). This was in accordance with the reported property of these phenols with formaldehyde[19]. Thus, in order to avoid the polymer formation, the medium (alcohol) was taken in excess (about 50 ml for 2 g of reactants) and the reaction flask was shaken occasionally.

TABLE I

*2-Aryl/alkyl-3-phenylamino-quinazolin-4(3H)-ones**



(I)

Compound Nos.	X^1	X^2	m.p. °C**	Yield %	Important IR peaks (cm^{-1})
			$R=CH_3$		
1.	H	H	165	60	710, 760, 1370, 1450, 1570, 1600, 1680, 2950, 3020, 3260
2.	H	Br	135	62	575, 700, 780, 1375, 1455, 1565, 1600, 1675, 2945, 3030, 3275
3.	Br	Br	169–170	66	570, 710, 750, 870, 1370, 1450, 1575, 1600, 1670, 2940, 3030, 3300
4.	H	I	160–161	58	500, 700, 770, 1380, 1460, 1570, 1600, 1670, 2950, 3280
			$R = C_6H_5$		
5.	H	H	158–159	70	700, 750, 1370, 1460, 1575, 1590, 1670, 3050, 3240
6.	H	Br	176–178	63	575, 700, 770, 1375, 1450, 1560, 1600, 1670, 3030, 3260
7.	Br	Br	180–181	67	575, 710, 760, 875, 1375, 1460, 1570, 1600, 1675, 3050 3270
8.	H	I	170–172	60	510, 710, 760, 1375, 1450, 1570, 1600, 1680, 3050, 3300

* All the compounds gave correct analysis for 'C', 'H' and 'N'.

** m.p. were taken in open capillaries and are uncorrected.

Pharmacology—Six of the compounds were screened for their action on the central nervous system and for their toxicity test.

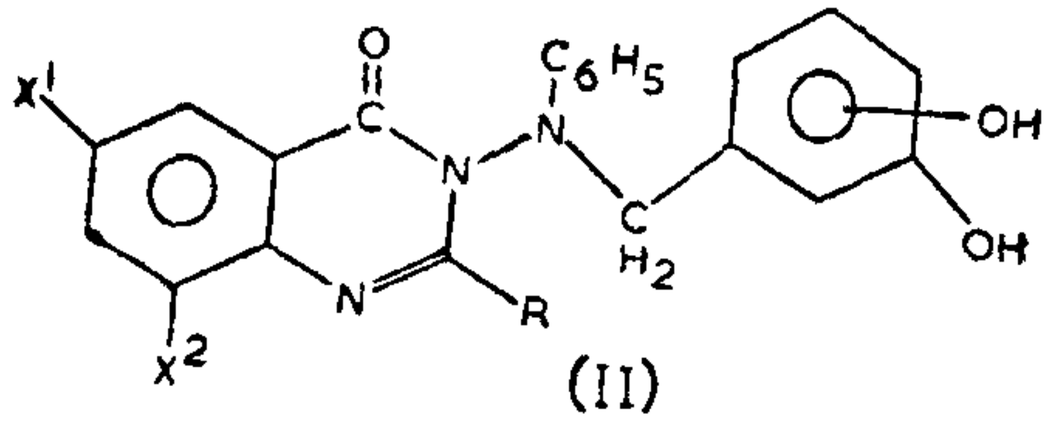
For toxicity test, the compounds were administered intraperitoneally to albino mice of either sex in different doses and the approximate lethal doses in 50% of the animals tested (ALD_{50}), were determined by the method of Weil[20]. The ALD_{50} are noted in Table III.

For their action on the central nervous system (CNS) the compounds were administered to albino mice at 1/5 of ALD_{50} and their behavioural changes in spontaneous motor activity and reactivity to sound and touch, were noted. To substantiate these observations on the SMA and reactivity, mobility counts were taken in the actophotometer, equipped with photocells. Decrease in mobility counts, as against that of controlled mice, marked the depression on the central nervous system. Compounds 9 and 16 induced writhing (twisting of belly) also. All the compounds tested decreased the body temperature by 0·4–1·1° C (hypothermia). The pharmacological data are given in Table III.

Thanks are due to Dr. B. N. Dhawan, Head of the Pharmacology Department, C.D.R.I., Lucknow, for the pharmacological tests. The authors are also grateful to CSIR, New Delhi, for the award of S.R.F. to one of them (R. K. S.).

TABLE II

*2-Aryl/alkyl-3-[N-phenyl, N-(dihydroxyphenyl methyl)-amino]-6,8-disubstituted quinazolin-4 (3H)-ones**



(II)

Compound Nos.	X^1	X^2	R	m.p. °C**	Important IR peaks (cm^{-1})
			Positions of –OH groups = 3,4-dihydroxy-		
9.	H	H	CH_3	170–172	710, 760, 800, 840, 1320, 1370, 1450, 1600, 1680, 2950, 3020, 3475
10.	H	Br	CH_3	158–160	580, 700, 760, 800, 830, 1325, 1375, 1455, 1610, 1675, 2940, 3030, 3475
11.	Br	Br	CH_3	187-188	575, 700, 750, 800, 840, 1320, 1370, 1450, 1600, 1685, 2940, 3030, 3475
12.	H	I	CH_3	165	500, 700, 770, 800, 840, 1330, 1380, 1460, 1600, 1680, 2950, 3050, 3480
13.	H	H	$-C_6H_5$	196–197	710, 760, 800, 830, 1330, 1370, 1450, 1590, 1680, 3050, 3475
14.	H	Br	$-C_6H_5$	202–204	570, 710, 760, 800, 840, 1330, 1375, 1450, 1600, 1675, 3050, 3475
15.	Br	Br	$-C_6H_5$	200–201	575, 710, 750, 800, 850, 1320, 1375, 1450, 1610, 1680, 3050, 3475
16.	H	I	$-C_6H_5$	162–163	510, 710, 760, 800, 850, 1320, 1375, 1450, 1600, 1680, 3050, 3475
			Position of –OH groups = 2,4 dihydroxy		
17.	H	H	CH_3	169-170	710, 760, 800, 840, 1320, 1370, 1450, 1600, 1680, 2950, 3030, 3550
18.	H	Br	CH_3	264–265	580, 700, 760, 800, 840, 1320, 1375, 1460, 1600, 1680, 2940, 3050, 3550
19.	Br	Br	CH_3	198–200	580, 710, 750, 810, 850, 1330, 1380, 1450, 1610, 1685, 2940, 3030, 3500
20.	H	I	CH_3	210–211	500, 700, 760, 800, 840, 1330, 1370, 1460, 1600, 1680, 2950, 3020, 3550
21.	H	H	$-C_6H_5$	150–152	710, 760, 800, 840, 1325, 1375, 1455, 1600, 1685, 3050, 3550
22.	H	Br	$-C_6H_5$	186–188	570, 710, 760, 810, 850, 1320, 1370, 1450, 1600, 1680, 3030, 3550
23.	Br	Br	$-C_6H_5$	220–222	575, 700, 770, 800, 840, 1330, 1370, 1450, 1600, 1685, 3030, 3500
24.	H	I	$-C_6H_5$	152–153	500, 710, 760, 800, 840, 1330, 1375, 1455, 1610, 1680, 3030, 3550

* All the compounds gave correct analysis for 'C', 'H' and 'N',

** m.p. were taken in open capillaries.

TABLE III

Pharmacological data of some compounds described in Table II

Compound Nos.	ALD_{50}	Gross CNS observations at 1/5 of ALD_{50}				Mobility counts	0 hr	½ hr	1 hr	2 hr	3 hr
		SMA	Reactivity	Writhing	Hypothermia						
						Controlled	137	115	105	90	82
9.	681	↓	↓	(+)	0·4° C	Treated	104	89	44	28	26
13.	>1000	↓	↓	—	0·6° C		147	70	65	27	26
14.	>1000	↓	↓	—	0·7° C		136	109	85	77	74
16.	>1000	↓	↓	(+)	1·1° C		151	101	92	79	69
17.	>1000	↓	↓	(−)	0·8° C		176	92	67	44	41
19.	>1000	↓	↓	—	0·5° C		140	103	78	62	56

↓ = decreased; (+) = present; (−) = not effected.

1. Kacker, I. K. and Zaheer, O. H., *J. Indian Chem. Soc.*, 1951, **28**, 334.
2. Gujral, M L., Saxena, P. N. and Tewari, R. S., *Indian J. Med. Res.*, 1956, **43**, 637
3. Soularaic, A. and Gattesmann, C., *Life Science*, 1967, **6**, 1229.
4. Seth, P. K. and Parmar, S. S., *Can. J. Physiol. Pharmacol.*, 1965, **43**, 1019.
5. Mathieson, O., *French Pat.*, 1964, 1367738; through *Chem. Abstr.*, 1968, **84**, 1220.
6. Carlsson, A., *Pharmacol. Rev.*, 1959, **11**, 490.
7. Harnykiewicz, O., *Biochemistry and Pharmacology of Basal Ganglia*, eds. E Costa, J. Costa, and M. P., Yahr, 1966.
8. Ecrisson, A. D. and Watermann, B. G., *Neurology* 1971, **21**, 1129.
9. Werle, E. and Koch, W., *Biochem. Z.*, 1949, **319**, 305.
10. Von Euler, U. S , *Pharmacol. Rev.*, 1966, **18**, 29.
11. Pletcher, A., Gey, K. P. and Burkura, W. P., In *Hand Book of Exptl. Pharmacol.*, eds. Vol. 2, Eichler and Frah, Springer Verlag, Berlin, 1965.
12. Gorkin, V. Z., *et al.*, *Vop. Med. Klin.*, 1967, **3** (4), 413.
13. Calne, D. B , *Brit. Med. J.*, 1971, 3. 729.
14. Miller, E. M. and Wiener, L., *Neurol.* (*Minneap*). 1974, **24**, 484.
15. Wheeler, S. A. K. and Oats, W. M., *J. Amer. Chem. Soc.*, 1910, **32**, 770
16. Klemme, C. J. and Hunter, J. H., *J. Org. Chem.*, 1940, **5**, 227.
17. Tiwari, S. S. and Pandey, V. K., *J. Indian Chem. Soc.*, 1975, **52** (8), 736.
18. Bogert and Seil, *J. Amer. Chem. Soc.*, 1907, **29**, 517.
19 Finar, I. L., In *Organic Chemistry*, 5th ed., ELBS and Longman Group, London, 1973, **1**, 706.
20. Weil, C. S., *Biometrics*, 1952, **8**, 249.

ASSESSMENT OF HEAVY METAL TOXICITY

I. Effect on Microbial Population, Mineralization and Soil Respiration

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ABSTRACT

For the assessment of heavy metal toxicity on microbial population in the soil, three heavy metals (mercury, zinc and cadmium) were mixed in the soil samples in the range of 200–500 ppm. Soil respiration, C/N ratio and total microbial counts in soil were measured and a remarkable toxic effect especially on higher concentrations was observed. Mercury was found most toxic followed by zinc and cadmium. Experimental observations were supported by predicted linear regression equations.

INTRODUCTION

SOIL fertility is primarily governed by microbial activity which is highly sensitive to environmental conditions. The disturbance of cryptic ecological equilibrium reflects on the biotic activity. Introduction of heavy metal pollutants[1], being largely toxic and non-degradable, lowers the microbial populations and renders them inactive, especially at higher concentrations. Microbial activities are susceptible to the heavy metals consequently reflecting on the soil