dose levels of 200 mg/kg body weight. No major abnormalities were observed in animals during toxicity studies.

Conclusion

(+)Gossypol shows promising post-coital anti-implantation activity in fertile female albino rats at a dose level less than 10 mg/kg body weight by intraperitoneal route. By oral route, the compound is active at the dose of 30 mg/kg body weight.

The effect of (+)gossypol on autacoid induced spasm and on the release of histamine from mast cells suggest that the anti-implantation activity of (+)gossypol may be due to the inhibition of decidualization by blocking histamine release or by competitive binding with histamine receptors. (+)Gossypol may also possess slight oestrogenic activity.

(+)Gossypol seems to be non-toxic in the effective dose level now tested.

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SYNTHESIS AND CNS ACTIVITY OF 2-ARYL-3-(SUBSTITUTED-PHENOXYACETYL-HYDRAZONO)-METHYLENYL-INDOLES

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Abstract

Twelve of the title compounds have been synthesised by the reaction of 2-aryl-indol-3-aldehydes with substituted phenoxy acetyl hydrazines under mild acidic conditions of hydrazone's synthesis. The structures of these compounds have been confirmed by elemental analysis and the I.R. spectra. The compounds are non-toxic and psychotropics. The compounds have shown a marked effect on body temperature.

DIFFERENT indole derivatives impart a variety of reactions on the CNS such as depressant, anticonvulsant[1,2], analgesic,[3] antidepressant[4] and anti-Parkinsonian[5] activities. The indolyl chemical neurotransmitter, serotonin, itself has been found to exhibit variable CNS activities. According to Koelle[6], the effects and responses of serotonin on the CNS differ not only between the different species of animals but also between the individuals of the same species and even in different tests on the same animal. This has controversy regarding the effects of serotonin on the CNS. Furthermore, the hydrazines, hydrazides and hydrazones have been reported to be the inhibitors of monoamine oxidase[7,8] an important enzyme affecting the concentration of adrenergic neurotransmitters. In view of these valid observations, the authors have synthesised twelve "2-aryl-3-(substituted-phenoxyacetyl-hydrazono)-methylenyl-indoles" to observe the gross effects of them on the CNS of mice.

2-Aryl-indoles and 2-aryl-indol-3-aldehydes

These were prepared by the methods of 'Blades and Wilds'[9] and Weisbach *et al.*[10]

Substituted-phenoxyacetyl hydrazines

The method of Conti[11] was used for the synthesis of these compounds.

2-(4'-Chloro-phenyl)-3-(p-methyl-phenoxyacetyl hydrazono)-methylenyl-indole

It was synthesised by mixing 2-(4'-chloro-phenyl) indol-3-aldehyde (0·0025 mole) and 4-methyl-phenoxy-acetyl hydrazine (0·0025 mole) in ethanol (40 ml) containing 2 drops of glacial acetic acid. The solution

was refluxed on water bath. After 90 min, solid started to separate out from the refluxing mixture; heating was continued for two more hours. About 20 ml of ethanol was then distilled off from the reaction mixture. It was cooled at room temperature. The solid separated was filtered and recrystallised from ethanol; m.p. 228°C; yield—99%.

For $C_{24}H_{20}O_2N_3Cl$: N = 9·72% (10·06%)
C = 69·17% (68·98%)
H = 4·56% (4·79%).

I.R. (KBr) : 3200 cm^{-1} (doublet, 3050 cm^{-1}, 2900 cm^{-1}, 1680 cm^{-1}, 1610 cm^{-1}, 1560 cm^{-1}, 1500 cm^{-1}. 1410 cm^{-1}, 1300 cm^{-1}, 840 cm^{-1} and 740 cm^{-1}.

The peak at 1610 cm^{-1} (for C=N vibration) indicated hydrazone formation. The doublet at 3200 cm^{-1} represented –NH stretching for indole and for Co.NH groups. The band at 1680 cm^{-1} could be assinged to C=O and that at 1300 cm^{-1} to ether linkage. The N–H bending absorption appeared at 1560 cm^{-1}.

Similarly, other hydrazones were also synthesised and their relevant data are given in Table I.

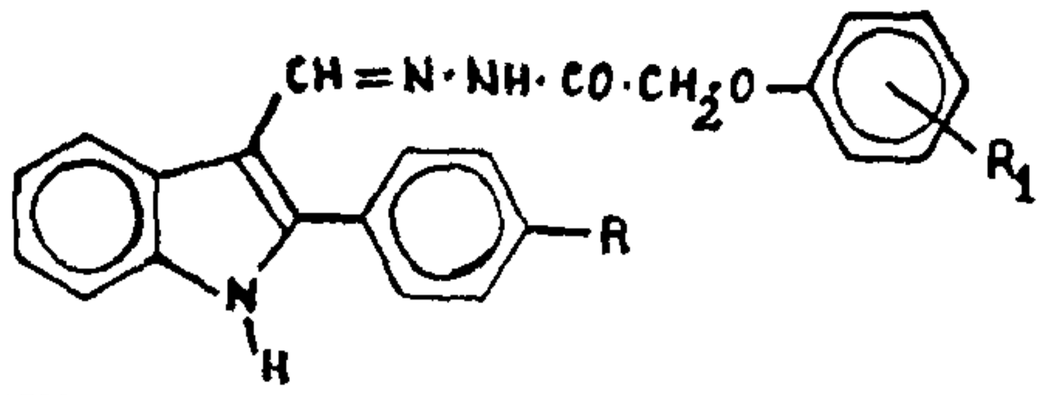
Pharmacology

All of the compounds were tested for their actions on the central nervous system and for their toxicity on the albino mice of either sex.

For toxicity test, the compounds were administered intraperitoneally to albino mice in different doses (464, 1000 and 215 mg/kg) and the approximate lethal dose in 50% of the animals tested (ALD_{50}) were determined by the method of Weil[12]. The ALD_{50} values are noted in Table II.

TABLE I

*2-Aryl-3-(substituted phenoxyacetyl hydrazono)-methylenyl-indoles**



Sl. No.	R_1	Molecular formula	M.P.** (°C)	Yield (%)
		R = CH_3		
1.	*o*-CH_3	$C_{25}H_{23}O_2N_3$	194	60
2.	*p*-CH_3	$C_{25}H_{23}O_2N_3$	222	62
3.	*o*-Cl	$C_{24}H_{20}O_2N_3Cl$	166	65
4.	*p*-Cl	$C_{24}H_{20}O_2N_3Cl$	228	65
5.	*o*-NO_2	$C_{24}H_{20}O_4N_4$	245	68
6.	*p*-NO_2	$C_{24}H_{20}O_4N_4$	256	70
		R = Cl		
7.	*o*-CH_3	$C_{24}H_{20}O_2N_3Cl$	192	85
8.	*p*-CH_3	$C_{24}H_{20}O_2N_3Cl$	228	99
9.	*o*-Cl	$C_{23}H_{17}O_2N_3Cl_2$	232	92
10.	*p*-Cl	$C_{23}H_{17}O_2N_3Cl_2$	270	87
11.	*o*-NO_2	$C_{23}H_{17}O_4N_4Cl$	280	99
12.	*p*-NO_2	$C_{23}H_{17}O_4N_4Cl$	282	90

* All the compounds were recrystallised from methanol and gave correct elemental analysis for nitrogen element.

** M.P. were taken in open capillaries and are uncorrected.

TABLE II

Gross CNS observations for compounds described in Table I, at 1/5th of ALD_{50}

Compound No.	ALD_{50} mg/kg	Gross CNS results			Mobility counts				
		SMA and reactivity	Respiration	Change in body temperature		0 hr	½ hr	1 hr	2 hrs	3 hrs.
					Controlled	253	189	174	146	129
1.	>1000	↑	↑	(–)	Treated	249	172	151	135	124
2.	>1000	↑	↑	(–)		246	164	141	133	124
3.	>1000	↑	↑	↓1·2		250	173	151	118	110
4.	>1000	↑	↑	↓0·6		243	168	148	117	107
5.	>1000	↑	↑	(–)		231	174	152	118	110
6.	>1000	↑	↑	↑1·1		240	172	160	122	110
7.	464	↓	↓	↑0·1		273	104	91	74	70
8.	681	↓	↓	↓0·1		293	136	139	116	110
9.	681	↓	↓	↓1·2		292	95	123	81	80
10.	>1000	↓	↓	(–)		247	162	138	124	114
11.	>1000	↓	↓	(–)		257	158	141	122	112
12.	>1000	↓	↓	(–)		244	169	142	127	118

↑ = increased, ↓ – decreased; (–) - not affected.

For their actions on the CNS, the compounds were administered to albino mice at 1/5th of ALD_{50} and their behavioural changes in spontaneous motor activity (SMA) and reactivity to sound and touch, were noted. These observations are also noted in Table II.

Results and Discussion

All the compounds have been found to be non-toxic. Six of the title compounds produced a depressant effect, while the other six induced stimulations on the CNS of albino mice. On this basis, the compounds may be said to be "psychotropics".

Since only small number of derivations have been taken regarding the structural variations a complete structure activity correlation was not possible. However, some conclusions could be drawn as follows:

(i) Based on the effects produced by the compounds on albino mice, the entire series may grossly be divided into two sections, relative to the nature of substituent R′ on the phenyl ring at position-2 of the indole nucleus, (*a*) when phenyl ring was substituted by $-CH_3$ group, compounds imparted stimulant effects on the CNS, irrelevant of the substituent in the side chain at position-3 of indoles (Compound Nos. 1–6) and (*b*) when an electronegative group (here Cl) was substituted on the phenyl ring at position-2 of indole nucleus, it invariably depressed the CNS functions of the animals (Compound Nos. 7–12).

(ii) The respiration also followed the same trends.

The effect of compounds on body temperature was variable for different compounds of the series. Compound Nos. 1, 2, 6, 10, 11 and 12 did not show any effect. Compound No. 4 decreased the body temperature by 0·6°C, whereas Compound Nos. 3 and 9 decreased it by 1·2°C. Compond Nos. 6 and 7 increased the body temperature by 1·1 and 0·1°C, respectively. Compound No. 8 decreased the body temperature by 0·1°C. It is evident that methyl substitution on the phenoxy group in the side chain at position 3 of indole did not produce any appreciable effect on the body temperature.

The compounds were also screened for antitremorine activity, but no significant effect was found.

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