Synthesis of 2-substituted phenyl-3-aryloxyacetyl hydrazono methylenyl-indoles as Central Nervous System Active Agents

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Summary: 2-Aryl -indol -3-aldehydes were condensed with aryloxyacetyl hydrazines under normal condition of 'azomethine' formation, to obtain twelve of the title compounds. The structures of these compounds have been confirmed by elemental analysis and the I.R. spectra. The compounds are non-toxic, CNS depressants and hypothermic on albino mice.

Indole derivatives have been described to be CNS depressants[1], anticonvulsants[2] and antiparkinsonian agents[3]. One of the important chemical neurotransmitters 'serotonin' is an indolyl derivative, which itself imparts various roles on the CNS[4]. Furthermore, some hydroazones have also been reported to be psychotropics[1] on the CNS of albino mice. These moieties have been indicated to alter the actions of brain neurotransmitters by affecting the concentration of enzymes, metabolizing them[5]. Therefore, the authors were prompted to synthesise the title compounds which contain both the aforesaid moieties, in order to ascertain their action on the CNS of albino mice.

The synthesis of compounds was done along Scheme-1.

In the preliminary investigation the final compounds were characterised by the T.L.C. and mixed melting point technique. They were finally identified by their elemental analyses and the I.R. spectroscopic studies. In the I.R. spectroscopy, the compounds imparted important peaks at 3350 and 3175 cm^{-1} (for cyclic and non-cyclic N-H stretch respectively), 1680 cm^{-1} (for C=O stretch) and 1595 cm^{-1} (for C=N grouping). The specific peaks for aldehydic group and the doublet for NH_2 of hydrazide were absent. These observations confirmed the condensation of hydrazide and indolaldehyde to form the hydrazone group.

Experimental

2-Substituted-phenyl indoles

These were prepared by the method of Calvaire and Polland[6].

2-Substituted phenyl-indole-3-aldehydes

The methods of Swaminathan et al[7] and Buchman et al[8] were adopted for the synthesis 2-phenylindol -3-aldehyde and 2-(4-methoxyphenyl) -indol-3-aldehyde respectively.

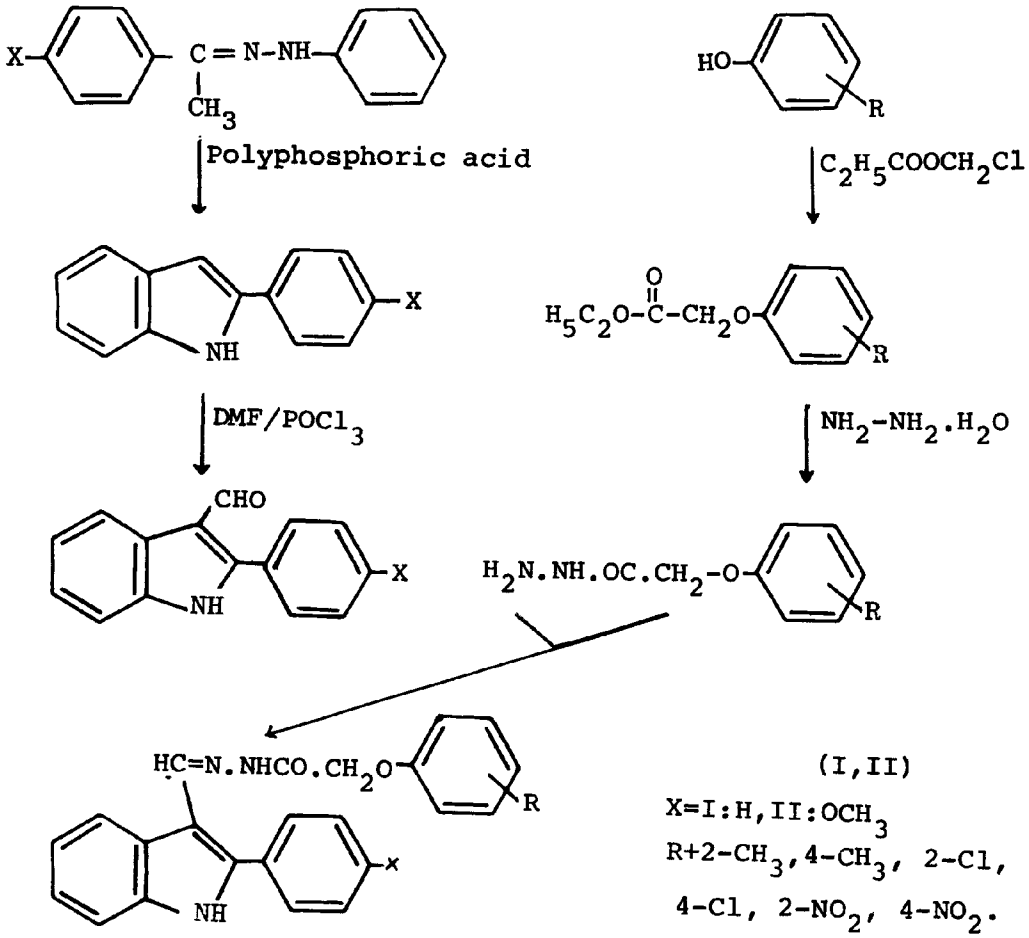
Substituted phenoxyacetyl hydrazines

The method of Conti[9] was utilized for the synthesis of hydrazides used.

2-Phenyl-3-(2-tolyloxyacetyl hydrazono)-methylenyl-indole

2-Phenyl indol-3-aldehyde (0.0025 mole) and 2-tolyloxyacetyl hydrazine (0.0025 mole) were dissolved in ethanol (25 ml.) and glacial acetic acid (2-3 drops) was added to it. The mixture was refluxed on water bath for 3 hrs. The solid was separated in hot solution. About 15 ml. of ethanol was distilled off and the reaction mixture was cooled. The solid separated was filtered, washed well with alcohol and recrystallised from ethanol: yield 90%; m.p. 205°C.

Anal. for $C_{24}H_{21}O_2N_3$:
N (Calcd.) = 10.96%; (Found) = 11.00%.
C (Calcd.) = 75.19%; (Found) = 74.62%.
H (Calcd.) = 5.48%; (Found) = 5.40%.
I.R. (KBr phase): 350, 3175, 3050, 2900, 1680, 1595, 1560, 1500, 1450, 1310, 1210, 750 and 700 cm^{-1} etc.



P.M.R. ($CDCl_3$) - δ 1.4 (s, 3H, CH_3), 4.45 (s, 2H,)- CH_2 - CO), 6.75 - 7.80 (m, 14H, 13Ar - H & ! HC = N-), 8.24 (s, 1H, NH indole) and 8.95 (s, iH, N-NH. CO).

Similarly, other hydrazones were synthesised and their relevant data are noted in Table-I.

Pharmacological Screenings

All of the compounds were tested for gross behavioural changes on the CNS and for their toxicity tests on the albino mice of either sex.

Toxicity studies

The compounds were administered intraperitoneally to albino mice of either sex in different doses and the death occurred after 24 hrs. were noted. Thus, approximate lethal doses in 50% of the animals tested (ALD_{50}) were calculated by the method of Wiel[10]. The results of toxicity tests are noted in Table-II. All of the compounds are non-toxic.

Central Nervous System Activities

For their actions on the CNS, the compounds were administered to a group of five albino mice weighing between 15-25 gms at the dose of 1/5 of ALD_{50}. One group of mice was given equivalent amount of normal aline instead of compound, and was treated as standard control. The behavioural changes in spontaneous motor activity (SMA) and reactivity to sound and touch were noted as compared to the controlled mice. The effects of compounds on the rate of respiration and tempera-

Table -I. 2-Substituted phenyl-3-(aryloxyacetyl hydrazono) methylenyl indoles (I, II)

Compound Nos.	R	m.p.* (°C)	%C Calcd./Found		%H Calcd./Found		%N Calcd./Found		Yield %
					X=H				
Ia.	2-CH_3	205	75.19	74.62	5.48	5.40	10.96	11.00	90
Ib.	4-CH_3	204	75.19	75.31	5.48	5.44	10.96	11.12	75
Ic.	2-Cl	202	68.40	68.88	4.46	4.04	10.40	10.43	72
Id.	4-Cl	236	68.40	68.47	4.46	4.44	10.40	10.60	75
Ie	2-NO_2	275	66.66	66.01	4.34	4.30	13.52	12.98	80
If.	4-NO_2	278	66.66	66.94	4.34	4.09	13.52	13.02	80
					X=OCH_3				
IIa	2-CH_3	198	72.64	71.99	5.56	5.50	10.16	9.89	75
IIb	4-CH_3	222	72.64	72.80	5.56	5.32	10.16	9.92	78
IIc	2-Cl	204	66.43	66.62	4.61	4.67	9.69	9.75	70
IId	4-Cl	245	66.43	66.62	4.61	4.67	9.69	9.34	75
IIe	2-NO_2	224	64.86	64.62	4.50	5.66	12.61	12.34	88
IIf.	4-NO_2	246	64.86	65.01	4.50	5.59	12.61	12.00	80

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

Table-II. ALD_{50} and gross CNS observations of compounds described in Table-I at 1/5 of ALD_{50}

Compound Nos.	ALD_{50} g/kg i.p.	Gross CNS observations SMA	Reactivity	Respiration	Hypothermia (°C)	Other effects
Ia.	> 1000	↓	↓	↓	0.8	(-)
Ib.	> 1000	↓	↓	↓	1.6	Writhing
Ic.	> 1000	↓	↓	↓	1.3	(-)
Id.	> 1000	↓	↓	↓	1.0	(-)
Ie.	> 1000	↓	↓	↓	0.5	Ptosis
If.	> 1000	↓	↓	↓	0.5	(-)
IIa.	> 1000	↓	↓	↓	0.5	(-)
IIb.	825	↓	↓	↓	0.5	Writhing
IIc.	825	↓	↓	↓	0.5	(-)
IId.	825	↓	↓	↓	0.3	Ptosis
IIe.	825	↓	↓	↓	0.4	(-)
IIf.	681	↓	↓	↓	0.4	(-)

Explanation of Signs – ↓ = decreased; (-) = absent; > = more than

ture, respective to the controlled mice were also noted (Table II).

All the compounds were also screened for their analgesic, electroshock induced anticonvulsant activity, antireserpine and anorexigenic activities. But, all of these activities were found to be insignificant in the series of compounds.

The compounds have been found to non-toxic, CNS depressants (decreased the spontaneous motor activity 'SMA' and reactivity to sound and touch), hypothermic (induced decrease in body temperature) and induced decrease in breathing rate of albino mice. Compounds Ib and IIb induced writhing (twisting of belley) and compounds Ie and IId induced ptosis (closing of eye-lids), hence showing more pronounced CNS depressant behaviour.

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References

1. R. Agrawal, R. K. Satsangi, S. Misra and S.S. Tiwari; *Curr. Sci.* **50(2)**, 66-68, (1981).
2. M.V. Shetty, P.Parimoo and Y.M. Chopra; *Eur. J. Med. Chem. Chim. Ther.;* **13**, 581, (1978).
3. C. Dumont, J. Guillaume and L. Nedelee; *Ger. offen.* 2, 738, 646 (cl. CO7D-401/04); *Chem. Abstr.;* **79**, 6229r, (1978).
4. G.B. Koelle; *Pharmacological Basis of Therapeutics;* eds. L.S. Goodman and A. Gilman; MacMillan (U;S.A.), pp. 416-614, (1975).
5. C. Kaiser and C.L. Zirkle; *Antidepressant Drugs (Medicinal* Chemistry); ed. A.Burger; Wiley Interscience; N.Y.; 2, 1488, (1970).
6. A. Calvaire and R. Polland. *Compt. Rend.;* 250, 3194, (1960).
7. S. Swaminathan and S. Ranganathan; *Chem. and Ind. (London);* 774, (1955).
8. G. Buchman and D. Rossner; *J. Parakt. Chem.;* **25**, 117, (1964).
9. L. Conti.; *Bull. Sci. Chim. Ind. Bolosna,* **22(1)**, 13-15, (1964), *Chem. Abstr.;* **61**, 4253e, (1964).
10. C.S.Wiel; *Biometrics,* **8**, 249, (1952).