digeriert und heiß filtriert. Aus den vereinigten Filtraten wurden ca. 3/4 des Ethers abdestilliert und der Rückstand im Kühlschrank 12 h stehengelassen. Die erhaltenen Kristalle wurden aus Cyclohexan umkristallisiert. Ausb.: 0,58 g (52 % d.Th.). Die Verbindung ist nach Schmp., Elementaranalyse, IR- und ^{1}H-NMR-Spektren mit dem bei der Kondensation von **1a** mit **2r** erhaltenen Produkt identisch.

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Synthesis and CNS Activity of *N,N*-Disubstituted 1-(Aminomethyl)-5-alkyl-3-(aryloxyacetylhydrazono)indolin-2-ones

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Isatin and 5-methylisatin were condensed with various aryloxyacetylhydrazides to furnish the 3-(aryloxyacetylhydrazono)-5-alkylindolin-2-ones **1–4**. When **1-4** were subjected to *Mannich* reaction, the *N,N*-disubstituted 1-(aminomethyl)-5-alkyl-3-(aryloxyacetylhydrazono)indolin-2-ones **5–8** were obtained. The compounds were CNS active and relatively non-toxic (albino mice).

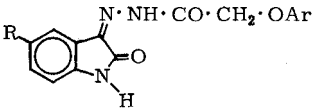
Synthese und ZNS-Aktivität von N,N-disubstituierten 1-(Aminomethyl)-5-alkyl-3-(aryloxyacetylhydrazono)-indolin-2-onen

Isatin und 5-Methylisatin wurden mit verschiedenen Aryloxy-acetylhydraziden kondensiert, um die 3-Aryloxyacetylhydrazono-5-alkyl-indolin-2-one **1–4** zu erhalten. Durch *Mannich* Reaktion wurden aus **1–4** die N,N-disubstituierten 1-(Aminomethyl)-5-alkyl-3(aryloxyacetylhydrazono)-indolin-2-one **5–8** erhalten. Die synthetisierten Substanzen sind ZNS-aktiv und relativ ungiftig (Albinomäuse).

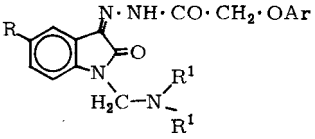
Indole derivatives play important roles in biological systems. Serotonin is a chemical neurotransmitter. Oxindole and its derivatives have been found to be effective on the Central Nervous System enzymes[1] and in some CNS diseases such as convulsions[2]. The hydrazines, hydrazides and hydrazones have been reported to be inhibitors of mono-amine oxidase[3–5], an important enzyme affecting the concentration of adrenergic neurotransmitters.

Alkyl substitution at position 5 of the indole ring imparts the spasmolytic effect to the nucleus[6]. Furthermore, it is also evident that different secondary amines like pyrrolidine, morpholine, piperidine and piperazines exert a variety of reactions on the CNS[7–10]. In view of these observations, the authors have synthesised sixteen 1-substituted-3-hydrazono-indolinones to observe their gross effects on the CNS of mice. The compounds have been found to be non-toxic and CNS active agents (depressants and stimulants).

For the synthesis of the title compounds, the starting materials 'Isatins' were prepared via *Sandmeyer* reaction and acid hydrazides were synthesised by hydrazinolysis of the corresponding methyl esters[11]. The condensation of these isatins with acid hydrazides in equimolar proportions in ethanol/acetic acid gave rise to the corresponding 3-aryloxyacetylhydrazono-indolin-2-ones **1–4**, and the subsequent '*Mannich* reaction' involving the active 'H' at position-1 of indolinone and secondary amines, gave the final compounds **5–8**. All the newly synthesised compounds gave satisfactory N elementary analyses. Further support of their structures was derived from their infrared spectral data.



1: R = H, Ar = 2-naphthyl
2: R = CH_3, Ar = 2-naphthyl
3: R = H, Ar = 4-NO_2-phenyl
4: R = CH_3, Ar = 4-NO_2-phenyl



5-8: $N(R^1)_2$ = Pyrrolidino, Morpholino, Piperidino, 4-N-Tolyl-piperazino

Experimental

Melting points: in open capillaries (uncorr.). *I.R. spectra*: Perkin-Elmer 177 spectrophotometer in KBr.

5-Substituted indolin-2,3-diones- these were prepared by the conventional method[12].

3-(2-Naphthyloxyacetylhydrazono)-indolin-2-one **(1a)**

It was synthesised by mixing 0.01 mole isatin and 0.01 mole 2-naphthyloxyacetic acid hydrazide in 50 ml ethanol containing 2–3 drops of glacial acetic acid and refluxing the reaction mixture for 4 h. It was cooled at room temp. and the solid separated was washed with ethanol and recrystallised from glacial acetic acid; m.p. above 290 °C, yield 98 %. – IR: 3225, 1700, 1680, 1510 (secondary amide), 1620 (C=N–) 3030, 1600, 1450, 830 and 750 cm^{-1} (aromatic C–H).

Similarly the other 5-alkyl-3-(aryloxyacetylhydrazono)-indolin-2-ones **2–4** were synthesised (Table 1).

1-Pyrrolidino methyl-3(2-naphthyloxyacetyl hydrazono) indolin-2-one **5a**

It was synthesised by adding 1 ml of the 37 % aqueous solution of formaldehyde to a suspension of 0.0025 mole **1** in 15 ml warm ethanol. 25 mmole Pyrrolidine was added and heated on a water bath for 10 min. The reaction mixture was allowed to stand at room temp overnight. The solid separated was washed with petroleum ether (b.p. 60–80 °C) and dried well in air. Finally, recrystallised from

Table 1: *5-Alkyl-3-(aryloxy acetyl hydrazono)indolin-2-ones* **1–4**

No.	Yield %	Molecular formula	M.P. °C	N Calcd.	N Found
1	96	$C_{20}H_{15}N_3O_3$	> 290	12.2	12.4
2	97	$C_{21}H_{17}N_3O_3$	259	11.7	11.9
3	94	$C_{16}H_{12}N_4O_5$	281	16.5	16.6
4	95	$C_{17}H_{14}N_4O_5$	253	15.8	16.0

chloroform/ petrolether (60–80 °C); m.p. 155°C; yield 70 %. $C_{25}H_{24}N_4O_3$ (428)-Calcd. N 13.1, Found 13.2. IR: 3350, 1720, 1510 (amide), 1485, 2800, 2900 (CH_2), 1620 (C=N), 3050, 1600, 1450, 830 and 750 cm^{-1} (aromatic C–H).

Similarly, the other N,N-disubstituted-1-(amino)-methyl-5-alkyl-3-(-aryloxyacetyl hydrazono)indolin-2-ones **5–8** were synthesised (Table 2).

Pharmacology

All the compounds of the series were screened for their toxicity and actions on the CNS of albino mice.

Tab. 2: *N,N-Disubstituted-1-(amino methyl)-5-alkyl-3(aryloxyacetylhydrazono)-indolin-2-ones* **5–8**

No.	$-N\begin{matrix}R^1\\R^2\end{matrix}$	R	Yield %	M.P. °C	Mol. Formula	N Calcd.	N Found
		Ar = 2-naphthyl					
5a	Pyrrolidino	H	70	155	$C_{25}H_{24}N_4O_3$	13.1	13.3
5b	Morpholino	H	75	180	$C_{25}H_{24}N_4O_4$	12.6	12.4
5c	Piperidino	H	72	174–175	$C_{26}H_{26}N_4O_3$	12.7	12.8
5d	4-N-p-Tolyl-piperazino	H	65	165	$C_{32}H_{31}N_5O_3$	13.1	12.9
6a	Pyrrolidino	CH_3	65	129–130	$C_{26}H_{26}N_4O_3$	12.7	12.9
6b	Morpholino	CH_3	68	115–116	$C_{26}H_{26}N_4O_4$	12.2	12.0
6c	Piperidino	CH_3	70	110–111	$C_{27}H_{28}N_4O_3$	12.3	12.5
6d	4-N-p-Tolyl-piperazino	CH_3	72	134–135	$C_{33}H_{33}N_5O_3$	12.8	12.6
		Ar = 4-NO_2-phenyl					
7a	Pyrrolidino	H	78	175–176	$C_{21}H_{21}N_5O_5$	16.6	16.8
7b	Morpholino	H	80	195	$C_{21}H_{21}N_5O_6$	16.9	16.7
7c	Piperidino	H	75	200	$C_{22}H_{23}N_5O_5$	16.0	15.8
7d	4-N-p-Tolyl-piperazino	H	70	185–186	$C_{28}H_{28}N_6O_5$	15.9	16.1
8a	Pyrrolidino	CH_3	70	174	$C_{22}H_{23}N_5O_5$	16.0	15.9
8b	Morpholino	CH_3	65	204	$C_{22}H_{23}N_5O_6$	15.5	15.7
8c	Piperidino	CH_3	68	202	$C_{23}H_{25}N_5O_5$	15.6	15.7
8d	4-N-p-Tolyl-piperazino	CH_3	75	168	$C_{29}H_{30}N_6O_5$	15.5	15.3

For the determination of their ALD_{50}, the method of *Weil*[13] was followed. The compounds were administered at doses of 464 and 1000 mg/kg weight of mice intraperitoneally as the gum acacia suspension. The gross CNS effects were observed using the same doses (Table 3).

For their actions on the CNS, these compounds were finally administered at $1/5^{th}$ of ALD_{50} and the behavioural changes in 'Spontaneous Motor Activity' (SMA) and reactivity to sound and touch were noted. Effect on body temperature due to compound administered was also observed. To substantiate the observations on SMA, the mobility counts were taken (Table 4).

The compounds are nontoxic and exert a variety of reactions on the CNS of albino mice, some of which are CNS depressive whereas others are largely stimulative. The compounds induced writhing (twisting of belley) at all doses, showing muscle relaxant properties. All compounds (except **8d**) have induced hypothermia ranging between 0.1–0.7°C. Some of the compounds have also induced other additional CNS activities, such as compounds **5c** and **5d** induced ataxia (staggaring), compounds, **6a, 8c** and **8d** induced straub-tail (erection of tail) and compounds **7a** and **7b** have induced piloerection.

The number of compounds synthesised was less to draw the confirmative structure-activity relationship.

Table 3: *Gross CNS observations and ALD_{50} of the Compounds* **5–8**

No.	Gross Central Nervous System observations						ALD_{50}
	Dose – mg/kg i.p.			1000 – mg/kg i.p.			
	SMA	Reactivity	Writhing	SMA	Reactivity	Writhing	mg/kg (i.P.)
5a	↓	↓	(+)	↓	↓	(+)	681
5b	↓	↓	(+)	↓	↓	(+)	681
5c	↑	↑	(+)	↑	↑	(+)	681
5d	↑	↑	(+)	↑	↑	(+)	1000
6a	↑	↑	(+)	↑	↑	(+)	>1000
6b	↑	↑	(+)	↑	↑	(+)	>1000
6c	↓	↓	(+)	↓	↓	(+)	>1000
6d	↓	↓	(+)	↓	↓	(+)	>1000
7a	↑	↑	(+)	↑	↑	(+)	>1000
7b	↑	↑	(+)	↑	↑	(+)	>1000
7c	↑	↑	(+)	↑	↑	(+)	>1000
7d	↑	↑	(+)	↑	↑	(+)	>1000
8a	↓	↓	(+)	↓	↓	(+)	>1000
8b	↓	↓	(+)	↓	↓	(+)	>1000
8c	↑	↑	(+)	↑	↑	(+)	>1000
8d	↑	↑	(+)	↑	↑	(+)	>1000

↑ = Increased, ↓ = decreased, (+) = present

Table 4: *Gross CNS observations and mobility counts at 1/5th of the ALD_{50} of Compounds* **5–8**

No.	SMA	Reactivity	Writhing	Respiration	Hypothermia (°C)	Other effects	Mobility counts				
							0h	½h	1h	2h	3h
						Controlled	250	186	178	161	146
5a	↓	↓	(+)	↓	0.5	(–) Treated	250	110	93	89	70
5b	↓	↓	(+)	↓	0.4	(–)	248	122	89	100	79
5c	↑	↑	(+)	↑	0.3	Ataxia	231	182	174	155	140
5d	↑	↑	(+)	↑	0.2	Ataxia	238	204	195	166	166
6a	↑	↑	(+)	↑	0.6	Straub tail	240	210	201	172	176
6b	↑	↑	(+)	↑	0.1	(–)	263	220	222	192	171
6c	↓	↓	(+)	↓	0.4	(–)	248	178	170	150	126
6d	↓	↓	(+)	↓	0.7	(–)	246	170	165	160	140
7a	↑	↑	(+)	↑	0.4	Piloerection	266	206	204	157	160
7b	↑	↑	(+)	↑	0.3	Piloerection	261	201	210	161	161
7c	↑	↑	(+)	↑	0.2	(–)	240	170	160	152	145
7d	↑	↑	(+)	↑	0.2	(–)	242	169	155	150	140
8a	↓	↓	(+)	↓	0.4	(–)	252	180	125	156	145
8b	↓	↓	(+)	↓	0.2	(–)	255	182	173	155	140
8c	↑	↑	(+)	↑	0.4	Straub tail	246	191	199	178	160
8d	↑	↑	(+)	↑	(–)	Straub tail	245	193	200	180	165

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