Synthesis and CNS activities of some newer indole derivatives

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Indole derivatives play important role in biological systems. Serotonin, an indole derivative is a well known chemical neurotransmitter[1]. Oxindole and its derivatives have been found to be effective on the CNS enzymes[2] and also in some CNS diseases[3,4]. Furthermore, different indole derivatives have shown variable therapeutic properties, such an CNS blocking[5] and antidepressant[6] activities. On the other hand, pyrazolinones have also been found to be the CNS active agents[7,8]. Thiazolidinones have a wide variety of effects on the CNS, including anaesthetic[9] and sedative[10] actions. Very recently, thiazolidinon-2-thione derivatives have been reported to possess CNS depressant and stimulant effects[11]. Indomethacin (a 1-aroyl substituted indole derivative) has been found to be analgesic and anti-inflammatory agent[12]. On the basis of aforesaid findings, it was thought worthwhile to introduce pyrazolinone and thiazolidinon-2-thione moieties at position-3 of indole nucleus and aroylating the subsequent products to synthesise 'indomethacin' like derivatives. This paper describes their synthesis and the actions on the CNS of albino mice.

Experimental

In the prefinal step, the active methylene groups of pyrazolinone and 4-oxo-thiazolidin-2-thione (I) moieties have been utilized for the 'Knoevenagel condensation' with indol-aldehydes (II) to give (III). The buffer of acetic acid and sodium acetate was used as important reaction condition, so as to provide basic acetate ion. In the final step the N-H at position-1 of indole nucleus was aroylated to give (IV). The structures of all the new compounds were confirmed by elemental percentage analysis and the I.R. spectroscopy.

The melting points were taken in open capillaries using A.R. H_2SO_4 bath and are uncorrected. The I.R. spectra were recorded in KBr phase and p.m.r. spectra were recorded in DMSO.

2-Aryl-indoles - were prepared by the method of Blades & Wild[13].

2-Aryl-indol-3-aldehydes - were prepared by the method of Weisbach[14].

1-Phenyl-3-methyl-5-oxo-pyrazoline- was prepared by the method of Vogel[15]

3-Phenyl-4-oxo-2-thion-thiazolidine- was prepared by the method of Brown et al[16]

2-Aryl-3-(1-phenyl-3-methyl-5-oxo-pyrazolin-4-yl)-methylenyl indoles (IIIa,b) : A mixture of 2-aryl-indole-3-aldehyde (0.-1 mole), 1-phenyl-3-methyl-5-oxo-pyrazoline (0.01 mole) anhydrous sodium acetate (5 gm) & gl. AcOH (50 ml) was refluxed for 4 hrs. on a sand bath with occasional shaking. Thereafter, it was cooled, poured with stirring in ice cold water (200 ml) and left overnight. The solid separated was filtered, washed well with water and recrystallised from alcohol (Table-I).

2-Aryl-3-(3-phenyl-4-oxo-2-thion-thiazalidin-5 - yl)-

methylenyl indoles (IIIc,d) : 3-Phynyl-4-oxo-2-tion-thiazolidine and 2-aryl-indol-3-aldehyde were condensed by the aforesaid method (Table-I).

1-Benzoyl-2-phenyl-3-(1-phenyl-3-methyl-5-oxo-pyrazolin-4yl)-methylenyl-indole : An equimolar mixture of 2-phenyl-3-(1-phenyl-3-methyl-5-oxo-pyrazolin-4yl)-methylenyl indole (0.0025 mole) and benzoyl chloride (0.005 mole) was refluxed in dry pyridine (25 ml) on sand bath for 8 hrs. Nearly 15 ml of pyridine was then distilled off at reduced pressure and the reaction mixture was cooled to room remperature. Thereafer, it was poured, with constant stirring, in crushed ice (200 gms) and left overnight. The solid separated was filtered and washed several times with ice cold water to remove pyridine and recrystallised from dilute alcohol, yield 70%, m.p 128° (Found N, 8.49 $C_{32}H_{23}O_2N_3$ requires N, 8.73%), IR: 3050, 2940 (Aromatic & aliphatic C-H), 1680 (tert. N-C=O), 1660 ( )C=CH) etc.

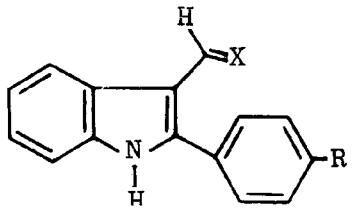
Similarly, other 1-aroyl-2-aryl-3-[(1-phenyl-3-methyl-5-oxo-pyrazolin-4-yl) /(3-phenyl-4-oxo-2-thion-thiazolidin-5- yl)] methylenyl-indoles (IVa-l) were synthesised by using appropriate III & aroyl chlorides (Table-II).

Pharmacology

All of the compounds were tested for their action on the Central Nervous System (CNS) and for their toxicity test on the albino mice of either sex.

For toxicity test, the compounds were administered intraperitioneally to albino mice in different doses and the approximate lethal dose in 50% of the tested animals (ALD_{50}), were determined by the method of Weil[17]. The ALD_{50} and the gross CNS activities at 1/5th of ALD_{50} are noted in Table-III.

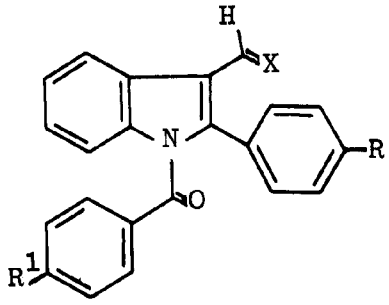
Table 1. 2-Aryl-3-[(1-phenyl-3-methyl-5-oxo-pyrazolin-4yl)/(3-phenyl-4-oxo-2-thion-thiazolidin-5yl)] methylenyl indoles (IIIa-d)



compd. No.	R	Molecular formula	M.P. (°C)	Yield (%)	% Nitrogen Calcd.	Found
	X=1-phenyl-3-methyl-5-oxo-pyrazolin-4-yl					
IIIa	H	$C_{25}H_{19}ON_3$	198	95	11.14	11.22
IIIb	OCH_3	$C_{26}H_{21}O_2N_3$	162	92	10.31	10.26
	X=3-phenyl-4-oxo-thion-thiazolidin-5 yl					
IIIc	H	$C_{24}H_{16}ON_2S_2$	140	89	6.79	6.82
IIId	OCH_3	$C_{25}H_{18}O_2N_2S_2$	204	85	6.33	6.39

IR$^+$(IIIa): 3400 (N-H), 2950 (C-H), 1680 (C=O), 1660 ( )C=CH-) etc.
(IIIc): 3390 (N-H), 3050, 2940 (C-H), 1680 (C=O), 1670 ()C=CH-), 1590 (N-H bending), 1220 (C=S) etc.
PMR$^+$(IIIa) : 1.85(s,3H,–CH_3), 6.79 to 8.2 (complex multiplet, 15H, 14 Ar-H & 1 -C=CH) & 8.37 (s, 1H, N-H).
(IIIc) : 6.92 to 7.74 (complex multiplet, 15H, 14 Ar-H & 1-C=CH), 8.35 (s, 1H, NH).

Table II. 1-Aroyl-2-aryl-3-[(1-phenyl-3-methyl-5-oxo-pyrazolin-4 yl)/(3-phenyl-4-oxo-2-thion-thiazolidin-5-yl)-methylenyl-indoles(IVa-l).



compd. No.	R	R_1	Mol. formula	m.p. (°C)	Yield (%)	% Nitrogen Calcd.	Found
		X=1-phenyl-3-methyl-5-oxo-pyrazolin-4-yl					
IVa	H	H	$C_{32}H_{23}O_2N_3$	128	70	8.73	8.49
IVb	H	Cl	$C_{32}H_{22}O_2N_3Cl$	150	65	8.14	7.94
IVc	H	NO_2	$C_{32}H_{22}O_4N_4$	154	78	10.64	10.66
IVd	OCH_3	H	$C_{33}H_{25}O_3N_3$	174	65	8.22	8.38
IVe	OCH_3	Cl	$C_{33}H_{24}O_3N_3Cl$	185	69	7.70	7.35
IVf	OCH_3	NO_2	$C_{33}H_{24}O_5N_4$	205	80	10.07	9.87
		X=3-phenyl-4-oxo-2-thion-thiazolidin-5-yl					
IVg	H	H	$C_{31}H_{20}O_2N_2S_2$	168	59	5.42	5.49
IVh	H	Cl	$C_{31}H_{19}O_2N_2S_2Cl$	184	63	5.08	5.36
IVi	H	NO_2	$C_{31}H_{19}O_4N_3S_2$	195	70	7.48	7.27
IVj	OCH_3	H	$C_{32}H_{22}O_3N_2S_2$	164	79	5.12	4.96
IVk	OCH_3	Cl	$C_{32}H_{21}O_3N_2S_2Cl$	130	65	4.82	4.75
IVl	OCH_3	NO_2	$C_{32}H_{21}O_5N_3S_2$	150	85	7.10	7.32

PMR (IV f): 1.82 (s, 3H, $-CH_3$), 3.85 (s, 3H, $-OCH_3$), 6.78 to 7.95 (complex multiplet, 18H, 17 Ar-H and 1 -C=CH). (IV j): 3.79)9s, 3H, $-OCH_3$), 6.89 to 7.91 (complex multiplet, 19H, 18 Ar-H & 1 -C=CH).

For their action 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), reactivity to sound & touch and the effect on body temperature were noted.

Visualising the date of pharmacological screenings (Table-III), it is evident that some of the compounds are depressant, whereas, the others are CNS stimulant. The compounds are of varying toxicity and it is evident that the p-nitro group on the phenyl ring at position-1 of the indole nucleus decreases the ALD_{50}. The CNS depressant compounds have induced hypother-

Table III. ALD_{50} and Gross CNS observations at 1/5th of the ALD_{50} of the compounds described in Table-II

Compd.	ALD_{50} (mg/kg)	Gross CNS observations at 1/5th of ALD_{50}			
		SMA & Reactivity	Writhing	Change in body temp. (°C)	Other effects
1.	> 1000	↓	(+)	↓ 0.6	(-)
2.	> 1000	↓	(+)	↓ 0.4	(-)
3.	681	↑	(+)	↑ 0.3	(-)
4.	> 1000	↓	(+)	↓ 0.2	(-)
5.	> 1000	↑	(+)	↑ 0.1	(-)
6.	825	↓	(+)	↓ 0.7	(-)
7.	1000	↑	(+)	↑ 0.5	(-)
8.	> 1000	↓	(-)	↓ 0.4	(-)
9.	681	↓	(+)	↓ 1.0	(-)
10.	1000	↓	(+)	↓ 1.1	Straub tail
11.	1000	↑	(+)	↑ 1.4	Piloerection
12.	681	↓	(-)	↓ 2.5	"

↑ = increased; ↓ = decreased, (+) = present, (-) = not affected

mia (decrease in body temperature), whereas, the stimulating compounds have induced hyperthermia (increase in body temperature). All the compounds (except Nos. 8 & 11) have induced writhing (twisting of belly), thereby showing their effect on muscles of belly.

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