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Synthesis and Anticonvulsant Activity of 3-Aryl/Alkyliminoindol-2-ones

G.S. SINGH, N. SIDDIQUI and S.N. PANDEY*
Department of Pharmaceutics, Institute of Technology
Banaras Hindu University, Varanasi-221 005, India

3-Aryl/alkyliminoindol-2-ones have been synthesized by the condensation of indole-2,3-dione with amines and characterised on the basis of analytical and spectral data. They have been screened for anticonvulsant activity by electroshock and chemoshock methods. Some of them have significant activity. The compound having naphthyl moiety showed 100% protection.

INTRODUCTION

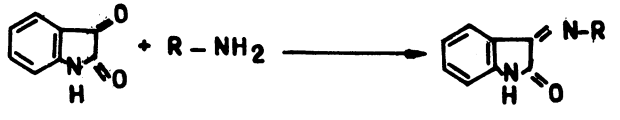
Studies on indole derivatives have acquired conspicuous significance in recent years as they are reported to have psychotropic, CNS depressent and anticonvulsant activities[1–3]. The literature reported the monohydrazones of indole-2,3-diones having potential anticonvulsant activity. This prompted us to synthesize 3-aryl/alkyliminoindol-2-ones (Ia-j) and evaluate them for anticonvulsant activity.

EXPERIMENTAL

Melting points were determined on Büchi apparatus. UV and IR spectra were recorded on Cary-14 and Perkin--Elmer 621 spectrophotometers, respectively. The PMR spectra were recorded on a Jeol FX90Q spectrometer using TMS as an internal standard.

3-Aryl/Alkyliminoindol-2-ones (Ia-j)

The compounds were synthesized according to scheme 1. The equimolecular amounts of indole-2, 3-dione and respective amines in ethanol were heated on water both for $\frac{1}{2}$ hr. The reaction mixture on keeping for another 1/2 hr at room temperature afforded Ia-j as yellow to dark brown crystals. The physical and PMR spectral data of these compounds are recorded in Table 1.



I a -j

Scheme 1

TABLE 1
PHYSICAL, PMR AND ANTICONVULSANT ACTIVITY DATA OF 3-ARYL/ALKYLIMINOINDOL-2-ONES (I)

Compd. No.	R / Y	M.pt. (°C)	Yield (%)	Mol. formula*	PMR ($CDCl_3$ / DMSO-d_6, δ)	ACA (% Protection)		
						Electroshock (MES)	Chemoshock	
							Picrotoxin[b]	Strychnine[c]
Ia	C_6H_5	205	76	$C_{14}H_{10}N_2O$	9.8 (bs, 1H, NH), 7.35 (m, 9H, arom.)	50	37.5	—
Ib	$C_6H_4CH_3$ - *p*	190	80	$C_{15}H_{12}N_2O$	9.8 (bs, 1H, NH) 7.32 (m, 8H, arom.), 2.30 (s, 3H, CH_3)	50	—	—
Ic	$C_6H_4OCH_3$ - *p*	220	62	$C_{15}H_{12}N_2O_2$	9.75 (bs, 1H, NH) 7.30 (m, 8H, arom.), 3.85 (s, 3H, OCH_3)	0	—	—
Id	C_6H_4Cl - *p*	240	65	$C_{14}H_9N_2OCl$	9.8 (bs, 1H, NH), 7.30 (m, 8H, arom.)	62.5†	25	25
Ie	C_6H_4Br - *p*	245	70	$C_{14}H_9N_2OBr$	9.8 (bs, 1H, NH), 7.30 (m, 8H, arom.)	50	25	—
If	C_6H_4Cl - *m*	220	54	$C_{14}H_9N_2OCl$	9.8 (bs, 1H, NH), 7.28 (m, 8H, arom)	37.5	—	—
Ig	$C_6H_5CH_2$	185	48	$C_{15}H_{12}N_2O$	10.0 (bs, 1H, NH), 7.30 (m, 9H, arom.), 4.45 (s,2H, benzylic)	62.5†	25	25
Ih	α-$C_{10}H_7$	240	75	$C_{18}H_{12}N_2O$	10.1 (bs, 1H, NH), 7.4 (m, 11H, arom.)	100‡	37.5	50

Compd. No.	R / Y	M.pt. (°C)	Yield (%)	Mol. formula*	PMR ($CDCl_3$ / DMSO-d_6, δ)	ACA (% Protection)		
						Electroshock (MES)	Chemoshock	
							Picrotoxin[b]	Strychnine[c]
Ii	C_6H_4·OCH_3 – *o*	152	45	$C_{15}H_{12}N_2O_2$	10.0 (bs, 1H, NH), 7.30 (m, 8H, arom.), 3.80 (s, 3H, OCH_3)	50	25	12.5
Ij	C_6H_{11}	140	65	$C_{14}H_{16}N_2O$	10.3 (bs, 1H, NH), 7.40 (m, 4H, arom.), 4.2 (s, 1H, N–CH), 1.8 (m, 10H, five C–CH_2)	25	—	—
	Phenobarbitone					100	—	—
	Phenytoin, .5 mg					60	—	—

*Analysis for C, H and N found within ± 0.3%.
n = 8, dose = 20 mg / kg (i.p.), a = 20, mg / kg (i.p.), b = 4.5 mg / kg (s.c.), c = 4 mg / kg (s.c.),
Polyethylene glycol control (picrotoxin) = 0% protection, saline control (strychnine) = 0% protection).
†P 0.05.
‡P 0.01.

Screening for anticonvulsant activity

Electroshock method[4]: Supermaximal electroshock of current intensity 60Hz using a Technoconvulsiometer were given to Albino rates of either sex (each weighing between 100-150 gm). The rats were previously administered with 20 mg/kg of test compounds solution in polyethyleneglycol. The abolition of the hind limb tonic extensor spasm was recorded as measure of anticonvulsant potency.

Chemoshock Method[5]: The animals of the control group received 0.5 ml saline (*i.p.*). The other group of animals were administered experimental drug solution (4.0 mg/kg, *i.p.*). After 3/4 hr, all the animals of both groups were injected with strychnine in a dose of 4 mg/kg (S.C.) and observed for another 3/4 hr for seizures.

The experiment was carried out for picrotoxin (4.5 mg/kgm. S.C.) by dissolving it in polyethyleneglycol in similar way.

RESULTS AND DISCUSSION

The compounds Ia-j have been characterised on the basis of satisfactory analytical and spectral data (Table 1). The UV spectra of the compounds showed absorption maxima at 250–266 nm. The IR spectra exhibited three bands at 1610 ± 5, 1715 and 3280–3350 cm^{-1} which have been assigned due to C=N, C=O and N–H stretching vibrations, respectively. The N–H proton appeared as a broad singlet in offset (δ 9.8–10.3) region of the PMR spectrum and was D_2O exchangeable.

Out of ten compounds, synthesized in the series, seven compounds protected either 50% or more animals from supramaximal electroshock. While the compounds with *p*-chlorophenyl and benzyl substituent gave significant results (62.5% protection), in Ii with naphthyl substitution the result was 100% protection and was similar to the activity of phenobarbitone. The compounds were also tested against picrotoxin and strychnine induced convulsion but were found to be less effective.

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