Possible Anticonvulsant Imidazolinones. Synthesis and Anticonvulsant Activity of 1*N*-(γ'-Picolinoyl)-4-substituted-benzylidene-2-methyl/phenyl-5-imidazolinone

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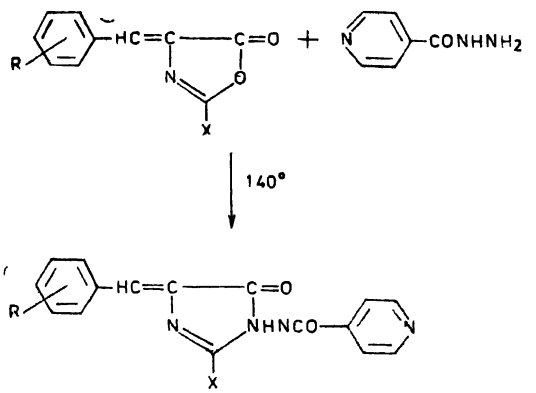
IMIDAZOLINONES have been found to be associated with several pharmacological activities[1]. As anticonvulsant activity of lower amino acids has

been also reported[2], it was of interest to incorporate these molecules into the imidazolinone derivatives.

Imidazolinone derivatives of the type 1 have been synthesised by condensation of isoniazid with 5-oxazolone derivatives which were prepared by Erlenmeyer condensation of glycine with different aldehydes in presence of sodium acetate and acetic anhydride. The compounds have been characterised by elemental analyses and ir spectral data and have been screened for their antimicrobial and anticonvulsant activity.



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Experimental

Melting points were determined in open capillary tubes and are uncorrected. Ir spectra (KBr) were recorded on a Shimadzu 435 spectrophotometer. The compounds were routinely checked for their homogenity by tlc on silica gel plates.

2-Methyl/phenyl-4-(substituted-benzylidene)-5-oxazolones: These were prepared by the reported method[3].

1-N-(γ'-Picolionyl)-4-(substituted-benzylidene)-2-methyl/phenyl-5-imidazolinone (1). *General procedure:* The 2-phenyl-4-benzylidene-5-oxazolone (2.49 g, 0.01 mol) was heated with an equimolar quantity of isoniazid (1.37 g, 0.01 mol) in an oil-bath at 140° for 1 h. The resulting jelly-like mass was recrystallised from methanol, (54%), m.p 185° (Found : C, 71.73 ; H, 4.30 ; N, 15.20. $C_{22}H_{16}N_4O_2$ calcd. for : C, 71.74 ; H, 4.35 ; N, 15.22%) ; ν_{max} 3 280 (NH amide), 2 850—2 900 (ArCH), 1 680 (NHCO amide), 1 610 (C=N), 1 550 (NH amide), 1 280 (C—N) and 1 040 cm^{-1} (NH def.).

Biological evaluation:

Antimicrobial activity: The imidazolinones (1) were screened for their antibacterial and antifungal activity using cup-plate method[4] at a concentration of 100 μg ml^{-1} using gram-positive bacteria *Staphylococcus aureus, Staphylococcus citrus* and gram-negative bacteria, *Escherichia coli* and *Psudomonas flourescens.* The antifungal testing was carried out against *Candida albicans* and *Aspergillus flavus.* The compounds showed moderate activities (11—21 mm zone of inhibition) against all the bacteria and fungi. Under identical condition, the standard antibiotics, ampicillin showed a zone of inhibition 16—22 mm, chloramphenicol 15—24 mm, cephalaxin 12—19 mm, tetracyclin 13—25 mm, and cimmitidin 15—21 mm against various stains of bacteria and fungi at a concentration of 50 μg ml^{-1}.

Anticonvulsant activity[8]*:* Twenty compounds were subjected to study their anticonvulsant activity[5].

Table 1—Physical Data of the Imidazolinones (1)*

Sl. no.	R	Mol. formula	M.p. °C	Yield %
	X=C_6H_5			
1.	9-Anthryl	$C_{30}H_{20}N_4O_2$	142	70
2.	Cinnamyl	$C_{24}H_{18}N_4O_2$	55	81
3.	3-Chlorophenyl	$C_{22}H_{15}N_4O_2Cl$	165	68
4.	4-Chlorophenyl	$C_{22}H_{15}N_4O_2Cl$	115	83
5.	3,4-Dichlorophenyl	$C_{22}H_{14}N_4O_2Cl_2$	130	66
6.	2,6-Dichlorophenyl	$C_{22}H_{14}N_4O_2Cl_2$	192	65
7.	3,4-Dimethoxyphenyl	$C_{24}H_{20}N_4O_4$	145	62
8.	Dimethylaminophenyl	$C_{24}H_{21}N_5O_2$	300	85
9.	2-(1-Furyl)	$C_{20}H_{14}N_4O_4$	178	70
10.	3-Hydroxyphenyl	$C_{22}H_{16}N_4O_3$	118	81
11.	4-Hydroxyphenyl	$C_{22}H_{16}N_4O_3$	142	63
12.	2-Methoxyphenyl	$C_{23}H_{18}N_4O_3$	110	76
13.	3-Methoxyphenyl	$C_{23}H_{18}N_4O_3$	115	59
14.	4-Methoxyphenyl	$C_{23}H_{18}N_4O_3$	121	60
15.	2-Nitrophenyl	$C_{22}H_{15}N_5O_4$	118	77
16.	3-Nitrophenyl	$C_{22}H_{15}N_5O_4$	130	69
17.	Phenyl	$C_{22}H_{16}N_4O_2$	185	54
18.	3-Methoxy-4-hydroxyphenyl	$C_{23}H_{18}N_4O_2$	169	71
19.	Thienyl	$C_{20}H_{14}N_4O_2S$	148	65
	X=CH_3			
20.	9-Anthryl	$C_{25}H_{18}N_4O_2$	283	63
21.	Cinnamyl	$C_{19}H_{16}N_4O_2$	210	70
22.	3-Chlorophenyl	$C_{17}H_{13}N_4O_2Cl$	115	80
23.	4-Chlorophenyl	$C_{17}H_{13}N_4O_2Cl$	156	66
24.	3,4-Dichlorophenyl	$C_{17}H_{12}N_4O_2Cl_2$	120	81
25.	2,6-Dichlorophenyl	$C_{17}H_{12}N_4O_2Cl_2$	175	64
26.	3,4-Dimethoxyphenyl	$C_{19}H_{18}N_4O_4$	201	61
27.	Dimethylaminophenyl	$C_{19}H_{19}N_5O_2$	140	59
28.	2-(1-Furyl)	$C_{15}H_{12}N_4O_3$	159	83
29.	3-Hydroxyphenyl	$C_{17}H_{14}N_4O_3$	192	67
30.	4-Hydroxyphenyl	$C_{17}H_{14}N_4O_3$	166	60
31.	2-Methoxyphenyl	$C_{18}H_{16}N_4O_3$	145	72
32.	3-Methoxyphenyl	$C_{18}H_{16}N_4O_3$	240	65
33.	4-Methoxyphenyl	$C_{18}H_{16}N_4O_3$	222	85
34.	2-Nitrophenyl	$C_{17}H_{13}N_5O_4$	292d	73
35.	3-Nitrophenyl	$C_{17}H_{13}N_5O_4$	180	80
36.	Phenyl	$C_{17}H_{14}N_4O_4$	298	58
37.	3-Methoxy-4-hydroxyphenyl	$C_{18}H_{16}N_4O_4$	192-3	67
38.	Thienyl	$C_{15}H_{12}N_4O_2S$	159	60

* All compounds gave satisfactory C, H and N analyses ; compouds sl. nos. 2-5 & 10, 14, 15, 17, 18, 23-26, 31, 33-37 were tested for anticonvulsant activity.

Anticonvulsant activity was determined against pentylene tetrazol induced scizures in albino mice (25—30 g). All compounds were suspended in 5% aqueous gum acacia to give concentration of 25% (w/v). The test compounds dissolved in propylene glycol were injected i.p. into a group of five mice at a dose of 100 mg/kg, and anticonvulsant activity was compared with phenobarbiton (a reference drug). Four hours after administration of com-

pounds, the mice were injected with pentylenetetrazol 100 mg/kg. The mice were observed for 60 min for occurrence of scizures. Chlonic spasm persisting for atleast 5 s was considered to be a threshold convulsion. Transient intermittent jerks and tremors were disregarded. Animal not exhibiting threshold convulsions during 60 min were considered protected. The numbers of mice protected in each group was recorded and the anticonvulsant activity of compounds was represented in terms of % protection. The mice were further observed for 24 h for recording mortality.

It appears that compounds of sl. nos. 15, 34 and 35 (Table 1) were most effective with highest protection and minimum mortality rate. Compounds of sl. nos. 5, 10, 22 and 24 displayed significant activity (70–80% protection) while most of the compounds exhibited moderate activity.

Moreover, these observation also led to the conclusion that the presence of NO_2 group increases the biological activity.

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