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SOME NEW DERIVATIVES OF ISOXAZOLE WITH EXPECTED ANTIMICROBIAL AND ANTICONVULSANT PROPERTIES

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Several new amide derivatives of 5- isoxazole have been prepared by condensing the appropriate amines with isoxazole carboxylic acid. In the case of ethyleneimine it gave a novel hydrochloride of isoxazole ethyleneimide. Their structures were assigned on the basis of analytical studies. All these compounds showed poor antimicrobial activity, while compounds 1 and 2 gave good protection against leptazol convulsions.

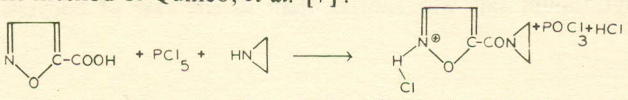
INTRODUCTION

Nitrofuradentin which is structurally related to isoxazole is a broad spectrum antibacterial agent and is used clinically as an effective bactericidal agent against the majority of urinary pathogens. A study of the structural modification of oxazole has been explored in the last decade. Derivatives of isoxazole are associated with diverse biological properties and some of them display a high order of antibacterial [1], antiandrogen [2], analgesic and anti-inflammatory properties [3]. It has been firmly established that an olefinic group conjugated with a carbonyl function is an important pharmacophoric feature among a number of antimicrobial agents [4, 5]. On the other hand Gunn *et al.* [6] reported that a majority of anticonvulsant drugs of great clinical values have a uride grouping as one of the important features for their activity. An attempt has been made in this work to prepare compounds with possible anticonvulsant and antimicrobial properties. However, an imide derivative of isoxazole gave an interesting hydrochloride.

MATERIALS AND METHODS

Melting points for all compounds were determined in open capillary tubes in the Thomas Hoover melting point apparatus and were uncorrected. IR spectra were run as (Nujol mulls) on Perkin-Elmer 273 model and UV spectra with a Pye Unicam SP 800 spectrophotometer. Elemental analyses were performed by the School of Pharmacy, London.

5-Isoxazole Carboxylic Acid. – Mesityl oxide was condensed with ethyl formate in equimolar quantities in the presence of sodium methoxide to give the sodium salt of *iso*propylidene acetylacetaldehyde. The resulting compound was purified with dried either and then condensed and cyclised with hydroxylamine hydrochloride in acidic medium to give the expected 3- and 5- isomeric mixture of *iso*butenylisoxazole. The isomeric separation of this mixture by fractional distillation was not possible; in order to separate the isomers, they were subjected to chromic acid oxidation and the respective acids were separated by the method of Quilico, *et al.* [7].



5-Isoxazole Ethyleneimide Hydrochloride (1). – 5-Isoxazole carboxylic acid (6 g, 0.053 mol) in dry ether (50 ml) was stirred with phosphorus pentachloride (13 g, 0.063 mol) in the fume cupboard. After stirring for 2½ hr at room temperature, the hydrogen chloride ceased to evolve, then ethyleneimine (0.86 g, 0.02 mol) was added and stirring was continued for further 2 hr. The solvent was evaporated and the residue was acidified with cold dilute hydrochloric acid and extracted with ethyl acetate (3 x 50 ml). On evaporation the combined extract gave a colourless solid in excellent yield, m.p. 110° (ethanol) γmax (Nujal) 3300, 3160, 3100 (NH), a broad peak centred at 1665 with shoulders at 1680 and 1612 $(CO)^{-1}$cm, νmax (ethanol) 208, 238, 304 nm (log ξ 4.28, 4.28 and 4.3) Found; C,41.4; H,4.0;N,15.7;Cl,20.4;$\overset{+}{M}$ 174.5. $C_6H_7N_2ClO_2$ requires C,41.3;H,4.0;N,16.0;Cl,20.3% $\overset{+}{M}$ 174.5 and its pk_a = 12.5), while the NMR spectrum showed the expected hydrogen and methylene protonic signals.

The other amide derivatives were prepared in a similar manner. It is rather interesting that none of the other derivatives was obtained as a hydrochloride.

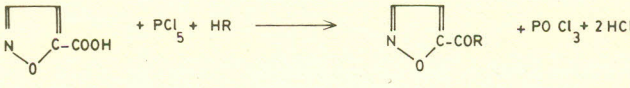
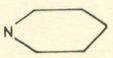
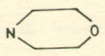


Table 1

No.	R	M.P.C (Ethanol)	(Microanalysis in %) Found	Requires	Formula
(2)	R1 = 	73	C 58.2 H 6.4 N 16.7	58.0 6.1 16.7	$C_8H_{10}N_2O_2$
(3)	R2 = 	82	C 59.8 H 6.8 N 15.6	60.0 6.6 15.5	$C_9H_{12}N_2O_2$
(4)	R3 = 	76	C 52.9 H 5.6 N 15.6	52.8 5.5 15.4	$C_8H_{10}N_2O_3$
(5)	R4 = 	96	C 68.2 H 5.1 N 12.2	68.4 5.3 12.3	$C_{13}H_{12}N_{12}O_2$

These compounds were characterised by their UV and IR spectra as well.

Antimicrobial Activity. These compounds were tested for their bacteriostatic activity *in vitro* against the following bacteria and fungi: *Staphylococcus aureus, Escherichia coli,* yeast, *Pseudomonas aeruginosa*, mold *(Aspergillus niger)* and *Penicillum* spp. The medium used was nutrient broth and the compounds were run at a concentration of 0.0001 to 0.01% w/v. The plates were incubated at 22-37° for a week. The observation showed poor activity against any of the tried organism under these conditions.

Anticonvulsant Activity. Albino mice of either sex of CFLP-ICI strain and adult male albino rats weighing nearly 200 g were taken from inbred stock. They were maintained on an adequate diet and allowed free access to food and water except during experiment. All compounds under test were dissolved or suspended in arachis oil vehicle and administered intraperitoneally. Leptazol was dissolved in saline vehicle and administered into an abdominal area remote from prior injections of test compounds. In every experiment control animals received an equivalent volume of injection vehicle.

Leptazol convulsions were introduced in the mice using the method prescribed by Swinyard *et al.* [8]. Mice in groups of 10 received injections of leptazol (100 mg/kg) at a period of one or two hr after the injection of the test compound. The anticonvulsant activity of the compounds were assessed by their ability to antagonise the effect of leptazol convulsions. The subsequent effects of laptazol were observed as reported by Qazi [9, 10]. The results

Table 2. Anticonvulsant activity of 5 amides compared with phenobarbitone.

Drug	Time after administration	% reduction in group seizure score
Phenobarbitone	1	68.8
(10 mg/kg. i.p.)	2	32.8
Compound 1	1	54.6
(400 mg/kg.i.p.)	2	24.0
Compound 2	1	60.2
(400 mg/kg.i.p.)	2	25.0
Compound 3	1	34.4
(400 mg/kg.i.p.)	2	27.3
Compound 4	1	35.5
(400 mg/kg.i.p.)	2	25.0
Compound 5	1	36.2
(400 mg/kg.i.p.)	2	30.2

obtained were then quantified using a seizure severity score [11].

All these compounds gave some protection against leptazol but the activity of 1 and 2 were more significant than the other amides reported above. However, their activity was less significant than that of phenobarbitone even though only a small amount of the latter was used. The antileptazol activity of compounds 1 and 2 were not persistent in duration like compound 5 [9, 10]. This might be due to faster rate of metabolism resulting due to the opening of heterocyclic rings of these compounds. These compounds were tested for their sedative activity following the procedure reported by Qazi [10]. They were less sadative than phenobarbitone at a dose level used for anticonvulsant activity.

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