

## ANTISPASMODIC ACTION OF 5-METHYL BENZOXAZOLINE-2-ONE: A PRELIMINARY STUDY

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During routine pharmacological screening of some new compounds on various systems it was observed that the compound 5-Methyl benzoxazoline-2-one (1) decreased the effect of histamine on guinea pig ileum. This study was undertaken to investigate further the effect of (1) on guinea pig ileum, using various spasmogens.

Ileal segments obtained from fasted guinea pigs (300-350gms) were mounted under 0.5g tension, in 10ml organ baths containing aerated Tyrode solution at 37°C. Isometric tension changes were recorded through a force displacement transducer connected to a Grass Polygraph. Dose response curves to four spasmogens namely, histamine, acetylcholine (ACh), 5-hydroxytryptamine (5HT) and barium chloride were obtained by cumulative addition of the agonist<sup>1</sup> and repeated in the presence of the test compound added in doses of  $1.3 \times 10^{-6}$  and  $2.6 \times 10^{-6}$  M. Six experiments were performed in each case.

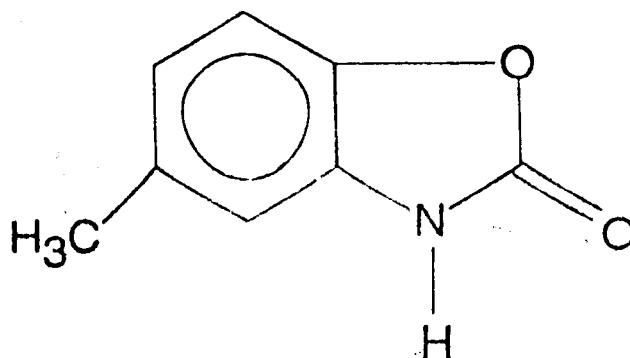
The compound (1) was prepared by the reaction of 2-amino-4-methyl phenol with urea. 2-amino-4-methyl phenol (2g) and urea (1.2g) were refluxed for 14 hours in dry pyridine. Excess pyridine recovered by distillation under reduced pressure and the residue column chromatographed over silica gel. Elution of column with ethyl acetate:petroleum ether (20:80) yielded (1) (1.85g) showing a melting point of 126°C. The compound was purified by repeated chromatography over silica gel till it gave a single spot on TLC.

MP is uncorrected. TLC was accomplished using silica gel G and developed with 20% ethyl acetate in petroleum ether and 2% methanol in chloroform and spots visualized with iodine. Proton magnetic resonance spectra (100MHz) were measured in deuterated chloroform. Mass spectrum was obtained at 70eV.

<sup>1</sup>H NMR δ : s at 2.35(3H); t at 6.95(2H); d at 7.1(1H) and bs at 9.95(1H).

MS: M<sup>+</sup> 149; 136; 135; 134; 91; 79; 69; 63; 52 and 51.

Structure of 5-Methyl benzoxazoline-2-one



Compound (1) inhibited the contractile responses to all the four spasmogens tested namely, 5-HT, ACh, barium chloride and histamine. There was a dose-dependent shift to the right with a depression in the maximum response, the effect being fully reversible on washing. This suggests a non-competitive type of antagonism. However, all the four spasmogens were not inhibited to the same extent. Depression of the maximum response at the dose of  $2.6 \times 10^{-6}$  M was most marked with 5-HT (88%) followed by ACh (66%), barium chloride (47%) and histamine (34%). The pD<sub>2</sub> values were 6.5, 5.9, 5.7 and 5.4 respectively. This indicates that it is not a non-specific antagonism of the papaverine or sympathomimetic type.

In the guinea pig ileum, besides acting on 5-HT<sub>3</sub> receptors, 5-HT is known to increase the release of ACh through 5-HT receptors<sup>2</sup>. Thus the dose-response curve to 5-HT is biphasic with a low potency phase involving 5-HT<sub>4</sub> receptors<sup>3,4</sup>.

In the present study, Compound (1) depressed both phases of the dose-response curve. The marked effect on 5-HT response cannot be attributed solely to an antimuscarinic action of the compound which was much less (66%) as compared to (88%) in the case of 5-HT. The varying inhibitory effect of the compound on four different spasmogens acting via diverse mechanisms suggests that its locus of

action may be at a post receptor site, at some step in the transduction pathway. Further work is needed to elucidate the exact mode of action of this compound.

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### PLASMA VISCOSITY MEASUREMENT TO REPLACE ESR?

Measurement of the erythrocyte sedimentation rate is an antique test which should be replaced by measurement of the plasma viscosity, says a letter in the New Zealand Medical Journal (1997;110:322). The viscosity test has none of the technical difficulties of measurement of the erythrocyte sedimentation rate, is highly reproducible, and has a narrow, well defined clinical range. Furthermore, the plasma may be stored for up to one week before the test is done, and that means that specimens may be sent by post.