precisely the same location with respect to flow. Theoretical and a full treatment of this particular feature will be published elsewhere.

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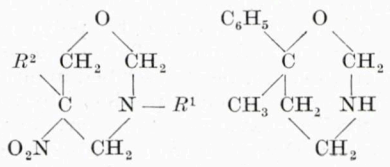
Anti-neoplastic Activity of Tetrahydro-1,3-oxazine Derivatives

It has been demonstrated that benz-1,3-oxazine derivatives inhibit the growth of Crocker sarcoma in mice[1]. This was partly confirmed by F. Bergel, at the Chester Beatty Research Institute, London (private communication).

Further confirmation of the anti-neoplastic activity of benz-1,3-oxazine derivatives was obtained by the Miyamura test, *in vitro*[2]. Similar results were obtained by Leonardi[3] when he repeated our experiments *in vitro*.

All these results seemed to be sufficiently promising to justify searching for anti-neoplastic substances among the derivatives of 1,3-oxazine. Simpler compounds, derivatives of 5-nitrotetrahydro-1,3-oxazines (I) and 6-methyl-6-phenyltetrahydro-1,3-oxazine (II) proved to be fairly efficient *in vitro*[2].



I II

$R^1 = CH_3$, $R^2 = CH_3$, *T* 398 (ref. 4) *T* 446 (ref. 7)
$R^1 = CH_3$, $R^2 = CH_2OH$, *T* 401 (ref. 4)
$R^1 = CH_3$, $R^2 = C_5H_{11}$, *T* 413 (ref. 5)
$R^1 = C_6H_{11}$, $R^2 = C_3H_7$, *T* 364 (ref. 6)

Their activity against the solid form of Ehrlich ascites carcinoma is shown in Table 1 and solid form of amytal ascites sarcoma in mice in Table 2.

It is believed that the active CH_2 group in position 2 is responsible for the anti-neoplastic activity of 1,3-oxazine derivatives.

Further experiments will be carried out with a number of the compounds (I) to elucidate the influence

Table 1. Inhibition of Ehrlich Ascites Carcinoma

Code No. of substance	Mouse strain	No. of mice in group	Daily dose of substance (mgm./mouse)	Average tumour weight (gm.)	$\sigma^* \pm g$	$m^\dagger \pm g$	Tumour inhibition (per cent)‡
T 364	*A*	12	0	2·4	0·79	0·23	
		10	12	1·3	0·52	0·16	45·8
	R III	12	0	2·7	0·79	0·23	
		10	12	1·3	0·94	0·29	51·8
T 398	*A*	12	0	2·4	0·79	0·23	
		10	12	0·8	0·56	0·18	66·7
	R III	12	0	2·6	0·79	0·23	
		10	12	0·8	0·51	0·16	69·2
T 413	*A*	12	0	1·8	0·50	0·14	
		10	12	0·9	0·57	0·18	50·0
	R III	12	0	1·5	0·57	0·16	
		10	12	0·5	0·22	0·07	66·7
T 446	*R* III	12	0	1·1	0·47	0·13	
		10	12	0·6	0·32	0·10	45·4

(See footnotes to Table 2).

Table 2. Inhibition of Amytal Ascites Sarcoma

Code No. of substance	Mouse strain	No. of mice in group	Daily dose of substance (mgm./mouse)	Average tumour weight (gm.)	$\sigma^* \pm g$	$m^\dagger \pm g$	Tumour inhibition (per cent)‡
T 364	*A*	12	0	2·3	0·45	0·13	
		10	12	1·0	0·39	0·12	56·5
	R III	12	0	1·8	0·71	0·20	
		10	12	0·8	0·41	0·13	55·5
T 398	*R* III	12	0	1·7	0·77	0·22	
		10	12	0·7	0·26	0·08	58·8
T 401	*A*	12	0	1·5	0·50	0·14	
		10	12	0·8	0·35	0·11	46·7
T 413	*A*	12	0	1·5	0·50	0·14	
		10	12	0·6	0·17	0·05	60·0
	R III	12	0	1·8	0·94	0·27	
		10	12	0·7	0·22	0·07	61·0
T 446	*R* III	12	0	1·7	0·66	0·19	
		10	12	0·7	0·39	0·12	58·8

$^* \sigma = \sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$ $\qquad$ $^\dagger m = \sqrt{\frac{\Sigma x^2 - \frac{(\Sigma x)^2}{n}}{n(n-1)}}$

‡ Calculated according to the formula : $\frac{P - M}{P}$ 100 = percentage inhibition. *P*, average tumour weight in control group ; *M*, average weight in treated group.

of various substituents on their anti-neoplastic activity.

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BIOLOGY

Fungitoxicity of Metal Ions

The relationship between the toxicity of metal cations and their physico-chemical properties has been considered in terms of electrode potential[1,2], insolubility of the metal sulphide[3], and electronegativity[4]. Danielli and Davies[4] suggested that the toxicity of metal ions is determined by their ability to form un-ionized complexes with ionogenic groupings at the cell surface, and they have taken the electronegativity values of the metals as a measure of the tightness of covalent binding to these groups. The application of this hypothesis to the toxicity of a number of metal salts to fungal conidia[5] has recently been questioned by Miller[6]. In his examination of my experimental results, Miller has arbitrarily disregarded the toxicities of metals less toxic than zinc by terming them "basically not toxic to fungus conidia" although they all possess measurable *ED*50 values. It was, of course, precisely to show that the same toxic mechanism may apply to a wide range of metal ions that these less toxic metals were examined.

Miller also criticizes the standard spore germination technique[7] as a measure of fungitoxicity. This technique determines the fungistatic ability (that is, inhibition of spore germination) of a fungicide as a function of the concentration of the external solution, and is closely related to the practical performance of fungicides. Moreover, the widespread use of this test for many years has established its value as a measure of the relative toxicity of protectant fungicides. Absolute toxicity values will only be obtained when the concentration of toxicant at cell receptor sites can be determined. For some years, McCallan and Miller[8] have advocated the ratio of the weight of fungicide accumulated by the fungal spores at the *ED*50 to the weight of spores as a measure of 'innate' toxicity. Although their ratio of μgm. toxicant/gm. spore weight is a most valuable measure of fungicidal activity and of the uptake of fungicides by spores[9], this weight ratio cannot be regarded as fundamentally related to absolute toxicity until much more information on the mode of action of fungicides and their possible detoxication by the cell is available.

The value of the electronegativity hypothesis may best be shown by an examination of the results of some recent experiments in which the fungitoxicity of twenty-two metal cations to conidia of *Botrytis fabae* Sardiña has been determined. The median effective doses (*ED*50) of unbuffered solutions of nitrates of potassium, sodium, barium (*ED*50 extrapolated), strontium, lithium, calcium, magnesium, manganese, zinc, beryllium, thallium, yttrium, lead, chromium, nickel, cobalt, palladium, copper, and silver, of mercurous and mercuric chloride, and of osmium tetroxide were estimated as before[5]. *B. fabae* conidia gave 98–100 per cent germination after 18 hr. incubation at 25° in distilled water, so that a spore stimulant was not required. In Fig. 1 logarithms of the *ED*50 values of the metal ions are plotted against the electronegativities of the metals as calculated by Pauling[10] and Haïssinsky[11]. Haïssinsky calculated electronegativities by Pauling's method for the whole Periodic Table, including values for some of the different valence states of the transition elements. Although electronegativities are not in their nature quantities which can be defined precisely, modern work has largely corroborated Pauling's original values[12].

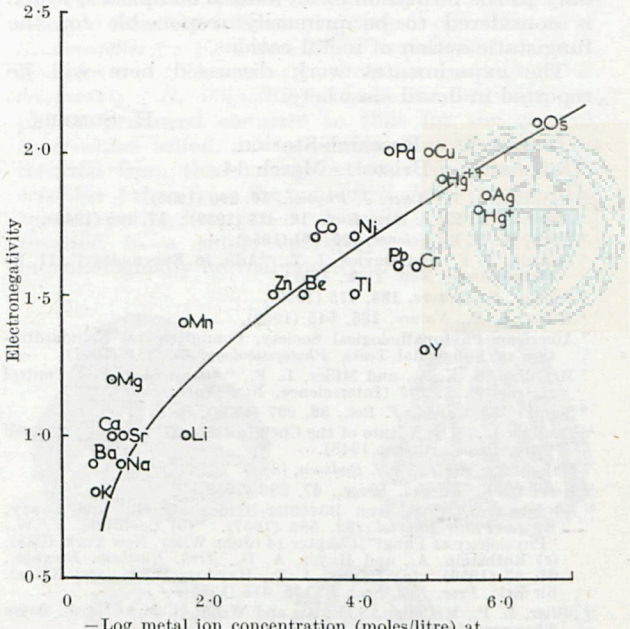

Fig. 1. Graph of toxicity of metal cations to *B. fabae* against electronegativity of the metal

Danielli and Davies[4] have shown that the values of Jones[2] for the toxicities of various cations to the planarian, *Polycelis nigra*, fit an exponential relationship of the form :

$$\log [M^{q+}] = \alpha - \gamma\exp(-0{\cdot}25x^2)$$

where $[M^{q+}]$ is the concentration of the metal cation of valency q in the bulk phase which gives the standard toxicity, x is the difference between the electronegativity of the metal and that of oxygen, and α and γ are constants. From the results in Fig. 1, $\log [M^{q+}]$ was plotted against $\exp(-0{\cdot}25x^2)$ and the regression line calculated, giving $\alpha = 1{\cdot}72$ (S.E., 0·59) and $\gamma = 13{\cdot}98$ (S.E., 1·48). These values of α and γ were used to plot the curve in Fig. 1 which, in spite of the anomalous position of yttrium, may be considered to