Evaluation of *N*-Haloacyl Analogs of α,α-Diphenyl-4-piperidinemethanol Against Ehrlich Ascites Carcinoma in Mice

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The antitumor activity of 8 haloamide derivatives of α,α-diphenyl-4-piperidinemethanol was studied in C3H agouti mice against the Ehrlich ascites carcinoma. The preliminary screening studies would seem to indicate that the chemotherapeutic effect of these compounds is potentially significant. There seems to be a definite correlation between structure and activity within the propionamide and acetamide analogs in that within each group of compounds the iodoamides have the highest order of activity; the bromoamides have intermediate activity; and the chloroamides have the least activity. The haloacetamide analogs seem to be more toxic than the corresponding halopropionamide derivatives.

In a previous paper (1) the synthesis and potential antitumor activity of a series of *N*-haloacyl derivatives of α,α-diphenyl-4-piperidinemethanol were reported. A continuation of the antitumor screening study shows that the compounds (Table I) have significant activity against Ehrlich ascites tumor in C3H mice.

EXPERIMENTAL[1]

Experiments were performed on 5–10-week-old C3H agouti mice purchased from the R. B. Jackson Memorial Laboratory, Bar Harbor, Maine. The testing procedure used was similar to that described by Linder (2) and Hauschka *et al.* (3).

Transplantation of the tumor was carried out by aseptically withdrawing ascites fluid from a donor mouse bearing a 7-day ascites tumor. Each experimental animal was inoculated i.p. with 2×10^6 ascites cells. Ten animals were used as controls and 10 animals for treatment. Mice were distributed into groups of comparable weight and treatment was begun 24 hr. after tumor implantation. The compounds were administered in peanut oil (1%) and control animals received corresponding volumes of peanut oil alone. Change in body weight was noted as a measure of the accumulation of tumor cells and ascitic fluid. Cell counts were used as a measure of the inhibition of tumor cell growth. The dosages recorded in Table II were administered in single intraperitoneal injections per day commencing 24 hr. after transplantation of the tumor and continuing for 3 days. The results recorded in Table II were determined on the sixth day after intraperitoneal transplantation of the tumor.

RESULTS

The chemotherapeutic activity of the halopropionamide analogs (I, IV, VII) against ascites tumor showed that the iodopropionyl derivative (VII) exhibited the greatest inhibition, and the relative activity within this group of compounds was VII > IV > I. The same order of activity was noted with regard to the haloacetamide analogs: iodoacetamide > bromoacetamide > chloroacetamide. The toxicity of haloacetyl derivatives was greater than that of the halopropionyl analogs. (See *Footnote c*, Table II.)

Table I.—Derivatives of α,α-Diphenyl-4-piperidinemethanol

Compd.
1-(3-Chloropropionyl)-α,α-diphenyl-4-piperidinemethanol (I)
1-(2-Chloropropionyl)-α,α-diphenyl-4-piperidinemethanol (II)
1-Chloroacetyl-α,α-diphenyl-4-piperidinemethanol (III)
1-(3-Bromopropionyl)-α,α-diphenyl-4-piperidinemethanol (IV)
1-(2-Bromopropionyl)-α,α-diphenyl-4-piperidinemethanol (V)
1-Bromoacetyl-α,α-diphenyl-4-piperidinemethanol (VI)
1-(3-Iodopropionyl)-α,α-diphenyl-4-piperidinemethanol (VII)
1-Iodoacetyl-α,α-diphenyl-4-piperidinemethanol (VIII)

Table II.—Results of Screening Tests *Versus* the Ehrlich Ascites Carcinoma[a]

Compd.	Dosage, mg./Kg./Day[c]	Mortality Treated Group	Av. Wt. Change, *T/C*. Gm.	Growth Inhibition Ratio[b]
I	20	0/10	1.9/4.5	5:1
II	20	0/10	0.5/4.4	2:1
III	10	0/10	−1.7/3.5	3:1
IV	20	0/10	3.2/5.3	20:1
V	20	0/10	−1.6/4.5	13:1
VI	10	2/10	−3.6/4.1	32:1
VII	20	0/10	−0.6/4.5	75:1
VIII	10	0/10	−2.1/4.2	27:1

[a] *T* = treated group; *C* = control group. [b] Ratio of the total number of tumor cells in control mice to number in treated animals. [c] Represents one-half the LD_{50} as determined in C3H mice.

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