Synthesis of Several *N,N'*-Haloacyl Analogs of *N,N'*-Diphenylethylenediamine as Potential Antineoplastic Agents

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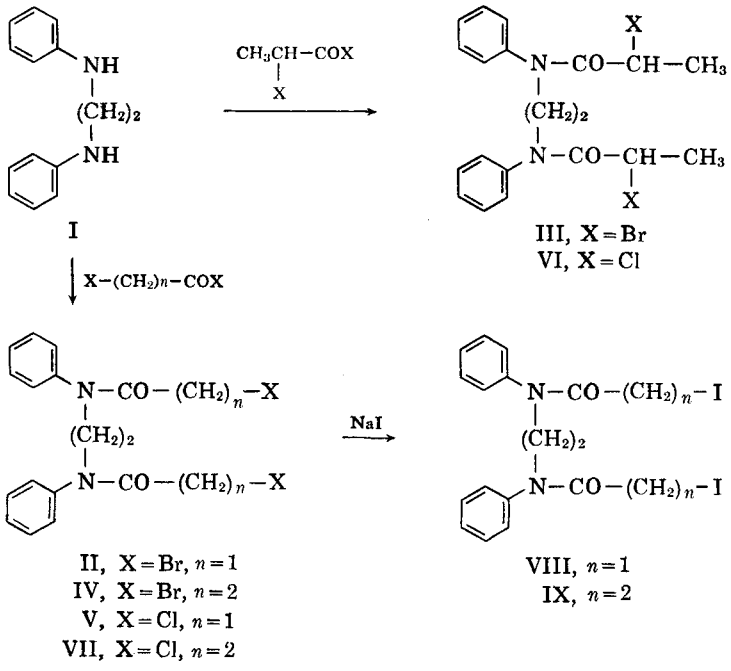
Several bis-haloacyl derivatives of *N,N'*-diphenylethylenediamine have been prepared for the purpose of evaluating their possible antineoplastic activity.

BASED ON the report by Carbon and co-workers (1) that certain bis-haloamides demonstrate antitumor activity, a group of diphenamide analogs (2) and a series of *N*-haloacyl derivatives of α,α-diphenyl-4-piperidinemethanol (3) have been previously reported. Preliminary antitumor screening results obtained in our laboratory show these compounds to have a high order of activity against the solid and ascites forms of Ehrlich tumor in C3H mice. The compounds reported here are haloacetyl and halopropionyl derivatives of *N,N'*-diphenylethylenediamine. Such compounds may interfere with vital enzymatic systems or nucleic acids within a cancer cell (4–9).

Peck *et al.* (10) studied the activity of several mono- and bifunctional nitrogen mustard analogs of acridine and quinoline amides and reported their effectiveness against Ehrlich ascites tumor. Sass *et al.* (11) reported the synthesis of difunctional bromo- and iodothioamides which show promise in cancer chemotherapy. The inhibition of Ehrlich ascites carcinoma and Sarcoma 180 by *N,N*-bis-(2-haloethyl)aliphatic amides was demonstrated by Gazza (12).

DISCUSSION

The synthetic procedure employed for the preparation of these derivatives of *N,N'*-diphenylethylenediamine may be outlined as follows. An anhydrous benzene solution of *N,N'*-diphenylethylenediamine (I) was treated with bromoacetyl bromide, 2-bromopropionyl bromide, and 3-bromopropionyl chloride to give *N,N'*-bis(bromoacetyl)-*N,N'*-diphenylethylenediamine, *N,N'* - bis(2 - bromopropionyl)-*N,N'*-diphenylethylenediamine, and *N,N'*-bis(3 - bromopropionyl) - *N,N'* - diphenylethylenediamine (compounds II, III, and IV, respectively). Treatment of the diamine (I) with chloroacetyl chloride, 2-chloropropionyl chloride, and 3-chloropropionyl chloride yielded *N,N'*-bis(chloroacetyl)-*N,N'*-diphenylethylenediamine (V), (*N,N'*-bis(chloropropionyl)-*N,N'*-diphenylethylenediamine (VI), and *N,N'*-bis-(3-chloropropionyl) - *N,N'* - diphenylethylenediamine (VII), respectively. Compound V was reported by Clark and Hams (13) to have fungicidal activity. The iodo analogs, *N,N'*-bis(iodoacetyl)-*N,N'*-diphenylethylenediamine (VIII) and *N,N'*-bis(3 - iodopropionyl) - *N,N'* - diphenylethylenediamine (IX), were synthesized by treating compounds



Scheme I

V and IV, respectively, with sodium iodide in acetone solution. (Scheme I.)

EXPERIMENTAL

The procedure used for the synthesis of the bromo and chloro analogs was similar to that described by Clark and Hams (13).

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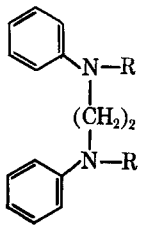
TABLE I.—*N,N'*-BIS(BROMOACYL) AND *N,N'*-(CHLOROACYL)AMIDES



Compd.	R[a]	M.p., °C.	Yield, %	Anal. Calcd.	Anal. Found
II	—$COCH_2$—Br	135–136	80	C, 47.60 H, 3.99 Br, 35.19 N, 6.17	C, 47.65 H, 4.02 Br, 35.23 N, 6.20
III	—$COCH(Br)CH_3$	183–185	75	C, 49.81 H, 4.60 Br, 33.14 N, 5.81	C, 49.90 H, 4.63 Br, 33.25 N, 5.89
IV	—$CO(CH_2)_2Br$	159–160	88	C, 49.81 H, 4.60 Br, 33.14 N, 5.81	C, 49.88 H, 4.59 Br, 33.20 N, 5.79
V	—$COCH_2$—Cl	153–154	84	C, 59.19 H, 4.97 Cl, 19.41 N, 7.67	C, 59.23 H, 4.95 Cl, 19.50 N, 7.60
VI	—$COCH(Cl)CH_3$	192–193	76	C, 61.07 H, 5.64 Cl, 18.03 N, 7.12	C, 61.01 H, 5.70 Cl, 18.15 N, 7.05
VII	—$CO(CH_2)_2Cl$	169–170	87	C, 61.07 H, 5.64 Cl, 18.03 N, 7.12	C, 61.00 H, 5.69 Cl, 17.99 N, 7.20

[a] The infrared spectra of all compounds were as expected [ν in cm.$^{-1}$ (KBr): 1650–1640 (C=O amide)].

General Method of Synthesis of N,N'-Bis(bromoacyl) and N,N'-Bis(chloroacyl)amides.—To a solution of 2.1 Gm. (0.01 mole) of *N,N'*-diphenylethylenediamine (I) in 25 ml. of anhydrous benzene was added in a dropwise manner 0.04 mole of haloacyl halide (in 25 ml. of anhydrous benzene). When the addition of the acyl halide was complete, the reaction mixture was placed in an oil bath and refluxed until the evolution of hydrogen halide had ceased. The solvent was removed *in vacuo* and the crude haloamide removed by filtration. The crude product was crystallized twice from ethanol–water to give the pure products in Table I.

N,N' - Bis(iodoacetyl) - N,N' - diphenylethylenediamine (VIII).—To an acetone solution of 3.6 Gm. (0.01 mole) of *N,N'*-bis(chloroacetyl)-*N,N'*-diphenylethylenediamine (V) was added 4.0 Gm. (0.026 mole) of an acetone solution of sodium iodide (previously dried at 120°). The reaction mixture was allowed to stand at room temperature for approximately 15 min., and then heated on a water bath at 50–60° for 1 hr. The solution was filtered while warm through a warm Büchner funnel and the filtrate was concentrated *in vacuo*. On the addition of a small amount of water and subsequent cooling, the crude iodoamide crystallized. The crude product was crystallized twice from ethanol–water to give 4.4 Gm. (80%) of pure iodoamide melting at 140–141°. ν cm.$^{-1}$ (KBr): 1640 (C=O amide).

Anal.–Calcd. for $C_{18}H_{18}I_2N_2O_2$: C, 39.44; H, 3.31; I, 46.30; N, 5.11. Found: C, 39.50; H, 3.42; I, 46.45; N, 5.18.

N,N' - Bis(3-iodopropionyl) - N,N' - diphenylethylenediamine (IX).—The procedure was the same as that used for the iodoacetyl analog (VIII). An acetone solution containing 4.8 Gm. (0.01 mole) of *N,N'*-bis(3-bromopropionyl)-*N,N'*-diphenylethylenediamine (IV) and 4.0 Gm. (0.026 mole) of sodium iodide in acetone was heated on a water bath at 50–60° for 1 hr. The pure product, isolated as before, weighed 4.3 Gm. (75%) and melted at 167–168°. ν cm.$^{-1}$ (KBr): 1640 (C=O amide).

Anal.—Calcd. for $C_{20}H_{22}I_2N_2O_2$: C, 41.68; H, 3.85; I, 44.05; N, 4.86. Found: C, 41.73; H, 3.79; I, 44.15; N, 4.80.

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