New Compounds: Synthesis of *N*-Haloacyl Analogs of 1-(*N*-β-Hydroxyethyl-4-piperidyl)-3-(4-piperidyl)propane as Potential Antineoplastic Agents

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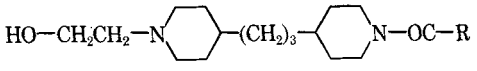
A series of haloamide analogs of 1-(*N*-β-hydroxyethyl - 4 - piperidyl) - 3 - (4 - piperidyl)propane has been synthesized for the purpose of studying their potential anticarcinogenic activity.

DURING THE past few years a number of potential mono- and difunctional alkylating agents have been prepared in this laboratory for the purpose of studying chemotherapeutic activity-structure relationships in regard to their value as antineoplastic agents. Based upon the experimental observations obtained in this laboratory (1–4) and those of other investigators (5–9), the synthesis of haloacetyl and halopropionyl derivatives of 1-(*N* - β - hydroxyethyl - 4 - piperidyl) - 3 - (4 - piperidyl)propane was undertaken.

It is theoretically possible that these compounds interfere with vital enzymatic systems or nucleic acids within a cancer cell through reversible and/or irreversible bonding to amine, sulfhydryl, or phosphoryl groups under physiological conditions. As noted by Triggle (10), the specificity of chemotherapeutic alkylating agents probably will reside in the carrier portion of the structure rather than in the alkylating moiety. Through this and following studies it is hoped that some additional information regarding the definition of the carrier moiety and specificity of action will be forthcoming, and that a structure will evolve which will possess a selective action against tumor cells.

TABLE I—*N*-HALOACYL ANALOGS OF 1-(*N*-β-HYDROXYETHYL)-4-PIPERIDYL-3-(4-PIPERIDYL)PROPANE



R	M.p., °C.	Yield, %	Anal. Calcd.	Anal. Found	Infrared cm.⁻¹ (KBr) (C=O Amide)	Infrared cm.⁻¹ (KBr) (OH)
—CH_2Cl	55–56	85	C, 61.70 H, 9.44 Cl, 10.71 N, 8.46	C, 61.65 H, 9.40 Cl, 10.80 N, 8.40	1650	3450
—CH_2CH_2Cl	88–89	79	C, 62.68 H, 9.64 Cl, 10.28 N, 8.12	C, 62.75 H, 9.69 Cl, 10.35 N, 8.02	1630	3450
—$CH(Cl)CH_3$	49–50	68	C, 62.68 H, 9.64 Cl, 10.28 N, 8.12	C, 62.60 H, 9.59 Cl, 10.30 N, 8.19	1640	3450
—CH_2Br	58–59	84	C, 54.40 H, 8.32 Br, 21.28 N, 7.46	C, 54.51 H, 8.40 Br, 21.19 N, 7.40	1640	3450
—CH_2CH_2Br	96–97	80	C, 55.52 H, 8.54 Br, 20.52 N, 7.19	C, 55.50 H, 8.60 Br, 20.45 N, 7.09	1630	3450
—$CH(Br)CH_3$	47–48	72	C, 55.52 H, 8.54 Br, 20.52 N, 7.19	C, 55.60 H, 8.50 Br, 20.59 N, 7.26	1640	3450
—CH_2I	59–60	80	C, 48.34 H, 7.40 I, 30.04 N, 6.64	C, 48.42 H, 7.45 I, 29.95 N, 6.59	1640	3450
—CH_2CH_2I	91–92	75	C, 49.54 H, 7.62 I, 29.08 N, 6.42	C, 49.51 H, 7.59 I, 29.19 N, 6.29	1640	3450

EXPERIMENTAL

The synthetic scheme for the preparation of the analogs of 1-(*N*-β-hydroxyethyl-4-piperidyl)-3-(4-piperidyl)propane[1] may be summarized as follows. (Scheme I.) To a solution of 5.02 Gm. (0.02 mole) of the parent amine (I) in 15 ml. of anhydrous

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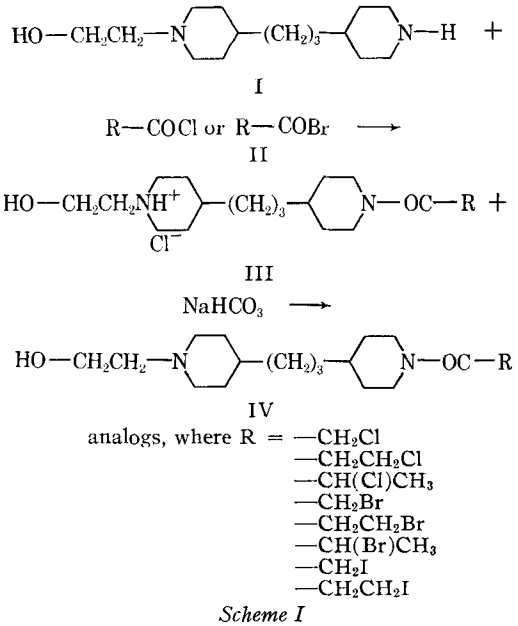
[1] Supplied by Reilly Tar and Chemical Corp., Indianapolis, Ind.



Scheme I

chloroform was added 0.02 mole of the haloacyl halide (II) (in anhydrous chloroform). An exothermic reaction occurred as the acylating agent was added dropwise at room temperature. When the addition of the acylating agent (II) was complete, the reaction mixture was refluxed for 30 to 60 min. The chloroform was evaporated *in vacuo*, and the solid remaining was dissolved in a minimum amount of absolute ethanol and the *in vacuo* evaporation operation repeated. The solid (III), a hygroscopic hydrochloride or hydrobromide salt, was treated with sodium bicarbonate and chloroform to give the crude product. The crude haloamides were recrystallized twice from aqueous ethanol to give the pure products listed in Table I. The iodoamides were synthesized as previously reported (1).

The infrared spectra of the compounds were obtained with a Perkin-Elmer Infracord. The melting points were determined with a Fisher-Johns melting point apparatus and are corrected values.

DISCUSSION AND RESULTS

The series of eight derivatives prepared in this work are: 1-(*N*-β-hydroxyethyl-4-piperidyl)-3-(*N*-chloroacetyl - 4 - piperidyl)propane, 1 - (*N* - β - hydroxyethyl - 4 - piperidyl) - 3 - (*N* - bromoacetyl-4 - piperidyl)propane, 1 - (*N* - β - hydroxyethyl - 4 - piperidyl) - 3 - (*N* - bromoacetyl - 4 - piperidyl)-propane, 1 - (*N* - β - hydroxyethyl - 4 - piperidyl) - 3 - (*N* - iodoacetyl - 4 - piperidyl)propane, 1 - (*N* - β - hydroxyethyl - 4 - piperidyl) - 3 - (*N* - β - chloropropionyl - 4 - piperidyl)propane, 1 - (*N* - β - hydroxyethyl - 4 - piperidyl) - 3 - (*N* - β - bromopropionyl - 4 - piperidyl)propane, 1 - (*N* - β - hydroxyethyl - 4 - piperidyl) - 3 - (*N* - β - iodopropionyl-4 - piperidyl)propane, 1 - (*N* - β - hydroxyethyl - 4-piperidyl) - 3 - (*N* - α - chloropropionyl - 4 - piperidyl)propane, and 1 - (*N* - β - hydroxyethyl - 4 - piperidyl) - 3 - (*N* - α - bromopropionyl - 4 - piperidyl)propane.

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