REFERENCES

(1) Haines, B. A., and Martin, A. N., THIS JOURNAL, 50, 228(1961).
(2) Hiestand, E. N., *ibid.*, 53, 1(1964).
(3) Hiestand, E. N., *Proc. Am. Assoc. Colleges Pharm. Teachers' Seminar*, 13, 125(1961).
(4) Gillespie, T., *J. Phys. Chem.*, 66, 1077(1962).
(5) Gillespie, T., *J. Colloid Sci.*, 15, 219(1960).
(6) Goodeve, C. F., *Trans. Faraday Soc.*, 35, 342(1939).
(7) Smoluchowski, M. v., *Z. Physik. Chem. (Leipzig)*, 92, 129(1917).
(8) Sheth, B. B., "Rheology of Pharmaceutical Emulsions," Ph.D. Thesis, University of Michigan, Ann Arbor, August 1960.
(9) Verwey, E. J. W., and Overbeek, J. Th. G., "Theory of the Stability of Lyophobic Colloids," Elsevier Publishing Co., Amsterdam, The Netherlands, 1948.

Synthesis of Several *N*-Haloacyl Analogs of α,α-Diphenyl-4-piperidinemethanol as Potential Antineoplastic Agents

By WILLIAM D. ROLL

Eight new derivatives of α,α-diphenyl-4-piperidinemethanol have been prepared to evaluate their anticarcinogenic activity: 1-(3-chloropropionyl)-α,α-diphenyl-4-piperidinemethanol, 1-(2-chloropropionyl)-α,α-diphenyl-4-piperidinemethanol, 1-chloroacetyl-α,α-diphenyl-4-piperidinemethanol, 1-(3-bromopropionyl)-α,α-diphenyl-4-piperidinemethanol, 1-(2-bromopropionyl)-α,α-diphenyl-4-piperidinemethanol, 1-bromoacetyl-α,α-diphenyl-4-piperidinemethanol, 1-(3-iodopropionyl)-α,α-diphenyl-4-piperidinemethanol, and 1-iodoacetyl-α,α-diphenyl-4-piperidinemethanol.

A SERIES OF derivatives of α,α-diphenyl-4-piperidinemethanol were synthesized to evaluate their possible antineoplastic activity. This report describes the synthesis of some *N*-haloacyl analogs of this amine.

Based on the report by Carbon and co-workers (1) that various bis-haloamides demonstrate antitumor activity, a group of diphenamide derivatives have been reported previously (2). The compounds reported herein are halopropionyl and haloacetyl derivatives of a 4-aralkylpiperidine. Theoretically, it is possible that such compounds might interfere with vital enzymatic systems or nucleic acids within a cancer cell through reversible and/or irreversible bonding by one of the following mechanisms (3–8):

1, $E{-}NH_2 + R_2N{-}CH_2CH_2{-}X \rightarrow E{-}NH{-}CH_2CH_2{-}NR_2$

2, $E{-}SR + R{-}NH{-}\overset{\overset{O}{\|}}{C}{-}CH_2{-}X \rightarrow E{-}S(R){-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}NHR$

3, $\equiv P{-}O^{\ominus} + R_2N{-}CH_2CH_2{-}X \rightarrow \equiv P{-}O{-}CH_2CH_2{-}NR_2$

4, $\equiv N + R_2N{-}CH_2CH_2{-}X \rightarrow \equiv N^{\oplus}\cdot CH_2CH_2{-}NR_2$

Baker *et al.* (9, 10) presented evidence for the inactivation of lactic dehydrogenase (LDH) and glutamic dehydrogenase (GDH) by 4-(iodoacetamido)salicylic acid by active-site-directed irreversible inhibition. It is known that LDH occurs in glycolyzing cells (11–13), and it has been studied extensively to establish some relationship to neoplastic disorders. Elevated levels of LDH have been reported in many cancerous conditions. Hill and Levi (14) and Bodanski (15) reported abnormal LDH levels in leukemia; Bierman *et al.* (16) reported abnormal levels in relation to lymphomas and leukemia; and Schenker (17) and Wroblewski (18) reported abnormal lactic dehydrogenase levels in body fluids in gastric cancer and central nervous system involvement by metastatic carcinoma. Busch and Nair (19) and Papaconstantinou and Colowick (20) have proposed that chemotherapeutic agents which would inhibit lactic dehydrogenase activity might be a factor in cancer chemotherapy, since lactic acid formation is a characteristic of neoplastic tissue. Potter (21) stated that the inhibition of some enzymes leads to the failure of hydrogen transport within the internal structure of the malignant cell. Wheeler and Alexander (22) re-

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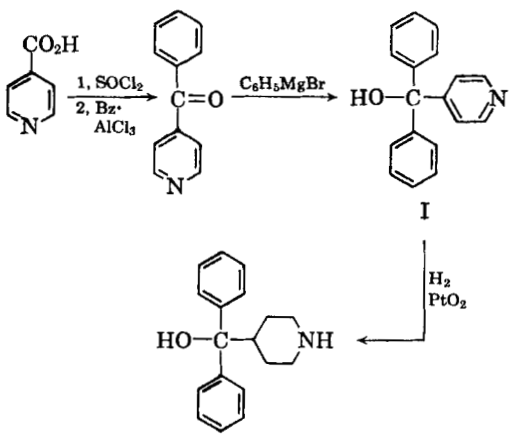
ported that treatment of either desoxyribonuclease or desoxyribonucleic acid with alkylating agents resulted in inhibition.

The synthetic procedure used for the preparation of these analogs of α,α-diphenyl-4-piperidinemethanol may be outlined briefly as follows. α,α-Diphenyl-4-pyridylcarbinol (I), synthesized by the procedure described by Villani *et al.* (23), was converted to α,α-diphenyl-4-piperidinemethanol (II) by a procedure similar to that described by Schumann *et al.* (24). Treatment of the aralkylpiperidine (II) with 3-chloropropionyl chloride, 2-chloropropionyl chloride, and chloroacetyl chloride gave 1-(3-chloropropionyl)-α,α-diphenyl-4-piperidinemethanol (III), 1-(2-chloropropionyl) - α,α - diphenyl - 4 - piperidinemethanol (IV), and 1-chloroacetyl-α,α-diphenyl-4-piperidinemethanol (V), respectively. Treatment of II with 3-bromopropionyl chloride, 2-bromopropionyl bromide, and bromoacetyl bromide yielded 1-(3-bromopropionyl)-α,α-diphenyl-4-piperidinemethanol, 1-(2-bromopropionyl)-α,α-diphenyl-4-piperidinemethanol, and 1-bromoacetyl-α,α-diphenyl-4-piperidinemethanol, compounds VI, VII, and VIII, respectively. The synthetic procedure used for the preparation of III through VIII was similar to that described in an earlier paper (2).



Scheme I

To introduce the 3-iodopropionyl and iodoacetyl groups, 1-(3-chloropropionyl)-α,α-diphenyl-4-piperidinemethanol (III) and 1-chloroacetyl-α,α-diphenyl-4-piperidinemethanol (V) were treated with sodium iodide in acetone. The products were 1-(3-iodopropionyl)-α,α-diphenyl-4-piperidinemethanol (IX) and 1-iodoacetyl-α,α-diphenyl-4-piperidinemethanol (X).

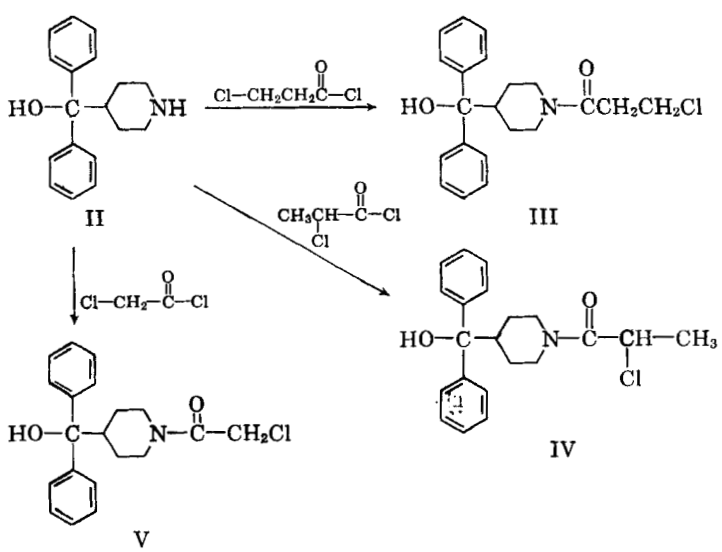
Compounds IX and X were also synthesized by treating the amine, compound II, with the corresponding acyl chlorides (iodoacetyl chloride and 3-iodopropionyl chloride). However, a higher yield and a purer product was obtained by the above procedure.

Preliminary pharmacological studies indicate that the haloacetyl analogs have an approximate LD_{50} of 600 mg./Kg. in mice, and the halopropionamide derivatives appear to be less toxic.

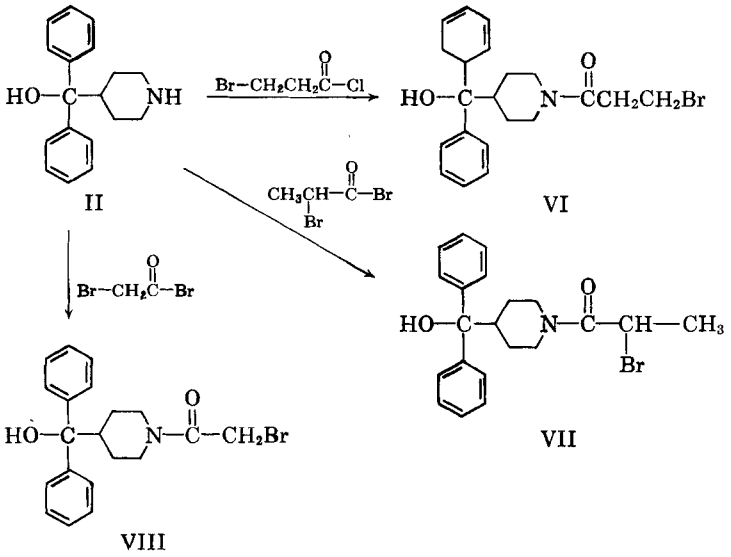
EXPERIMENTAL

The sequence of synthetic reactions is shown by Schemes I, II, III, and IV.

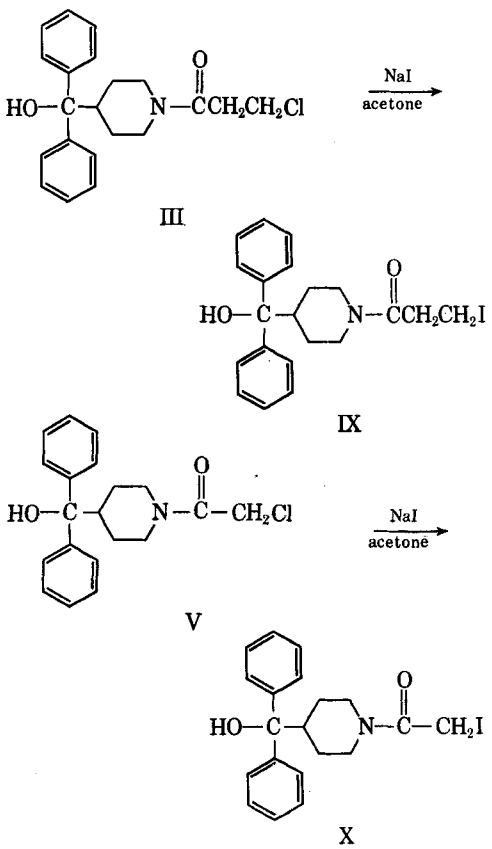
α,α-Diphenyl-4-pyridylcarbinol (I).—The procedure used for the synthesis of this intermediate



Scheme II



Scheme III



Scheme IV

was that described by Villani *et al.* (23), m.p. 235–236°.

α,α-Diphenyl-4-piperidinemethanol (II).—The synthetic procedure was that of Schumann *et al.* (24), m.p. 160° (HCl salt, m.p. 280–283°).

1 - (3 - Chloropropionyl) - α,α - diphenyl - 4-piperidinemethanol (III).—To a solution of 2.8 Gm. (0.01 mole) of II in 50 ml. of anhydrous chloroform was added in a dropwise manner 2.5 Gm. (0.02 mole) of 3-chloropropionyl chloride (in anhydrous chloroform). When the addition of the acyl chloride was complete, the reaction mixture was refluxed until the evolution of hydrogen chloride had ceased. The reaction mixture was concentrated *in vacuo* and the crude haloamide removed by filtration. The crude material was crystallized twice from methanol–water to give 3.2 Gm. (90%) of product, melting at 108–110°. γ in cm.$^{-1}$ (KBr): 3400 (OH); 1640 (C=O amide).

Anal.—Calcd. for $C_{21}H_{24}ClNO_2$: C, 70.51; H, 6.76; Cl, 9.91; N, 3.91. Found: C, 70.60; H, 6.73; Cl, 9.98; N, 3.88.

1 - (2 - Chloropropionyl) - α,α - diphenyl - 4-piperidinemethanol (IV).—The same procedure and identical quantities of reagents were used for the synthesis of compound IV as described under *compound III.* The product was crystallized from methanol–water to give 3.0 Gm. (83%) of product, melting at 197–198°. γ in cm.$^{-1}$ (KBr): 3400 (OH); 1640 (C=O amide).

Anal.—Calcd. for $C_{21}H_{24}ClNO_2$: C, 70.51; H, 6.76; Cl, 9.91; N, 3.91. Found: C, 70.57; H, 6.74; Cl, 9.94; N, 4.00.

1 - Chloroacetyl - α,α - diphenyl - 4 - piperidinemethanol (V).—The same procedure described for the preparation of the chloropropionyl analogs was used. To a solution of 2.8 Gm. (0.01 mole) of com-

pound II in 50 ml. of anhydrous chloroform was added a chloroformic solution of 2.3 Gm. (0.02 mole) of chloroacetyl chloride; when the addition of the latter was complete, the reaction mixture was refluxed until the evolution of HCl had ceased. The crude amide was crystallized twice from methanol–water. The product weighed 3.3 Gm. (96%) and melted at 121–122°. γ in cm.$^{-1}$ (KBr): 3400 (OH); 1640 (C=O amide).

Anal.—Calcd. for $C_{20}H_{22}ClNO_2$: C, 69.86; H, 6.45; Cl, 10.31; N, 4.07. Found: C, 69.90; H, 6.50; Cl, 10.40; N, 4.10.

1 - (3 - Bromopropionyl) - α,α - diphenyl - 4-piperidinemethanol (VI).—A solution of 3.8 Gm. (0.02 mole) of 3-bromopropionyl chloride in anhydrous chloroform was added dropwise to a 2.8 Gm. (0.01 mole) solution of the amine (II) in anhydrous chloroform at room temperature. When the addition of the acyl halide was complete, the reaction mixture was refluxed until the evolution of hydrogen chloride had ceased. The reaction mixture was concentrated *in vacuo* and the crude haloamide removed on a Büchner funnel and washed several times with cold water. The crude material was crystallized twice from methanol–water to give 3.4 Gm. (84%) of product melting at 109–110°. γ cm.$^{-1}$ (KBr): 3400 (OH); 1630 (C=O amide).

Anal.—Calcd. for $C_{21}H_{24}BrNO_2$: C, 62.69; H, 6.01; Br, 19.86; N, 3.48. Found: C, 62.73; H, 5.99; Br, 19.90; N, 3.53.

1 - (2 - Bromopropionyl) - α,α - diphenyl - 4-piperidinemethanol (VII).—A solution of 2.8 Gm. (0.01 mole) of the amine (II) in anhydrous chloroform was cooled to 5°. A chloroformic (dry) solution of 4.3 Gm. (0.02 mole) of 2-bromopropionyl bromide, previously cooled to 5°, was added to this in a dropwise manner. When the addition of the haloacyl halide was complete, the mixture was refluxed until the evolvement of hydrogen bromide was no longer apparent. The reaction mixture was concentrated *in vacuo* and the crude amide removed by filtration. Two recrystallizations of the crude material from aqueous methanol gave 1.2 Gm. (79%) of pure product, melting at 100–101°. γ in cm.$^{-1}$ (KBr): 3400 (OH); 1670 (C=O amide).

Anal.—Calcd. for $C_{21}H_{24}BrNO_2$: C, 62.69; H, 6.01; Br, 19.86; N, 3.48. Found: C, 62.60; H, 6.04; Br, 19.90; N, 3.51.

1 - Bromoacetyl - α,α - diphenyl - 4 - piperidinemethanol (VIII).—The procedure described under *compound VII* was employed. To a 2.8 Gm. (0.01 mole) solution of the amine (II) in anhydrous chloroform was added 4.0 Gm. (0.02 mole) of bromoacetyl bromide (in anhydrous chloroform). The crude amide was isolated as previously described; after two recrystallizations from methanol–water, the pure product weighed 3.3 Gm. (85%) and melted at 143–145°. γ in cm.$^{-1}$ (KBr): 3400 (OH); 1640 (C=O amide).

Anal.—Calcd. for $C_{20}H_{22}BrNO_2$: C, 61.88; H, 5.72; Br, 20.59; N, 3.61. Found: C, 61.95; H, 5.75; Br, 20.65; N, 3.57.

1 - (3 - Iodopropionyl) - α,α - diphenyl - 4-piperidinemethanol (IX).—To an acetone solution of 3.6 Gm. (0.01 mole) of 1-(3-chloropropionyl)-α,α-diphenyl-4-piperidinemethanol (III) was added 2.0 Gm. (0.013 mole) of an acetone solution of sodium iodide (previously dried at 120°). The reaction mixture was heated on a water bath at 50–60° for a period of 1 hour. The solution was filtered while warm through a Büchner funnel, and the filtrate was concentrated *in vacuo*. On the addition of water and subsequent cooling, the crude iodoamide crystallized. After two recrystallizations from ethanol–water, the pure product melted at 96–97°; yield, 3.6 Gm. (80%). γ in cm.$^{-1}$ (KBr): 3400 (OH); 1640 (C=O amide).

Anal.—Calcd. for $C_{21}H_{24}INO_2$: C, 56.13; H, 5.38; I, 28.24; N, 3.12. Found: C, 56.19; H, 5.40; I, 28.18; N, 3.18.

1 - Iodoacetyl - α,α - diphenyl - 4 - piperidinemethanol (X).—The synthetic procedure was the same as that described under *compound IX*. An acetone solution containing 3.4 Gm. (0.01 mole) of 1 - chloroacetyl - α,α - diphenyl - 4 - piperidinemethanol (V) and 2.0 Gm. (0.013 mole) of sodium iodide was heated on a water bath at 50–60° for 1 hour. The pure product, isolated as described under *compound IX*, weighed 3.7 Gm. (82%) and melted at 137–138°. γ in cm.$^{-1}$ (KBr): 3400 (OH); 1640 (C=O amide).

Anal.—Calcd. for $C_{20}H_{22}INO_2$: C, 55.18; H, 5.09; I, 29.15; N, 3.22. Found: C, 55.09; H, 5.10; I, 29.20; N, 3.28.

REFERENCES

(1) Carbon, J. A., Brehm, S. M., and Ratajczyk, J. S., Abstracts presented to the American Chemical Society, St. Louis, Mo., meeting, March 1961, p. 11-N.
(2) Roll, W. D., THIS JOURNAL, **53**, 686(1964).
(3) Ross, W. C. J., *Ann. N. Y. Acad. Sci.*, **68**, 669(1958).
(4) Stacy, K. A., *et al.*, *ibid.*, **68**, 682(1958).
(5) Lawley, P. D., *Ann. Rept. Brit. Emp. Cancer Campaign*, **36**, 16(1958).
(6) Lawley, P. D., and Brookes, P., *ibid.*, **38**, 3(1960).
(7) Lawson, W. B., and Schramm, H. J., *J. Am. Chem. Soc.*, **84**, 2017(1962).
(8) Gundlach, G., and Turba, F., *Biochem. Z.*, **335**, 573 (1962).
(9) Baker, B. R., *et al.*, *J. Am. Chem. Soc.*, **83**, 3713 (1961).
(10) Baker, B. R., Lee, W. W., and Tong, E., *J. Theoret. Biol.*, **3**, 459(1962).
(11) Long, C., King, E. J., and Sperry, W. M., "Biochemists Handbook," E. and F. Spon Ltd., London, 1961.
(12) Fishman, W. H., "The Physiopathology of Cancer," 2nd ed., Paul B. Hoeber, Inc., New York, N. Y., 1960, pp. 732–760.
(13) Fishman, W. H., "The Plasma Protein," Vol. 2, Academic Press Inc., New York, N. Y., 1960, pp. 59–103.
(14) Hill, B. R., and Levi, C., *Cancer Res.*, **14**, 513(1954).
(15) Bodanski, O., "Advances in Cancer Research," Vol. 6, Academic Press Inc., New York, N. Y., 1961, pp. 1–80.
(16) Bierman, H. R., *et al.*, *Cancer Res.*, **17**, 660(1957).
(17) Schenker, S., *Am. J. Digest. Diseases, NS* **4**, 412(1959).
(18) Wroblewski, F., Decker, B., and Wroblewski, R., *Am. J. Clin. Pathol.*, **28**, 269(1957).
(19) Busch, H., and Nair, P. V., *J. Biol. Chem.*, **229**, 377 (1957).
(20) Papaconstantinou, J., and Colowick, S. P., *ibid.*, **236**, 278, 285(1961).
(21) Potter, V. R., *Federation Proc.*, **17**, 691(1958).
(22) Wheeler, G. P., and Alexander, J. A., *Arch. Biochem.*, **72**, 476(1957).
(23) Villani, F. J., King, M. S., and Papa, D., *J. Org. Chem.*, **17**, 249(1952).
(24) Schumann, E. L., Van Campen, M. G., Jr., and Pogge, R. C., U. S. pat. 2,804,422(August 27, 1957); through *Chem. Abstr.*, **52**, 1558*f*(1958).