ether. It formed yellowish small plates or large irregular prisms melting at 213–214°, resolidifying and melting again at 221–222°.

*Anal.* Calcd. for $C_{19}H_{20}N_3OCl$: C, 66.76; H, 5.90. Found: C, 66.28; H, 5.35.

*Hydrochloride.* A suspension of the base in methanol was neutralized with an equivalent amount of 5*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol and separate ether. The hydrochloride formed colorless flat needles melting at 187–189°.

*Anal.* Calcd. for $C_{19}H_{21}N_3OCl_2$: C, 60.32; H, 5.60. Found: C, 60.28; H, 6.05.

The mother liquor after the separation of the benzodiazepine *N*-oxide (XIIb) described above was concentrated *in vacuo* and the residue crystallized from a mixture of ether and petroleum ether yielding 4 g. of yellowish crystals melting at 103–104°. After recrystallization from petroleum ether the quinazoline *N*-oxide (XIIId)[3] formed rosettes of yellowish needles melting at 106–107°.

*Anal.* Calcd. for $C_{19}H_{20}N_3OCl$: C, 66.76; H, 5.90. Found: C, 66.77; H, 6.11.

*Hydrochloride.* A suspension of the base in methanol was neutralized with the equivalent amount of 5*N* methanolic hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of methanol, acetone, and petroleum ether. The hydrochloride formed fine white needles melting at 187–189°. It gave a melting point depression with the hydrochloride of the isomeric benzodiazepine *N*-oxide (XIIb).

*Anal.* Calcd. for $C_{19}H_{21}N_3OCl_2$: C, 60.32; H, 5.60. Found: C, 60.23; H, 5.54.

*6-Chloro-2-dimethylaminomethyl-4-phenylquinazoline 3-oxide* (XIVa). A solution of 100 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in 250 cc. of dioxane was added to 150 cc. of a 50% solution of dimethylamine in dioxane. The mixture was left at room temperature for 20 hr., cooled with ice, acidified with 3*N* hydrochloric acid, and extracted with ether to remove neutral impurities. The aqueous layer was then made alkaline with 50% potassium hydroxide (ice was added to keep the mixture cold) and extracted with benzene. The benzene layer was dried with sodium sulfate, concentrated *in vacuo* to a small volume, and diluted with petroleum ether. The crystalline precipitate was recrystallized from a mixture of acetone and petroleum ether. It formed fine yellowish needles melting at 133–134°. The yield was 93 g. (90%).

*Anal.* Calcd. for $C_{17}H_{16}N_3OCl$: C, 65.07; H, 5.14. Found: C, 65.44; H, 4.86.

*Hydrochloride monohydrate.* A solution of the base in methanol was neutralized with 1*N* hydrochloric acid. The solution was concentrated *in vacuo* and the residue crystallized from a mixture of isopropyl alcohol and ether. The salt formed yellowish needles melting at 172–173°.

*Anal.* Calcd. for $C_{17}H_{19}N_3O_2Cl$: C, 55.45; H, 5.20. Found: C, 55.79; H, 5.30.

*6-Chloro-2-(1-piperazinylmethyl)-4-phenylquinazoline 3-oxide* (XIVb). A suspension of 15 g. of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I) in a solution of 30 g. of piperazine hydrate in 250 cc. of methanol was stirred for 20 hr. The precipitated reaction product was filtered off, the filtrate was concentrated *in vacuo*, combined with the precipitate, and dissolved in hydrochloric acid. The acidic solution was washed with methylene chloride and insoluble impurities were filtered off. The aqueous solution was cooled, made alkaline, and the reaction product extracted with methylene chloride. The organic solution was dried, partially concentrated *in vacuo*, and diluted with ether. The reaction product precipitated in yellowish prisms (10.2 g.) melting at 174–175°. After recrystallization from hot benzene with the addition of ether and petroleum ether, the product formed long flat prisms or plates melting at 175–176°. The infrared spectrum showed that the compound had the quinazoline 3-oxide structure.

*Anal.* Calcd. for $C_{19}H_{19}OClN_4$: C, 64.31; H, 5.40. Found: C, 64.60; H, 5.33.

*Dihydrochloride.* The base was dissolved in the calculated amount of 0.5*N* methanolic hydrochloric acid and the salt was precipitated by the addition of ether and petroleum ether. It can be recrystallized from methanol, containing a small amount of water, and ether. It formed colorless plates melting at 178–180°.

*Anal.* Calcd. for $C_{19}H_{21}OCl_3N_4$: C, 53.35; H, 4.95. Found: C, 52.88; H, 5.41.

*Acknowledgment.* We are indebted to Dr. L. O. Randall and his co-workers for the pharmacological information, to Dr. A. Motchane, Mr. S. Traiman, and Dr. V. Toome for the infrared and ultraviolet spectra, and to Dr. Al Steyermark and his staff for the microanalyses. Mr. L. A. Dolan was helpful in the preparation of larger amounts of starting materials and intermediates.

NUTLEY 10, N. J.

---

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE]

# New 5-Substituted 6-Azauracils[1]

PAULINE K. CHANG

*Received July 7, 1960*

The 5-position of 6-azauracil (*asym*-triazine-3,5-dione) may be halogenated to yield the 5-chloro, 5-bromo, and 5-iodo derivatives. By reaction of 5-bromo-6-azauracil with molten ammonium acetate, 5-amino-6-azauracil was obtained. 5-Hydroxy-6-azauracil was prepared from the amino compound by basic hydrolysis or by reaction with nitrous acid. The acid dissociation constants, ultraviolet spectra, and infrared spectra were measured.

Recent work on the antitumor activity of 6-azauracil (*asym*-triazine-3,5-dione,1)[2,3] has suggested that its various derivatives substituted at the 5-position might have biological interest. For

(1) This work was supported by a grant (CY-2817) from the National Cancer Institute, Public Health Service. Presented in part before the Division of Medicinal Chemistry, 136th Meeting of the American Chemical Society, September 1959, Atlantic City, N. J.

(2) M. T. Hakala, L. W. Law, and A. D. Welch, *Proc. Amer. Assoc. Cancer Research*, 2, 113 (1956).

(3) J. J. Jaffe, R. E. Handschumacher, and A. D. Welch, *Yale J. Biol. & Med.*, 30, 168 (1957).

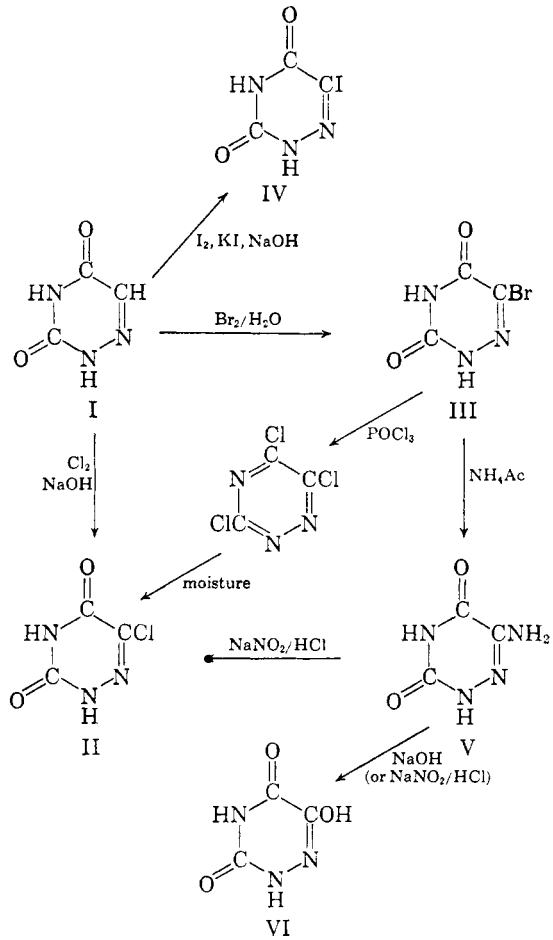
example, the 5-alkyl-6-azauracils,[4] as compared to 6-azauracil, possessed enhanced narcotic activity in mice.[5] The present paper deals with the preparation of several new 5-substituted 6-azauracils (6-substituted *asym*-triazine-3,5-dione).

Bromination of 6-azauracil was found to proceed with ease to give the 5-bromo derivative in excellent yield.[6] However, chlorination and iodination required the presence of base and the yields dropped to 40% and 15%, respectively. 5-Bromo-6-azauracil reacts with phosphorus oxychloride to give an intermediate containing neither hydrogen nor bromine; it is believed to be trichloro-*asym*-triazine,[7] which reacts with moisture instantly to give 5-chloro-6-azauracil.

When 5-bromo-6-azauracil was refluxed with molten ammonium acetate under an atmosphere of ammonia, a 50% yield of crude 5-amino-6-azauracil (V) was obtained. The amino compound underwent basic hydrolysis smoothly to give a 70% yield of 5-hydroxy-6-azauracil (*asym*-triazine-3,5,6-trione, VI). It is of interest to note that this compound is the hitherto unknown asymmetric isomer of cyanuric acid. Rätz and Schroeder report that reaction of oxamic acid hydrazide and phosgene failed to produce the desired VI.[8] A poorer yield of VI, together with an equal amount of II, could also be obtained *via* diazotization of the amino compound in concentrated hydrochloric acid. However, when the diazotization was carried out in 48% fluoboric acid in an attempt to prepare 5-fluoro-6-azauracil by a modified Schieman reaction,[9] only substances which lack absorption in the ultraviolet were isolated, suggesting that the triazene ring had been ruptured. 5-Amino-6-azauracil does not react with ethylene oxide (either in the cold or in a sealed tube at 100°) to give 5-bis(2-hydroxyethyl)-amino-6-azauracil as in the case of 5-aminouracil.[10] When 5-bromo-6-azauracil was refluxed with diethanolamine in a solution of ethylene glycol monomethyl ether, instead of the expected 5-bis(2-hydroxyethyl)-amino-6-azauracil, a one to one complex, which regenerates the starting materials upon acid treatment was obtained.

The acid dissociation constants and ultraviolet absorption spectra are shown in Table I. It can be seen that the acidity of the halogenated 6-azauracils increases from iodine to bromine to chlorine, parallel to their increasing electron-withdrawing

REACTION SCHEME




effect. The very low $pk_a$ value of 5-hydroxy-azauracil may be compared to that of 4-methyl-6-hydroxypyrimidine, which is reported to have a value of 2.15.[11]

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

| 6-Azauracil | pKa | 0.1*N* HCl max, mμ | 0.1*N* HCl $\epsilon_{max}$ | 0.1*N* NaOH max, mμ | 0.1*N* NaOH $\epsilon_{max}$ |
|---|---|---|---|---|---|
| 5-H | 6.90[4] | 258 | 5590 | 286 | 3770 |
| 5-Cl | 5.80 | 270 | 5500 | 297 | 5680 |
| 5-Br | 6.05 | 274 | 5000 | 299 | 6240 |
| 5-I | 6.27 | 291 | 5010 | 306 | 6110 |
| 5-$NH_2$ | 7.35 | 296 | 4065 | 289 | 4050 |
| 5-OH | 2.95 | 246 | 4960 | 250 | 2886 |

The infrared spectra of these *asym*-triazines all show broad peaks in the 3.0–3.6 μ region and very sharp doublets in the 5.75–5.95 μ region because of the —C(=O)—NH— groups. The substituted imine bond, which normally has a weak peak at 6.25 μ, shifts in the 6.25–6.45 μ region depending on the

(4) P. K. Chang, *J. Org. Chem.*, 23, 1951 (1958).
(5) A. D. Welch, R. E. Handschumacher, and J. J. Jaffe, unpublished data.
(6) This compound was first prepared by Dr. R. E. Handschumacher.
(7) P. K. Chang and T. L. V. Ulbricht, *J. Am. Chem. Soc.*, 80, 976 (1958).
(8) R. Rätz and H. Schroeder, *J. Org. Chem.*, 23, 2017 (1958).
(9) J. A. Montgomery and K. Hewson, *J. Am. Chem. Soc.*, 82, 463 (1960).
(10) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, 80, 6459 (1958).
(11) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1004 (1951).

substitution at the 6-position. As in the 6-alkyl-*asym*-triazine-3,5-dione series, the medium peak at 13.42–13.6 $\mu$ region may be ascribed to the ring.[4]

## EXPERIMENTAL[12]

*5-Chloro-6-azauracil* (II). This compound may be prepared by either of two methods. The first method, using 6-azauracil as the starting material, is simpler in operation.

A. *Chlorination of 6-azauracil.* A 5.65-g. sample (0.05 mole) of 6-azauracil and 8 g. (0.2 mole) of sodium hydroxide was placed in 500 ml. of water. Chlorine was bubbled through the mixture at a moderate rate at room temperature with stirring until the *p*H of the solution became 1.5. After evaporation of the solution to dryness on a water aspirator at 60°, the residue was extracted with ethyl acetate in a Soxhlet extractor. The crude 5-chloro-6-azauracil, 2.95 g., was obtained after removal of ethyl acetate (40%). After recrystallization from water, it melted at 225–227°.

*Anal.* Calcd. for $C_3H_2ClN_3O_2$: C, 24.42; H, 1.36; N, 28.48; Cl, 24.03. Found: C, 24.50; H, 1.28; N, 28.34; Cl, 23.85.

B. *Chlorination of 5-bromo-6-azauracil and hydrolysis to 5-chloro-6-azauracil.* A mixture of 5-bromo-6-azauracil (7.8 g., 0.04 mole) in 40 ml. of phosphorus oxychloride was refluxed at 125° until the mixture became homogeneous (48 hr.). Most of the excess phosphorus oxychloride was removed on a water aspirator, and the residue distilled *in vacuo* to give a colorless oil, b.p. 72°/3 mm., yield 2.2 g. (30%). The oil was added dropwise to 6 ml. of methanol. Hydrogen chloride was evolved and the solution was concentrated to give a colorless substance, 1.2 g. (70% conversion). After recrystallization from water, it melted at 225–227°.

*5-Bromo-6-azauracil* (III). A mixture of 6-azauracil (5 g., 0.026 mole), bromine (5 ml.) and water (75 ml.) was stirred with a magnetic stirrer for 27 hr. The colorless crystalline product was filtered and dried (4.7 g.). Concentration of the filtrate gave an additional 2.94 g. (total yield of 5-bromo-6-azauracil, 90%). After recrystallization from water it had m.p. 232–234°.

*Anal.* Calcd. for $C_4H_2BrN_3O_2$: C, 18.77; H, 1.05; N, 21.89; Br, 41.62. Found: C, 18.75; H, 1.04; N, 22.02; Br, 41.57.

*5-Iodo-6-azauracil* (IV). A mixture of 1.13 g. (0.01 mole) of 6-azauracil, 5 g. (0.02 mole) of iodine, 5.3 g. of potassium iodide, and 1.6 g. of sodium hydroxide in 35 ml. of water was refluxed for 40 hr. After acidification to *p*H 2 with concd. hydrochloric acid, the mixture was first extracted with carbon tetrachloride to remove excess iodine then followed by continuous extraction with ether for 24 hr. The residue after removal of the ether was taken up with 100 ml. of water, made alkaline (*p*H 10–11) with concd. ammonium hydroxide and put on a Dowex 1 (chloride) column. After washing with water, the column was eluted with 0.005*N* hydrochloric acid. 6-Azauracil was eluted first, followed by 5-iodo-6-azauracil. The residue after removal of the acid was recrystallized from water to yield 0.37 g. of 5-iodo-6-azauracil (15%), m.p. 218–220°.

*Anal.* Calcd. for $C_3H_2IN_3O_2$: C, 15.76; H, 0.84; N, 17.58. Found: C, 15.94; H, 0.92; N, 17.90.

*5-Amino-6-azauracil* (V). In a 35-ml. 3-necked flask was placed 4.8 g. (0.025 mole) of 5-bromo-6-azauracil and 6 g. of ammonium acetate. The mixture was heated in an oil bath to 170°. The solids melted and refluxed for 24 hr. under an atmosphere of ammonia. The solution was allowed to cool and taken up with 5 ml. of water. The remaining solid, crude 5-amino-6-azauracil, was filtered; yield 1.7 g. (53%). After recrystallization from water, it melted at 310–315°.

*Anal.* Calcd. for $C_3H_4N_4O_2$: C, 28.13; H, 3.14; N, 43.74. Found: C, 28.04; H, 3.19; N, 43.71.

*5-Hydroxy-6-azauracil* (VI). A solution of 256 mg. (2 mmoles) of 5-amino-6-azauracil in 10 ml. of 1*N* sodium hydroxide was refluxed for 2 hr. To the cooled solution was added 10 g. of damp Dowex 50 to remove the sodium ion. When the filtrate from the Dowex 50 was reduced to dryness on a water aspirator, 253 mg. of impure 5-hydroxy-6-azauracil was obtained. After recrystallization from water, it melted at 228–230° (70%).

*Anal.* Calcd. for $C_3H_3N_3O_3.1/2H_2O$ (sample dried at 60°/0.1 mm.): C, 26.10; H, 2.92; N, 30.47. Found: C, 26.29; H, 2.86; N, 30.02. Calcd. for $C_3H_3N_3O_3$ (sample dried at 140°/0.1 mm.): C, 27.91; H, 2.34; N, 32.55. Found: C, 28.13; H, 2.45; N, 32.44.

*Reaction of nitrous acid and 5-amino-6-azauracil.* A mixture of 256 mg. (2 mmoles) of 5-amino-6-azauracil in 5.3 ml. of 28% hydrochloric acid was cooled to −10°. A solution of sodium nitrite (0.33 g./ml.) was added dropwise below 5° until the mixture gave a permanent positive test on the potassium iodide–starch test paper (0.5 ml.). The mixture was stirred for an additional hour at 0–5°. It was then diluted with 3 ml. of water and heated on a steam bath for 0.5 hr., during which all solids dissolved. After the solution was boiled for 5 min., it was cooled to yield 56 mg. of crude 5-hydroxy-6-azauracil as a pale yellow solid. The filtrate was reduced to dryness on a water aspirator. Extraction of the residue with ethyl acetate yielded 50 mg. of 5-chloro-6-azauracil.

*Infrared spectra.* The spectra were measured in pressed potassium bromide disks on a Perkin-Elmer double-beam instrument, model 21.

*Ultraviolet spectra.* The spectra were measured on a Beckman spectrophotometer, model DU. Solutions were made up in volumetric flasks from weighed quantities of the compounds.

*Dissociation constants.* The $pK_a$'s were determined potentiometrically in duplicate using a Photovolt *p*H meter, model 110. A solution of 0.0005 mole of the compound in 100 ml. of carbon dioxide-free water was titrated with 0.066*N* sodium hydroxide.

*Acknowledgment.* The author wishes to express her thanks to Professor A. D. Welch for his interest in and encouragement of this work.

NEW HAVEN, CONN.

(12) Melting points are uncorrected. Analysis by Huffman Microanalytical Labs., Wheatridge, Col., and by Schwarzkopf Microanalytical Labs., Woodside, N. Y.