[CONTRIBUTION FROM THE ROLLIN H. STEVENS MEMORIAL LABORATORY OF THE DETROIT INSTITUTE OF CANCER RESEARCH]

Some 6-Substituted Uracils[1]

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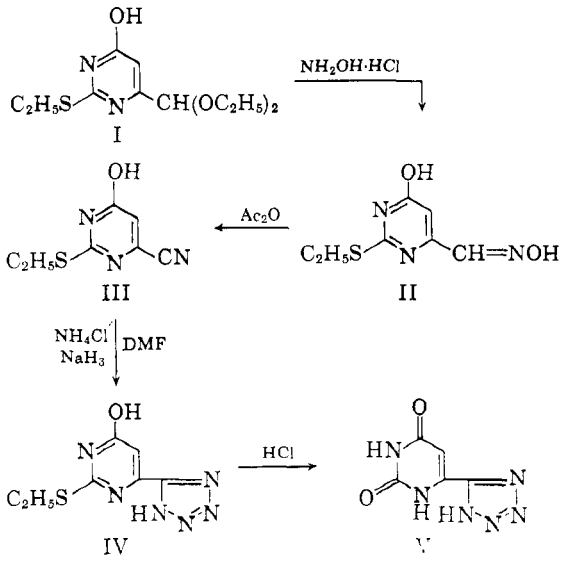
A number of 6-substituted uracils have been synthesized as part of a search for inhibitors of nucleic acid metabolism 6-(1H-Tetrazol-5-yl)uracil (V), an analog of orotic acid (6-uracilcarboxylic acid), has been obtained by two routes. The ether cleavage of 6-chloro-(VIIId) and 6-bromo-2,4-dimethoxypyrimidine (VIIIe) with dilute mineral acid gives the corresponding 6-halouracils IXa and b. 6-Chlorouracil, on treatment with sodium iodide in dimethylformamide, affords IXc in high yield.

The interaction of (2,4-dimethoxy-6-pyrimidinyl)trimethylammonium chloride (VIIIa) and sodium azide in aqueous solution gives the azidopyrimidine (VIIIb) in good yield while the action of anhydrous potassium fluoride on VIIIa in diethylene glycol leads to 2,4-dimethoxy-6-fluoropyrimidine (VIIIc). Attempts to convert VIIIb and VIIIc to the corresponding uracil derivative were unsuccessful.

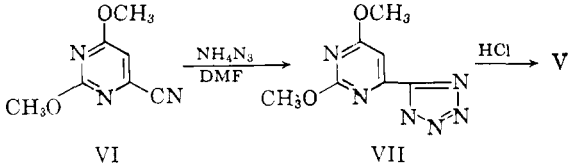
It has been shown that 6-uracilsulfonamide[2] and 6-uracil methyl sulfone inhibit the conversion of orotic acid (6-uracilcarboxylic acid) to orotidine-5′-phosphate by a partially purified pyrophosphorylase of yeast.[3] However, these compounds proved ineffective as an inhibitor of a number of microorganisms.[4] The present investigation was prompted by the possibility that examination of a wider spectrum of 6-substituted uracils might lead to a more potent inhibitor of nucleotide metabolism.

It has been suggested that analogs of biologically active carboxylic acids, in which the carboxyl placed by a 5-tetrazolyl group, might interfere with the normal utilization of the respective carboxylic acids.[5] This suggestion has prompted syntheses of tetrazole analogs of both several alpha-amino acids[6] and alpha-keto acids.[7] Accordingly, it was of considerable interest to synthesize the 5-tetrazolyl analog of orotic acid.

Treatment of 2-ethylmercapto-4-hydroxy-6-diethoxymethylpyrimidine[8] (I), with hydroxylamine hydrochloride in aqueous solution gave the corresponding aldoxime (II) in 86% yield. Dehydration of the oxime with acetic anhydride and sodium acetate afforded 2-ethylmercapto-4-hydroxy-6-pyrimidinecarbonitrile (III) in 80% yield. The interaction of the nitrile and ammonium azide[9] in dimethylformamide gave 2-ethylmercapto-4-hydroxy-6-(1H-tetrazol-5-yl)pyrimidine (70%) (IV) which, on acid hydrolysis, was converted to 6-(1H-tetrazol-5-yl)uracil (V) in 83% yield.



A more direct approach to V presented itself following the completion of the above work with the report of a convenient synthesis of 2,4-dimethoxy-6-pyrimidinecarbonitrile[10] (VI) (*vide infra*). The conversion of VI to 2,4-dimethoxy-6-(1H-tetrazol-5-yl)pyrimidine (VII) was accomplished in high yield with ammonium azide in dimethylformamide. Cleavage of the dimethyl ether, VII, with concentrated hydrochloric acid gave a solid with essentially the same ultraviolet and infrared absorption spectra as V.



(1) This work was supported in part by research grant CY-2903 from the National Cancer Institute, Public Health Service, and in part by an institutional grant from the United Foundation of Greater Detroit allocated through the Michigan Cancer Foundation.

(2) S. B. Greenbaum, *J. Am. Chem. Soc.*, **76**, 6052 (1954).

(3) W. L. Holmes, *J. Biol. Chem.*, **223**, 677 (1956).

(4) W. L. Holmes and A. D. Welch, *Cancer Research*, **16**, 251 (1956).

(5) R. M. Herbst, *Essays in Biochemistry*, S. Graff, ed., John Wiley and Sons, Inc., New York, 1956, pp. 141–55.

(6) J. M. McManus and R. M. Herbst, *J. Org. Chem.*, **24**, 1643 (1959).

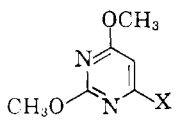
(7) B. E. Fisher, A. J. Tomson, and J. P. Horwitz, *J. Org. Chem.*, **24**, 1650 (1959).

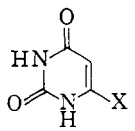
(8) T. B. Johnson and L. H. Cretcher, *J. Am. Chem. Soc.*, **37**, 2144 (1915).

(9) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).

(10) W. Klötzer, *Monatsch.*, **87**, 526 (1956).

Efforts were next directed toward the possibility of preparing the complete series of 6-halouracils (IX) of which only 6-chlorouracil (IXa) had previously been described.[11,12] The facile conversion of 2,4-dimethoxy-6-chloropyrimidine (VIIId) to IXa by the action of mineral acid,[11] suggested the possibility of obtaining the entire series of 6-halouracils from the corresponding 2,4-dimethoxy-6-halopyrimidine (VIII, c, d, e, and f).





VIIIa. X = $\overset{+}{N}(CH_3)_3Cl$
b. X = N_3
c. X = F
d. X = Cl
e. X = Br
f. X = I

IXa. X = Cl
b. X = Br
c. X = I
d. X = F

Recently, Klötzer[13] reported that 2- and 6-pyrimidinyl quaternary ammonium salts, on treatment with anionic reagents such as cyanide and phenoxide ions, gave chiefly the corresponding pyrimidylation products. On the other hand, the interaction of the quaternary salts and such nucleophiles as malonic ester, phthalimide, and halide ions gave methylation products of these anions. In accord with these observations, it was found that (2,4-dimethoxy - 6 - pyrimidinyl)trimethylammonium chloride (VIIIa) reacted smoothly with aqueous sodium azide to give 6-azido-2,4-dimethoxypyrimidine (VIIIb) in 76% yield. However, the reaction of VIIIa with anhydrous potassium fluoride in diethylene glycol, contrary to the prior report, afforded 2,4-dimethoxy-6-fluoropyrimidine (VIIIc) in 42% yield. No attempt was made to determine the extent of the methylation reaction and the concomitant formation of 2,4-dimethoxy-6-dimethylaminopyrimidine which would be expected to constitute a competitive path of reaction.

2,4 - Dimethoxy - 6 - iodopyrimidine (VIIIf) was readily obtained by the action of sodium iodide on VIIId in dimethylformamide while the interaction of 2,4,6-tribromopyrimidine and two equivalents of sodium methoxide provided 6-bromo-2,4-dimethoxypyrimidine (VIIIe) in reasonably good yield.

The demethylation of 6-chloro-(VIIId) and 6-bromo-2,4-dimethoxypyrimidine (VIIIe) with concentrated mineral acid led to a replacement of the halogen by a hydroxyl group and the formation of barbituric acid as the sole product. A similar observation has been recorded in the attempted ether cleavage of 2,4-dimethoxy-6-pyrimidinesulfonic acid with mineral acid.[14] The desired 6-chloro-(IXa) and 6-bromouracil (IXb) were obtained in reasonably good yield using dilute mineral acid in acetic acid. On the other hand, the demethylation of 6-azido-(VIIIb) and 6-fluoro-2,4-dimethoxypyrimidine (VIIIc) with dilute mineral acid, under a variety of conditions gave barbituric acid as the only isolable product. Moreover, a similar course of reaction was observed in the ether cleavage of VIIIf. However, the desired 6-iodouracil (IXc) was obtained in 70% yield by the action of sodium iodide on IXa in dimethylformamide.

The results of the present study indicate that a halogen or azide function located at the 6-position of 2,4-dimethoxypyrimidine is relatively labile with respect to acid catalyzed nucleophilic displacement. This type of displacement on the pyrimidine nucleus has been explained by assuming that the initial addition of a proton to one of the nitrogens stabilizes a positive charge at the carbon atom involved[14,15] and that an appropriate neutral transition state is subsequently obtained.[16]

The biological evaluation of the pyrimidines prepared in the present study is incomplete and will be reported elsewhere.

EXPERIMENTAL[17]

2-Ethylmercapto-4-hydroxy-6-pyrimidinecarboxaldoxime (II). A solution of 14 g. (0.054 mole) of 2-ethylmercapto-4-hydroxy-6-diethoxymethylpyrimidine[8] and 7.6 g. (0.11 mole) of hydroxylamine hydrochloride in a mixture of 75 ml. of ethanol and 200 ml. of water was refluxed for 15 min. A crystalline solid was deposited on cooling the reaction mixture to 10° which was collected, washed with water, and dried; wt. 9.7 g. (89%), m.p. 254–256° dec. A single recrystallization from ethanol gave colorless needles; m.p. 255–256° dec.

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.2; H, 4.6. Found: C, 42.7; H, 4.7.

A sulfur-free solid, wt. 0.5 g., m.p. 300°, was deposited from the initial filtrate on standing which has tentatively been assigned the structure 6-uracilcarboxaldoxime.

Anal. Calcd. for $C_5H_5N_3O_3 \cdot H_2O$: C, 34.7; H, 4.1; N, 24.3. Found: C, 34.8; H, 4.3; N, 24.2.

2-Ethylmercapto-4-hydroxy-6-pyrimidinecarbonitrile (III). A solution of 5.0 g. (0.025 mole) of II in 50 ml. of acetic anhydride was refluxed for 1.5 hr. after which 1.0 g. of sodium acetate was added and the reaction mixture refluxed for an additional 1.5 hr. After standing overnight at room temperature, the solution was evaporated to dryness under diminished pressure and the brown residue triturated with water, filtered, and dried; wt. 3.6 g. (89%), m.p. 185–195°. A single recrystallization from aqueous ethanol gave yellow needles; m.p. 210–211°.

Anal. Calcd. for $C_7H_7N_3OS$: C, 46.4; H, 3.9; N, 23.2. Found: C, 46.4; H, 3.9; N, 22.8.

2-Ethylmercapto-4-hydroxy-6(1H-tetrazol-5-yl)pyrimidine (IV). A mixture of 2.33 g. (0.015 mole) of III, 1.06 g. (0.02

(11) W. R. Boone and T. Leigh, Br. Patent **677,342**; *Chem. Abstr.*, **47**, 9369 (1953).

(12) After the present study had been completed, W. Pfleiderer and G. Nübel, *Ann.*, **631**, 168 (1960), reported a second preparation of IXa.

(13) W. Klötzer, *Monatsch*, **87**, 536 (1956).

(14) S. B. Greenbaum and W. L. Holmes, *J. Am. Chem. Soc.*, **76**, 2899 (1954).

(15) C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1941).

(16) B. Lythgoe, *Quart. Revs. (London)*, **3**, 198 (1949).

(17) All melting points are uncorrected. Microanalyses were provided by Micro-Tech Laboratories, Skokie, Ill. Ultraviolet absorption spectra were determined in water with a Cary Model 11 recording spectrophotometer

mole) of ammonium chloride and 1.3 g. (0.02 mole) of sodium azide in 25 ml. of dimethylformamide was held at 80° for 23 hr. The salts were removed by filtration and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in water, the solution adjusted to *p*H 2 with concentrated hydrochloric acid and the yellow solid was collected; wt. 2.58 g. (93%), m.p. 255–258° dec. The product was next dissolved in 10% sodium hydroxide, the solution treated with Norit, and the product reprecipitated with concentrated hydrochloric acid; m.p. 267–270° dec. Two recrystallizations from water provided an analytical sample; m.p. 270–271° dec.

Anal. Calcd. for $C_7H_8N_6OS$: C, 37.5; H, 3.6; N, 37.5. Found: C, 37.9; H, 3.9; N, 37.5.

6-(1H-Tetrazol-5-yl)uracil (V). A solution of 0.45 g. (2 mmoles) of IV in 10 ml. of concd. hydrochloric acid was refluxed for 6 hr. during which time a solid was deposited. The amorphous product, wt. 0.3 g. (84%), darkened at 290° but showed no melting point up to 335°. The solid was dissolved in 10% sodium hydroxide, the solution treated with Norit, and the product reprecipitated with concentrated hydrochloric acid. The solid was then collected, washed with water, and dried. The purified material darkened at 290° with no definite melting point at 340°, λ_{max} 287 mμ (E × 10^{-3} = 12.09).

Anal.[18] Calcd. for $C_5H_4N_6O_2$: C, 33.3; H, 2.7; N, 46.7. Found: C, 33.4; H, 2.3; N, 45.37; 45.27.

2,4-Dimethoxy-6-(1H-5-tetrazol-5-yl)pyrimidine (VII). A stirred mixture of 1.0 g. (6 mmoles) of 2,4-dimethoxy-6-pyrimidinecarbonitrile,[10] 5.0 g. of ammonium chloride, and 6.0 g. of sodium azide in 25 ml. of dimethylformamide was held at 80° for 24 hr. The inorganic salts were removed by filtration and the filtrate evaporated to dryness under diminished pressure. The residue was dissolved in water, the solution adjusted to *p*H 2 with concentrated hydrochloric acid and the product collected; wt. 0.98 g. (78%), m.p. 195–200° dec. A single recrystallization from water gave colorless needles; m.p. 200–201° dec., λ_{max} 281 mμ (E × 10^{-3} = 9.95).

Anal. Calcd. for $C_7H_8N_6O_2$: C, 40.4; H, 3.9; N, 40.4. Found: C, 40.3; H, 3.9; N, 40.0.

A solution of 0.5 g. (2.4 mmoles) of VII in 10 ml. of concd. hydrochloric acid was refluxed for 1 hr. during which time a solid was deposited. The product was collected, washed with water, and dried; wt. 0.37 g. (85%). This material darkened at 300° but showed no melting point up to 335°. The infrared and ultraviolet spectra of this material were essentially superimposable with the corresponding spectra of V.

6-Azido-2,4-dimethoxypyrimidine (VIIIb). A stirred solution of 18.7 g. (0.08 mole) of 2,4-dimethoxy-6-pyrimidinyl)-trimethylammonium chloride[13] (VIIIa) and 20.8 (0.32 mole) of sodium azide in 160 ml. of water was held at 80° for 0.5 hr. The oil that was deposited solidified on storing the reaction mixture in a refrigerator overnight. The solid crystallized from aqueous methanol in the form of a colorless mat of needles; wt. 11.0 g. (76%), m.p. 38–39°. A second recrystallization from aqueous methanol provided an analytical sample; m.p. 41–42°, λ_{max} 272 mμ (E × 10^{-3} = 13.5), λ_{max} (chloroform) 4.72 μ (azide).

Anal. Calcd. for $C_6H_7N_5O_2$: C, 39.8; H, 4.0. Found: C, 39.9; H, 3.8.

2,4-Dimethoxy-6-fluoropyrimidine (VIIIc). A mixture of 11.7 g. (0.05 mole) of VIIIa and 8.5 g. (0.15 mole) of anhydrous potassium fluoride in 100 ml. of diethylene glycol was heated to 80° under reduced pressure (*ca.* 400 mm.) for 1 hr. at which time the evoluation of trimethylamine had ceased. The mixture was cooled, extracted (3 × 50 ml.) with ether and the dried extract evaporated under reduced pressure. The oily residue crystallized from aqueous methanol to give 3.2 g. (42%) of product; m.p. 52–54°. A second recrystallization from aqueous methanol gave colorless needles; m.p. 54–56°, λ_{max} 245.5 mμ (E × 10^{-3} = 6.32).

Anal. Calcd. for $C_6H_7FN_2O_2$: C, 45.6; H, 4.5; N, 17.7. Found: C, 45.8; H, 4.4; N, 18.0.

6-Bromo-2,4-dimethoxypyrimidine (VIIIe). The conversion of 2,4,6-tribromopyrimidine[19] to 6-bromo-2,4-diethoxypyrimidine, described by Langley,[20] is the basis of this analogous preparation of VIIIe.

A mixture of 16 g. (0.05 mole) of 2,4,6-tribromopyrimidine and 50 ml. of benzene was stirred until solution was complete. Absolute methanol (50 ml.) was then added and the flask cooled. A solution of sodium methoxide (2.3 g., 0.1 g.-atom in 50 ml. absolute methanol) was added dropwise with stirring and maintaining the temperature of the reaction mixture below 20°. After standing overnight at room temperature, a few drops of acetic acid were added and the mixture evaporated to dryness under diminished pressure. Water was then added to the residue, the solid collected, washed with water, and dried; wt. 8.9 g. (80%), m.p. 75–77°. Several recrystallizations from petroleum ether (b.p. 30–60°) gave colorless needles; m.p. 90–91°, λ_{max} 261 mμ (E × 10^{-3} = 8.47).

Anal. Calcd. for $C_6H_7BrN_2O_2$: C, 32.9; H, 3.2; N, 12.8. Found: C, 33.4, H, 3.1; N, 13.0.

2,4-Dimethoxy-6-iodopyrimidine (VIIIf). A mixture of 5.0 g. (0.0286 mole) of VIIId and 20 g. of sodium iodide in 50 ml. of dimethylformamide was refluxed for 1 hr. under an atmosphere of nitrogen. The solvent was removed under reduced pressure, the residue triturated with water and the solid collected; wt. 3.2 g. (42%), m.p. 173–175°. A single recrystallization from ethanol gave colorless prisms; m.p. 175–176°, λ_{max} 275 mμ (E × 10^{-3} = 9.18).

Anal. Calcd. for $C_6H_7IN_2O_2$: C, 27.1; H, 2.7; I, 47.7. Found: C, 27.5; H, 2.9; I, 47.5.

6-Chlorouracil (IXa). A solution of 5.25 g. (0.05 mole) of 6-chloro-2,4-dimethoxypyrimidine[21,22] (VIIId) in a mixture of 450 ml. of glacial acetic acid and 58 ml. of 2*N* hydrochloric acid was refluxed for 1 hr. The mixed acids were evaporated under reduced pressure and the residue twice recrystallized from water to give 2.44 g. (55%) of a white amorphous solid; m.p. 298–300° dec. (lit.[11] 300° dec.), λ_{max} 264 mμ.(E × 10^{-3} = 8.47)

Anal. Calcd. for $C_4H_3ClN_2O_2$: C, 32.8; H, 2.2; N, 19.1; Cl, 24.2. Found: C, 32.9; H, 2.3; N, 19.2; Cl, 24.2.

6-Bromouracil (IXb). A solution of 13.2 g. of VIIIe (0.06 mole) in a mixture of 40 ml. of 48% hydrobromic acid and 160 ml. of glacial acetic acid was heated to 80° for *ca.* 1 min. and then allowed to stand for 20 hr. at room temperature. The product was collected, washed with acetic acid, and dried; wt. 4.2 g. The tan solid darkened at 250–270° but showed no melting point up to 340°. The filtrate was evaporated to dryness and the residue crystallized from methanol to give 1.8 g. of solid. The combined solids, 6.0 g. (52%) were recrystallized from methanol giving colorless prisms which darkened at 270° but showed no evidence of melting at 340°, λ_{max} 266 mμ (E × 10^{-3} = 8.83).

Anal. Calcd. for $C_4H_3BrN_2O_2$: C, 25.2; H, 1.6; N, 14.7; Br, 41.8. Found: C, 25.3; H, 1.7, N, 14.4; Br, 41.5.

6-Iodouracil. A mixture of 5.0 g. (0.034 mole) of IXa and 20 g. of sodium iodide in 50 ml. of dimethylformamide was refluxed under an atmosphere of nitrogen for 1 hr. The solvent was removed under diminished pressure, water

(18) All attempts to obtain a satisfactory nitrogen analysis were unsuccessful.

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(21) H. J. Fisher and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 727 (1932).

(22) S. B. Greenbaum and W. L. Holmes, *J. Am. Chem. Soc.*, **76**, 2899 (1954).

added to the residue, and the solid collected; wt. 5.9 g. (73%), m.p. 270–271° dec. The product crystallized from ethanol as colorless prisms; m.p. 279–280° dec., λ_{max} 268 mμ (E × 10^{-3} = 9.98).

Anal. Calcd. for $C_4H_3IN_2O_2$: C, 20.2; H, 1.3; N, 11.8; I, 53.3. Found: C, 20.7; H, 1.5; N, 12.4; I, 53.1.

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[CONTRIBUTION FROM THE BIOLOGICAL SCIENCES DIVISION, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] LX. Synthesis of 5-Diazoacetyluracil and Related Compounds

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The synthesis of 5-diazoacetyluracil (XI) from 5-acetyluracil (III) was accomplished by treatment of the oximino ketone (X) of III with chloramine. In another attempted approach to XI, 5-bromoacetyluracil (V) was prepared and was converted to a number of interesting 5-substituted uracils. A new synthesis of 6-acetyluracil (XX) was developed and unsuccessful attempts were made to convert it to 6-diazoacetyluracil.

Most of the alkylating agents that have interest as anticancer compounds possess the bis(2-chloroethyl) amino moiety as the alkylating group.[2] Azaserine (*O*-diazoacetyl-L-serine)[3] and DON (6-diazo-5-oxo-L-norleucine)[4] also have interesting antitumor properties. It has been proposed[2] that these diazoacetyl compounds and the nitrogen mustards might be considered as members of a broad class of anticancer agents which consist of metabolites bearing an alkylating group that function by irreversible inhibition of the corresponding enzymes. To test this hypothesis two diazoacetyl derivatives of 3-phenylpropionic acid were prepared[5] in order to compare their antitumor activities with those of the analogous nitrogen mustards—*e.g.*, chlorambucil.[6] This manuscript describes the preparation of 5-diazoacetyluracil (XI) in order that its anticancer activity might be compared with that of the corresponding nitrogen mustard, uracil mustard.[7]

The reaction between sodium nitrite and the salt of an α-amino ketone constitutes one of the common synthetic approaches to α-diazo ketones; this was the preparative method for 6-diazo-5-oxo-L-norleucine.[8] Accordingly, the initial sequence visualized for the preparation of XI required the prior synthesis of a salt of 5-glycyluracil (VIII). The use of Johnson and Bergmann's[9] method to cyclize ureidomethylene acetoacetic ester (II),[10] which, in turn, was prepared from ethoxymethylene acetoacetic ester (I),[10] gave a reasonable yield of 5-acetyluracil (III). Bromination of the ketone (III), suspended in methanol, proceeded readily to give 5-bromoacetyluracil (V.) That side-chain bromination to give V had occurred rather than ring bromination at C-6 was demonstrated in two ways. First, treatment of V with dimethyl sulfoxide followed by the reaction of the product with phenylhydrazine gave the osazone (VII) of the glyoxal formed by oxidation of V with dimethyl sulfoxide.[11] Secondly, the reaction of V with pyridine gave the pyridinium salt which was cleaved with aqueous base to uracil-5-carboxylic acid (IV),[12] identical with an authentic sample of IV.

The bromo ketone (V) underwent ready displacement with azide ion to give the azido ketone (VI). Hydrogenation of a suspension of VI in dilute hydrochloric acid solution using a palladium catalyst afforded the hydrochloride of VIII which was best characterized as the crystalline picrate. Alternatively, the action of an acetic acid solution of hydrogen bromide[13] on VI reduced the azide group and yielded VIII, isolated as the picrate. Hydro-

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, see E. J. Reist, J. H. Osiecki, A. Benitez, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 0000 (1961).

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(3) For a summary of chemical and biological data, see Cancer Chemotherapy Reports, No. 7, 65 (1960), a publication of the Cancer Chemotherapy National Service Center, National Institutes of Health.

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