was taken up with petroleum ether (b.p. 30–40°). After the solution had been concentrated to about 50 ml. and kept at −20° for 5 hr., 11 g. of crystals precipitated.

A further crop of crystals (11.1 g.) was obtained, when the mother liquor was concentrated to about 25 ml. and cooled again to −20°, thus improving the yield of XXIII to 91.4%. The melting point of this compound was 56–57° and showed no depression with an authentic sample.

The tertiary amine salts XX and XXI, respectively, were converted into XXIII by the same procedure; yield: 94.2% and 87%, resp.

2-Hydroxy-4,6-dimethyl-s-triazine (XXIV). A mixture of the triethylamine salt XVIII (8.6 g., 0.02 mole), triethylamine (12.32 g., 0.12 mole), 2% palladium on carbon (12 g.), and methanol (150 ml.) was shaken at room temperature with hydrogen. After the absorption of hydrogen was complete, the catalyst was filtered and a solution of sodium hydroxide (4.8 g., 0.12 mole) in methanol (50 ml.) was added to the filtrate, whereby the triethylamine hydrochloride was converted into triethylamine and sodium chloride. After the precipitated sodium chloride was removed by filtration, the filtrate was evaporated to dryness at reduced pressure. The residue was taken up with absolute ethanol, a further crop of insoluble sodium chloride removed by filtration, and the 2-hydroxy-4,6-dimethyl-*s*-triazine (XXIV) precipitated with ether. The precipitate was sublimed *in vacuo* (bath temperature 160–178° at 0.05–0.02 mm), yielding 2 g. (80%) of pure XXIV; m.p. 236–237° (lit.[6] m.p. 230–231°). A mixed melting point with an authentic sample showed no depression.

By the same procedure, XXIV was obtained from the *N*-ethylpiperidine salt (XX), yield 84%.

Acknowledgment. The author is indebted to the Olin Mathieson Chemical Corporation for their generous support of this work. He also wishes to thank Dr. C. J. Grundmann for stimulating discussions.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Synthesis and Reactions of 5-Bromomethyl- and 5-Chloromethyluracil

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The chlorination of 6-methyl-2-methylmercapto-4-pyrimidinol (I) with *N*-chlorosuccinimide in the presence of benzoyl peroxide gives only the nuclear halogenated product, 5-chloro-6-methyl-2-methylmercapto-4-pyrimidinol (III), and not the isomeric 6-chloromethyl derivative (II) as was previously assumed.[4] 5-Chloromethyluracil (VI) was prepared by the reaction of 5-hydroxymethyluracil (V) with thionyl chloride in the presence of pyridine. Similarly, the treatment of V with hydrogen bromide in glacial acetic acid results in the formation of 5-bromomethyluracil (VII). A few displacement reactions of these compounds are presented, including the preparation of the thiamine analog, 3-(2′,4′-dihydroxy-5′-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide (XI).

The halogenated thymine derivatives, 5-bromomethyluracil (VII) and the corresponding chloro compound (VI), have long been desired as reactive intermediates for the introduction of the thyminyl residue into other molecules.[1] Although Johnson and his coworkers were successful in preparing 5-chloromethyl-6-methyluracil from the reaction of 6-methyluracil with chloromethyl methyl ether, the synthesis of 5-chloromethyluracil by this method was not possible.[1c] These workers apparently did not attempt the direct conversion of 5-hydroxymethyluracil (V) to the corresponding 5-halomethyl derivatives, as the former compound (V) was erroneously thought to be quite unstable, decomposing readily to formaldehyde and uracil.[2] Recent work, however, has shown that 5-hydroxymethyluracil (V) is a reasonably stable compound and may be prepared in good yield from uracil and formaldehyde in alkaline solution.[3]

A compound, obtained by the interaction of *N*-chlorosuccinimide with thymine in chloroform containing benzoyl peroxide, was assigned the 5-chloromethyluracil (VI) structure in 1954.[4] However, this structural assignment seemed to us fairly unlikely, as (1) the chlorine in their compound was stable to boiling ethanol or water, whereas halomethylpyrimidines are notoriously labile compounds,[1c,5] and (2) *N*-chlorosuccinimide is known to be ineffective in producing allylic substitution.[6] We have discovered that the compound of West and Barrett[4] is, in reality, 5-chloro-6-ethoxy-5-methylhydrouracil, a compound previously obtained by Johnson and Sprague[7] from another route. These findings are corroborated by a recent paper,[8] which has appeared since our work was completed.

Because of the above facts, it was desirable to investigate a second allylic chlorination reported in the West and Barrett paper.[4] These workers ob-

(1) (a) D. Riehl and T. B. Johnson, *Rec. trav. chim.*, **59**, 87 (1940); (b) M. M. Endicott and T. B. Johnson, *J. Am. Chem. Soc.*, **63**, 1286 (1941); (c) M. M. Endicott and T. B. Johnson, *J. Am. Chem. Soc.*, **63**, 2063 (1941).

(2) T. B. Johnson and A. Litzinger, *J. Am. Chem. Soc.*, **58**, 1940 (1936).

(3) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).

(4) R. A. West and H. W. Barrett, *J. Am. Chem. Soc.*, **76**, 3146 (1954).

(5) T. Okuda and C. C. Price, *J. Org. Chem.*, **24**, 14 (1959).

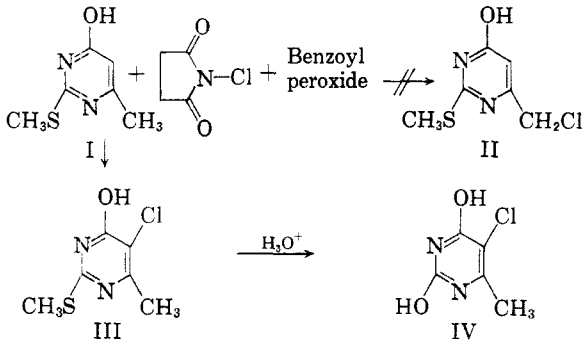
(6) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(7) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **59**, 2436 (1937).

(8) J. H. Burckhalter, R. J. Seiwald, and H. C. Scarborough, *J. Am. Chem. Soc.*, **82**, 991 (1960).

tained a compound, m.p. 230–235°, from the *N*-chlorosuccinimide reaction with 6-methyl-2-methylmercapto-4-hydroxypyrimidine (I) in chloroform containing benzoyl peroxide. Although correct analyses could not be obtained, these authors assigned the compound the structure, 6-chloromethyl-2-methylmercapto-4-hydroxypyrimidine (II), as it was converted by hot aqueous hydrochloric acid to 6-chloromethyluracil, a compound previously prepared by Johnson, *et al.*[9] Neither analyses nor infrared spectra were reported for the latter compound, however.

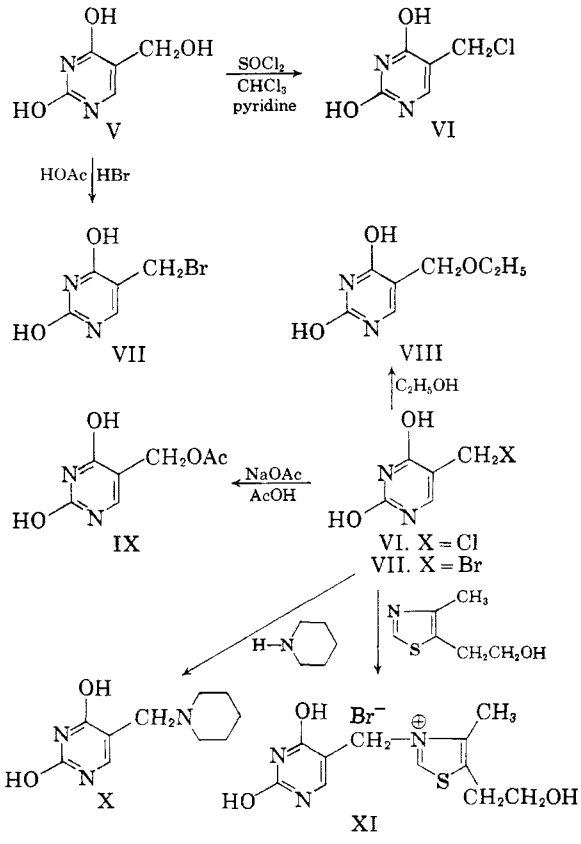
Several repetitions of the *N*-chlorosuccinimide reaction with I did not give the 230–235° material. The only product, regardless of whether the reaction was carried out in dry chloroform or carbon tetrachloride, was a crystalline material, m.p. 269–270°, and empirical formula $C_6H_7ClN_2OS$. This substance was identified as the isomeric compound 5-chloro-6-methyl-2-methylmercapto-4-hydroxypyrimidine (III) by hydrolysis to the known 5-chloro-6-methyluracil (IV).[10] In no case could we obtain the isomeric 6-chloromethyl derivative (II).



The synthesis of 5-chloromethyluracil[11,12](VI) was accomplished simply by treating 5-hydroxymethyluracil (V) with thionyl chloride in dry chloroform containing a little dry pyridine. The analogous 5-bromomethyl compound (VII) was readily obtained by treatment of V with hydrogen bromide in glacial acetic acid. As might be expected from theoretical considerations, the halogen atom in these molecules is extremely reactive; *e.g.*, treatment with warm water or ethanol for only one to two minutes is sufficient to remove all the halogen. A virtually quantitative yield of 5-ethoxymethyluracil (VIII) can be obtained merely by recrystallization of either material from ethanol.

Although 5-bromomethyluracil (VII) could be obtained analytically pure by recrystallization from glacial acetic acid, we were unable to completely purify 5-chloromethyluracil (VI) because of its extreme insolubility in all solvents tried (*e.g.*, glacial acetic acid, *N*,*N*-dimethylformamide, diethylene glycol dimethyl ether, etc.). The structure of VI was proven, however, by (1) conversion to 5-ethoxymethyluracil (VIII) in warm ethahol, (2) conversion to 5-piperidinomethyluracil (X) by treatment with piperidine in dioxane solution, and (3) conversion to 5-acetoxymethyluracil (IX) in glacial acetic acid containing sodium acetate. The identical products could be obtained in a like manner from 5-bromomethyluracil (VII).

The availability of the 5-halomethyluracils has now made possible the ready preparation of 5-substituted aminomethyluracils, such as X, by simple substitution reactions. These compounds were previously obtained by roundabout methods, *e.g.*, 5-aminomethyluracil (thyminyl amine) was obtained by the Curtius degradation of uracil-5-acetic acid.[13]



Treatment of 5-bromomethyluracil (VII) in anhydrous diglyme or dioxane with 5-(2′-hydroxy-

(9) T. B. Johnson and L. H. Chernoff, *J. Am. Chem. Soc.*, 36,1742 (1914).

(10) R. Behrend, *Ann.* **236**, 57 (1886); T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **60**, 1622 (1938).

(11) This compound has also been prepared by the chloromethylation of uracil in aqueous hydrochloric acid (see ref. 8 and 12). Although Skinner, *et al.* (ref. 12) state that attempts to convert 5-hydroxymethyluracil (V) to 5-chloromethyluracil (VI) using thionyl chloride in pyridine gave only the quaternary salt formed from VI and pyridine, we have found that the reaction proceeds quite satisfactorily using slightly more than the theoretical quantity of pyridine in chloroform.

(12) W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *J. Org. Chem.*, **25**, 149 (1960).

(13) T. B. Johnson and A. Litzinger, *J. Am. Chem. Soc.*, **57**, 1139 (1935); A. Litzinger and T. B. Johnson, *J. Am. Chem. Soc.*, **58**, 1936, 1940 (1936).

ethyl)-4-methylthiazole gave an excellent yield of the thiamine analog, 3-(2′,4′-dihydroxy-5′-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide (XI). The use of diethylene glycol dimethyl ether rather than dioxane as solvent in this reaction is preferable, as the product is more readily crystallized and purified.

Biological testing of many of these compounds is now in progress and will be reported elsewhere.

EXPERIMENTAL[14]

5-Chloro-6-methyl-2-methylmercapto-4-hydroxypyrimidine (IV). A mixture of 15.6 g. (0.10 mole) of 6-methyl-2-methylmercapto-4-hydroxypyrimidine,[15] 14.7 g. (0.11 mole) of *N*-chlorosuccinimide, 3.63 g. (0.015 mole) of benzoyl peroxide, and 250 ml. of purified chloroform was heated under reflux for 16 hr. (drying tube). The mixture was cooled and the crystalline material filtered with suction and air-dried to give 10.5 g. of crude product, m.p. 267.5–269°. An additional 0.6 g. was obtained by concentration of the chloroform mother liquor and washing with water to remove succinimide. Recrystallization of the combined solids from methyl Cellosolve gave 9.7 g. (51%) of colorless prismatic needles, m.p. 269–270° with sublimation; reported[4] m.p. 270° dec.

Anal. Calcd. for $C_6H_7ClN_2OS$: C, 37.79; H, 3.70; Cl, 18.59; N, 14.69. Found: C, 37.99; H, 3.65; Cl, 18.40; N, 14.85.

A repetition of this reaction using purified carbon tetrachloride as solvent gave a 69.5% yield of product, which was identical in all respects with that obtained above. In no case could we isolate any of the isomeric compound, 6-chloromethyl-2-methylmercapto-4-hydroxypyrimidine (II).

Hydrolysis of 1.9 g. (0.01 mole) of compound V with 25 ml. of aqueous hydrochloric acid (1:1) at 100° for 5 hr. gave 1.6 g. (100%) of *5-chloro-6-methyluracil* (IV), m.p. >300°. The infrared spectrum of this compound was identical with that of an authentic sample of IV, prepared by the method of Behrend.[10]

Anal. Calcd. for $C_5H_5ClN_2O_2$: C, 37.39; H, 3.14; Cl, 22.08; N, 17.44. Found: C, 37.71; H, 3.25; Cl, 22.11; N, 17.64.

5-Bromomethyluracil (VII). Five grams (0.0352 mole) of 5-hydroxymethyluracil (V)[3] was added to 100 ml. of 32% hydrogen bromide in glacial acetic acid, and carefully warmed on the steam bath for 8 hr. (drying tube). The mixture was cooled, filtered with suction, and the colorless powder washed thoroughly with dry ether. There was thus obtained 5.7 g. (79.0%) of product, m.p. >330° (capillary) with slow decomposition. A small sample was recrystallized from glacial acetic acid to obtain colorless tiny needles, m.p. >330° dec. This sample was dried overnight at 100° *in vacuo* for analysis.

Anal. Calcd. for $C_5H_5BrN_2O_2$: C, 29.29; H, 2.46; Br, 38.98. Found: C, 29.32; H, 2.72; Br, 38.47, 38.55.

This material (VII) was extremely reactive toward water or ethanol, and was routinely stored in a vacuum dessicator over potassium hydroxide pellets.

5-Chloromethyluracil (VI). Five grams (0.0352 mole) of 5-hydroxymethyluracil (V)[3] was added to 50 ml. of purified chloroform containing 3.0 ml. dry pyridine, and, with mechanical stirring, 5.5 g. (0.042 mole) of thionyl chloride in 10 ml. of chloroform slowly added. The mixture was refluxed for 0.5 hr. (drying tube), and the colorless solid filtered with suction and washed with dry ether. This crude product weighed 5.75 g. (100%), sintered at 268–270° and decomposed at 315–320°. This compound could not be obtained analytically pure because of its high reactivity toward hydroxylic solvents, coupled with its high insolubility in more inert solvents. An analysis for chlorine of the crude material was low.

Anal. Calcd. for $C_5H_5ClN_2O_2$: Cl, 22.08. Found: 17.89, 18.10.

The infrared spectrum of VI indicated a complete loss of the peak at 2.9 μ, usually assigned to the aliphatic hydroxyl group. The spectrum of the starting material (V) contains a strong peak at this frequency.

Identical products were obtained from substitution reactions using either this compound (VI) or 5-bromomethyluracil (VII).

5-Ethoxymethyluracil (VIII). 5-Bromomethyluracil (VII) (0.50 g.; 0.0024 mole) was boiled with 20 ml. of ethanol until a clear solution was obtained (about 3 min. required). Upon cooling, a colorless solid separated (0.30 g.;72 %), m.p. 212–214° dec. An analytical sample, prepared by recrystallization from ethanol, consisted of a colorless microcrystalline powder, m.p. 217–218° dec.

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.39; H, 5.92; N, 16.46; O, 28.23. Found: C, 49.57; H, 5.88; N, 16.61; O, 28.29.

This compound has been previously prepared by another route, reported[3] m.p. 212°.

5-Piperidinomethyluracil (X).[8] One gram (0.0049 mole) of 5-bromomethyluracil (VII) was added portionwise to 15 ml. of dry dioxane containing 2 ml. of piperidine. After refluxing gently for 75 min., the mixture was cooled to 5° and the colorless solid filtered with suction. This material was extracted with 15 ml. of boiling dioxane, filtered while hot to remove piperidine hydrochloride, and cooled to 5°. The resulting product was recrystallized from ethanol to give 0.45 g. (44%) of colorless leaflets, m.p. > 300°. For analysis, a small sample was recrystallized from ethanol and dried *in vacuo* at 75°.

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.41; H, 7.22; N, 20.09. Found: C, 57.49; H, 7.34; N, 20.23.

This material is quite soluble in water, but only slightly soluble in cold ethanol or dioxane.

5-Acetoxymethyluracil (IX). 5-Bromomethyluracil (VII) (1.0 g.; 0.005 mole) was mixed with 10 ml. of glacial acetic acid containing 0.80 g. (0.01 mole) of anhydrous sodium acetate. The mixture was heated to reflux for 5 min., cooled to room temperature, and filtered with suction. Additional product was obtained by dilution of the acetic acid mother liquor with ether. The combined solids were recrystallized from water to obtain 0.58 g. (63%) of colorless leaflets, m.p. 217–223° dec., when placed on the block at about 160° and heated fairly rapidly. When heated slowly from room temperature, the compound did not melt under 300°.

Anal. Calcd. for $C_7H_8N_2O_4$: C, 45.65; H, 4.38; N, 15.22. Found: C, 45.26; H, 4.89; N, 15.93.

This compound has been previously obtained by another route, but was presented without analytical data as m.p. >300°.[3]

3-(2′,4′-Dihydroxy-5′-pyrimidylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide (XI). One gram (0.0050 mole) of 5-bromomethyluracil (VII) was added to 15 ml. of dry, redistilled diethylene glycol dimethyl ether containing 0.82 g. (0.0057 mole) of 5-(2′-hydroxyethyl)-4-methylthiazole (Merck), and heated on the steam bath for 1 hr. (drying tube). The mixture was cooled and filtered with suction. The crude product (m.p. 221–222°) was recrystallized by dissolving in a minimum of hot methanol, filtering, and adding 2 volumes of dry diethylene glycol dimethyl ether. The colorless prisms thus obtained weighed 1.1 g. (63%), m.p. 219–221° dec. when placed on the block at 180°. It melted at 215–217° dec. when heated slowly from room temperature.

(14) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus.

(15) R. List, *Ann.*, **236**, 1 (1886); H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903).

Anal. Calcd. for $C_{11}H_{14}BrN_3O_3S$: C, 37.94; H, 4.06; Br, 22.95; N, 12.07. Found: C, 38.04; H, 4.36; Br, 22.93; N, 12.08.

The yield in a second run using three times the above quantities was 74%. The reaction could also be run in dioxane solution, but the gummy product was difficult to crystallize and purify.

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NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL SCIENCES, UNIVERSITY OF IDAHO]

Preparation of Some Alkyl-Substituted Monohydroxamic Acids, *N*-Acyl-*O*-alkylhydroxylamines. I

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In order to initiate a study of the reactions of the alkyl hydroxamates, the preparation of representative benzo-, aniso-, toluo-, aceto-, and propionhydroxamic esters has been carried out by the reaction of sodium and potassium salts of hydroxamic acid with alkyl halides. Several dialkyl hydroxamates were also obtained as by-products in these reactions. The infrared spectra of these compounds were studied and the bands attributed to N—H stretching, C=O stretching, amide II, and C—O stretching were observed.

The preparation of a number of hydroxamic acid esters has been carried out in order subsequently to study their reactions. The reaction of a hydroxamic acid salt with an alkyl halide was used to prepare the hydroxamic acid esters.[2,3]

Esters of aromatic hydroxamic acids were made using a procedure similar to that of Fuller and King,[4] who prepared *n*-butyl benzohydroxamate. Potassium salts of the hydroxamic acids were prepared by the reaction of ethyl esters with hydroxylamine and potassium hydroxide.[5] In this preparation the potassium salt precipitates from methanolic solution. Barium toluhydroxamate was also prepared by the reaction of the mother liquor from the potassium toluhydroxamate preparation with barium chloride. When the potassium or barium salt, sodium carbonate, and a primary alkyl halide in alcohol-water solution were stirred together and warmed, the alkyl hydroxamates were obtained in good yields. A ferric chloride spot test was used to follow the reaction. This color test changed from an initial dark purple to a final pale red during an interval that varied from two days, when the solutions were refluxed, to three weeks, when the solutions were stirred at room temperature.

The aceto- and propionhydroxamic acid esters were prepared in essentially the same manner. Ethyl acetate and ethyl propionate, respectively, were allowed to react with hydroxylamine and sodium methoxide in absolute methanol, and without isolation of the hydroxamic acid salt an alkyl halide, sodium carbonate, and water were added to prepare the hydroxamic ester.

Both the aromatic and aliphatic acid esters were worked up in the same way. The alcohol was removed by distillation from the reaction mixture, and the product was taken up in chloroform. Extraction of the chloroform with sodium bicarbonate removed all unchanged carboxylic acid formed by saponification of the starting material. The hydroxamic ester was extracted from the chloroform with sodium hydroxide. This alkaline solution was acidified and the hydroxamic ester was taken up in chloroform.

Dialkylhydroxamate esters were found in a number of the preparations in the chloroform solutions after they had been extracted with sodium hydroxide. In a few cases these were purified, and in some cases they were found to be intractable oils. We are uncertain of the structures of the dialkylhydroxamates. The several possible isomeric structures are *N*,*O*-dialkylhydroxamates(I) and syn- and anti- forms of the *O*,*O'*-dialkylhydroxamates (II). All of the dialkyl benzohydroxamates

I II

that have been reported in the literature have been assigned structure II.[2,4,6,7] On the other

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(2) H. L. Yale, *Chem. Revs.*, **33**, 209 (1944).

(3) F. Mathis, *Bull. soc. chim. France*, **5**, D9 (1953).

(4) A. T. Fuller and H. King, *J. Chem. Soc.*, 963 (1947).

(5) C. R. Hauser and W. B. Renfrow, Jr., *Org. Syntheses*, Coll. Vol. II, 67 (1953); W. B. Renfrow and C. R. Hauser, *J. Am. Chem. Soc.*, **59**, 2312 (1937).