Wohl-Ziegler Reaction on 6-Methyluracil and its Homologues

By Tarozaemon NISHIWAKI and Toshinao GOTO

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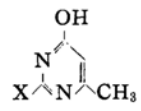
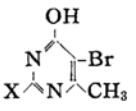
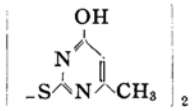
In general, a free radical mechanism has been presented for the Wohl-Ziegler reaction of allylic methyl groups with *N*-bromosuccinimide, but some abnormal reactions such as aromatic nuclear bromination and addition of bromine to olefinic double bonds by this reagent have been believed to proceed via an ionic mechanism. Since hydroxyl groups in the 2-, 4-, or 6-position of pyrimidines tend to increase electron availability at the 5-position in the ring, it seems very interesting to investigate whether such pyrimidines as 6-methyluracil (I), 2-mercapto-6-methyluracil (II), and 2-amino-6-methyluracil (III) are brominated with NBS at allylic side chain or at a nucleus.



(I) X=OH
(II) X=SH
(III) X=NH_2



(IV) X=OH
(VI) X=SH
(VII) X=NH_2



(V)

The Wohl-Ziegler reactions on methylpyrimidines are scarecely known. 5-Methyl-barbituric acid[1] and 5-methyl-2,4,6-trichloropyrimidine[2] are brominated at the methyl groups while 2-methyl-4H-pyrido-(1,2-a)-4-pyrimidone[3] are brominated at the nucleus. With *N*-chlorosuccinimide (NCS) uracil, thymine and 2-methylmercapto-6-methyluracil gave nuclear-substituted product in glacial acetic acid and allylic side chain substituted-products in chloroform plus benzoyl peroxide[4].

When the reaction of 6-methyluracil (I) and NBS was undertaken under the classical free radical condition, a halogen-containing product, which decomposed at 251°C, was obtained. Analytical values indicated that this was the brominated compound of I. The melting point of 5-bromo-6-methyluracil (IV), however, was reported to be 247°C (decomp.) by Matsukawa et al.[5] and to be 241°C (decomp.)

1) T. Nishiwaki, unpublished work.
2) M. Hasegawa, *Pharm. Bull. (Japan)*, **1**, 387 (1953).
3) R. Adams et al., *J. Am. Chem. Soc.*, **76**, 1845 (1954).
4) R. West et al., ibid, **76**, 3146 (1954).
5) T. Matsukawa et al., *J. Pharm. Soc. Japan (Yakugaku Zasshi)*, **70**, 134 (1950).

by Kurtev et al.[6] The site of the bromine atom in the present compound was concluded to be at C_5-position by its unreactive character (e. g. unsuccessful condensation with ethyl malonate)[7] and also by the fact that chlorination of this material yielded 5-bromo-2, 4-dichloro-6-methylpyrimidine[5]. Attempted bromination of 6-methyl-2,4-dichloropyrimidine and 5-bromo-6-methyluracil failed even under illumination with electric light.

2-Mercapto-6-methyluracil (II) was then brominated under the analogous condition. The reaction products were separated by the difference of solubility in ethyl acetate. Ethyl acetate insoluble compound contained no halogen, decomposed gradually over 290°C and could be recrystallized from methanol. From the analytical data, this compound was inferred to be identical with the starting material or with the disulfide (V), solvated with methanol. However, the latter structure was denied because of unsuccessful reduction with sodium borohydride and of the positive reaction for the thiol group with sodium nitroprusside. The reduction of disulfide bond with sodium borohydride was reported by Walton et al.[8] This compound was identified as the starting material by successive benzylation using Bucher's method[9]. From ethyl acetate soluble fraction, a halogen-containing compound with m. p. 256°C (decomp.) was obtained, which was shown to be 5-bromo-2-mercapto-6-methyluracil (VI) by analysis, comparison of its physical data with that reported by Barrett et al.[10,11], positive sodium nitroprusside reaction and failure to brominate this product further, while the expected compound would be susceptible to the further bromination at reactive C_5-position, if the bromine had attacked the allylic methyl group. Direct bromination of pyrimidines having alkyl- or aryl-free sulfhydryl group at C_2-position had scarecely been reported and Barrett et al. prepared 5-brom-2-mercapto-6-methyluracil (VI) through demethylation of 5-bromo-2-methylmercapto-6-methyluracil by hydrogen iodide. However, it has been revealed that this compound was conveniently prepared by the present method, though in low yield. As 2-methylmercapto-6-methyluracil was substituted at an allylic side chain by NCS, it was also anticipated that this pyrimidine could be brominated at the same position. However, contrary to the authors' expectation, none of the halogen-containing product was obtained, resulting in the quantitative recovery of the starting material.

Under the same condition 2-amino-6-methyluracil (III) was also shown to be brominated at the nucleus by NBS. The reaction product, 5-bromo-2-amino-6-methyluracil (VII), seemed to be unstable in water, because the aqueous solution of this pyrimidine became acidic.

It has also been disclosed that these pyrimidines (I), (II), (III) were brominated at C_5-position even in the absence of benzoyl peroxide, in about the same yield as that when benzoyl peroxide was present. From these results it seems possible to conclude that electrophilic attack by NBS took place at C_5-position of these three hydroxylpyrimidines.

During the course of this work, the attempt has been made to synthesize 5-bromo-2-benzylmercapto-6-methyluracil. However, this product could not be purified without causing hydrolysis to 5-bromo-6-methyluracil.

Experimental

5-Bromo-6-methyluracil (IV). — Mixtures of 6-methyluracil (12.6 g.), NBS (17.8 g.), benzoyl peroxide (20 mg.) and carbon tetrachloride (100 ml.) were refluxed for 2.5 hr. on a steam bath. After cooling, the solid was collected, and was heated in ethyl acetate (100 ml.) for 50 min. The ethyl acetate insoluble material, after being collected while hot, was successively washed with ethanol (20 ml.), water (10 ml.), and dried at 100°C for one hour, which was recrystallized from glacial acetic acid (charcoal), to give 5-bromo-6-methyluracil, colorless needles, (9.67 g.), m. p. (uncorrected) 251°C (decomp.).

Anal. Found: C, 29.61; H, 2.50; N, 13.44. Calcd. for $C_5H_5BrN_2O_2$: C, 29.29; H, 2.45; N, 13.66%.

5-Bromo-2, 4-dichloro-6-methylpyrimidine. — The above brominated pyrimidine (IV) (1.50 g.) was heated with mixtures of phosphorous oxychloride (8 ml.) and dimethylaniline (8 ml.) for one hour on an oil bath. The excess of dimethylaniline was removed under reduced pressure, the residue was poured on crushed ice (100 g.). Ether extraction afforded, after removal of the solvent, a compound, b. p. 65~70°C/10 mmHg. It has solidified and then was recrystallized from petroleum ether (b. p. 30~60°C), colorless needles (100 mg.), m. p. (uncorrected) 40~42.5°C. Matsukawa et al. gave m. p. 42~43°C for 5-bromo-2, 4-dichloro-6-methylpyrimidine.

6) B. Kurtev et al., *Chem. Abstr.*, **47**, 1607 (1953).
7) None reactivity of halogen atom at C_5-position of pyrimidine has been discussed. Cf. J. Chesterfield et al., *J. Chem. Soc.*, **1955**, 3478.
8) E. Walton et al., *J. Am. Chem. Soc.*, **76**, 4748 (1954).
9) K. Bucher, *Pharm. Acta Helv.*, **26**, 145 (1951).
10) H. Barrett, U. S. Pat., 2,585,615 (1952).
11) H. Barrett et al., *J. Am. Chem. Soc.*, **70**, 1753 (1948).

Bromination of 2-Mercapto-6-methyluracil.—Mixtures of 2-mercapto-6-methyluracil [12] (1.4 g.), NBS (1.8 g.), benzoyl peroxide (10 mg.) and carbon tetrachloride (20 ml.) were refluxed for 45 min. on a steam bath. After cooling, the solid was collected, which was again heated with ethyl acetate (20 ml.) for 15 min. The ethyl acetate insoluble material, after being collected while hot, was successively washed with ethanol (10 ml.), water (10 ml.) and dried at 100°C for one hour, which was twice recrystallized from methanol (charcoal) to give light cream-colored rectangulars, (300 mg.). This compound began to decompose over 290°C.

Anal. Found: C, 42.22; H, 3.98; N, 18.58. Calcd. for $C_5H_5N_2OS \cdot \frac{1}{4}CH_3OH$ (II): C, 41.98; H, 4.69; N, 18.66%.

Ethyl acetate filtrate was evaporated to dryness and the residue was twice recrystallized from a large volume of ethanol (charcoal) to give 5-bromo-2-mercapto-6-methyluracil, in small needles (100 mg.), m. p. (uncorrected) 256°C (decomp.).

Anal. Found: Br, 36.20. Calcd. for $C_5H_5BrN_2OS$: Br, 36.15%.

By concentration of the mother liquor, succinimide (300 mg.) was recovered.

Barrett gave m. p. 260°C (decomp.) for 5-bromo-2-mercapto-6-methyluracil (VI) [10].

2-Benzylmercapto-6-methyluracil.—Bucher's preparative method for this compound was slightly modified as follows.

A solution of the above ethyl acetate insoluble, bromine-free pyrimidine (m. p. was over 290°C) (210 mg.) in 0.5 N aqueous sodium hydroxide (3 ml.) was refluxed with benzyl chloride (1 ml.) and ethanol (8 ml.) for 20 min. on a steam bath. After being refrigerated overnight, the precipitate was collected, washed with water and recrystallized from ethanol to give 2-benzylmercapto-6-methyluracil in rods (120 mg.), m. p. (uncorrected) 183~184°C.

Bucher gave m. p. 183~184°C for this compound [9].

5-Bromo-2-amino-6-methyluracil (VII).—Mixtures of 2-amino-6-methyluracil [13] (1.25 g.), NBS (1.78 g.), benzoyl peroxide (10 mg.) and carbon tetrachloride (20 ml.) were refluxed for one hour on a steam bath. After cooling, the solid was collected, which was again heated in ethyl acetate (20 ml.) for 20 min. on a steam bath. The ethyl acetate insoluble material, being collected while hot, was washed with water (10 ml.) and dried at 100°C for one hour (1.69 g.). Recrystallization from water (charcoal) gave 5-bromo-2-amino-6-methyluracil as cream-colored plates (220 mg.), m. p. (uncorrected) 249~250°C (decomp.).

Todd et al. gave m. p. 250°C (decomp.) for this *pyrimidine* [14]. The recrystallization mother liquor (pH 4.0) was concentrated at reduced pressure to about 5 ml. (pH 2.6), which was adjusted to pH 7 with 1 N aqueous sodium hydroxide to give colloidal substance.

In the bromination of the above three pyrimidines (I)—(III) in the absence of benzoyl peroxide, yields and melting points were shown in Table I.

TABLE I. BROMINATION OF I, II AND III IN THE ABSENCE OF BENZOYL PEROXIDE with NBS

Pyrimidines examined		Yield	m. p. (decomp.), °C
I	(0.6 g.)	(400 mg.)	249
II	(1.4 g.)	(50 mg.)	256
III	(1.2 g.)	(200 mg.)	246

Bromination of 2-benzylmercapto-6-methyluracil.—2-Benzylmercapto-6-methyluracil (4.0 g.) was dissolved in glacial acetic acid (50 ml.) containing acetic anhydride (2.5 ml.). To this solution was added bromine (5 ml.) in glacial acetic acid (20 ml.) with stirring during 10 min. After heating on a steam bath for 15 min. with stirring, a yellow precipitate was collected (3.0 g., m. p. 200°C, decomp.) which was recrystallized from 95% ethanol (charcoal) to give colorless rods, m. p. (uncorrected) 249~250°C (decomp.). Recrystallization from absolute ethanol or glacial acetic acid also gave the same hydrolized compound, 5-bromo-6-methyluracil.

Anal. Found: N, 13.58; Br, 38.69. Calcd. for $C_5H_5BrN_2O_2$: N, 13.66; Br, 38.98%.

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The Research Laboratory
Oriental Photo Industrial Co., Ltd.
Nishiochiai, Shinjuku-ku, Tokyo

12) H. Snyder et al., *J. Am. Chem. Soc.*, **76**, 2441 (1954).
13) J. Jaeger, *Ann.*, **262**, 365 (1891).
14) A. Todd et al., *J. Chem. Soc.*, **1947**, 41.