UDC 547.853.07

8) Tarozaemon Nishiwaki : Bromination of Pyrimidines by N-Bromosuccinimide.

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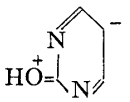
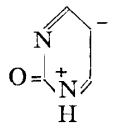
Since the discovery of N-bromosuccinimide (NBS) as an allylic brominating reagent by Ziegler and his associates,[1] ample evidence has been presented that this type of reaction proceeds through a radical chain mechanism.[2~4] However, some cases have been known where aromatic compounds were ring-brominated by this reagent, mechanism of which has been considered to be an ionic one on the basis of their experimental conditions.[5,6]

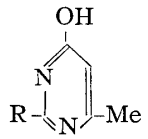
In heterocyclic compounds, the case is somewhat complicated due to the presence of a heteroatom and competition is observed between the side-chain and the ring bromination, even in the presence of benzoyl peroxide, on methyl-substituted thiophenes and benzofurans.[7~9]

In pyrimidine series, while 1,3-arrangement of the nitrogen atoms produces effect which reinforces each other and causes reduced electron availability in the 2-, 4-, and 6-positions, and to a small extent in the 5-position, and hydroxyl, amino, or mercapto group in the 2-, 4-, and 6-positions tends to increase electron availability at the 5-position. The resonance forms having a negative charge at the 5-position in 2-hydroxypyrimidine are shown below.





Previously, the author reported that 6-methyluracil (I) and its 2-mercapto- and 2-amino homologs (II and III) were brominated to give the corresponding 5-bromo compound by NBS in carbon tetrachloride in the absence, and further in the presence, of benzoyl peroxide.[10] If these reactions proceed through electrophilic attack of the 5-position by NBS, it is assumed that polar environmental factors would further facilitate these reactions. To prove this, bromination of an assortment of pyrimidines (I~XXIV) by NBS was undertaken in glacial acetic acid, sometimes in the presence of catalysts, such as aluminium chloride, stannic chloride, ferric chloride, or picric acid. The result showed that pyrimidines having one or two potentially tautomeric groups were all preferentially brominated at the 5-position, although in some mercaptopyrimidines, complicated results were observed.



(I) R=OH (III) R=NH_2
(II) R=SH (IV) R=SMe

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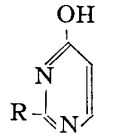
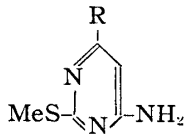
1) K. Ziegler, A. Späth, E. Schaaf, W. Schumann, E. Winkelmann : Ann., **551**, 80 (1942).
2) H. Dauben, Jr., L. McCoy : J. Am. Chem. Soc., **81**, 4863 (1959).
3) C. Djerassi : Chem. Revs., **43**, 271 (1948).
4) L. Horner, E. Winkelmann : Angew. Chem., **71**, 349 (1959).
5) H. Schmid : Helv. Chim. Acta, **29**, 1141 (1946).
6) E. Braude, E. Waight : J. Chem. Soc., **1952**, 1116.
7) E. Campaigne, W. LeSuer : J. Am. Chem. Soc., **70**, 1555 (1948).
8) K. Dittmer, R. Martin, W. Herz, S. Cristol : *Ibid.*, **71**, 1201 (1949).
9) H. Erlenmeyer, W. Grubenmann : Helv. Chim. Acta, **30**, 297 (1947).
10) T. Nishiwaki, T. Goto : Bull. Chem. Soc. Japan, **33**, 26 (1960).

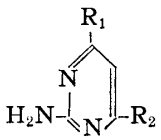
For example, in the case of 2-mercapto-6-methyluracil (II), 2-mercaptouracil (VI), and 2,4-dimercapto-6-methylpyrimidine (XVII), none of the bromo compounds was isolated, though (II) gave its 5-bromo compound in 5% yield in carbon tetrachloride.[10] As immediate reaction took place invariably with separation of free bromine on adding NBS to the hot suspension of these mercaptopyrimidines in glacial acetic acid, oxidation products, such as sulfides or disulfides, might partly be produced, separation of reaction mixtures being difficult because of their extremely insoluble properties in organic solvents. Such an oxidation of mercapto compound with NBS was observed on 2-mercapto-5-methylimidazole by Heath, Lawson, and Rimington.[11]



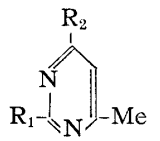
(V) R=OH
(VI) R=SH
(VII) R=NH_2
(VIII) R=SMe
(IX) K=SEt



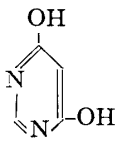
(X) R=OH
(XI) R=Cl



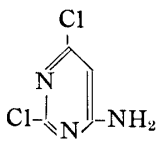
(XII) $R_1=R_2=H$
(XIII) $R_1=R_2=Cl$
(XIV) $R_1=R_2=Me$
(XV) $R_1=SH$, $R_2=Me$
(XVI) $R_1=Ph$, $R_2=Me$



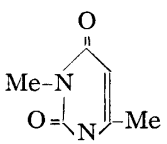
(XVII) $R_1=R_2=SH$
(XVIII) $R_1=R_2=Cl$
(XIX) $R_1=R_2=OMe$
(XX) $R_1=SMe$, $R_2=H$
(XXI) $R_1=SMe$, $R_2=Cl$



(XXII)



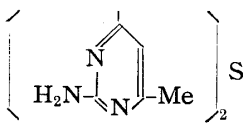
(XXIII)



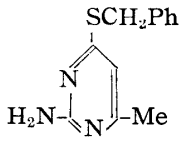
(XXIV)

However, in 2-amino-4-mercapto-6-methylpyrimidine (XV), corresponding 5-bromo compound was obtained in 19% yield, the structure of which was established by comparison with authentic sample prepared by reaction of 2-amino-4-chloro-5-bromo-6-methylpyrimidine and thiourea.

Reaction of halo compound with thiourea is considerably influenced by experimental condition. Thus, generally, mercapto compound is isolable in absolute ethanol, while aqueous ethanol is favorable for the formation of sulfide. In extensive invesigation on the synthesis of mercaptopyrimidines, Polonovski and Schmitt[12] reported that bis(2-amino-6-methyl-4-pyrimidinyl) sulfide (XXV) was the only isolable product on the reaction of 2-amino-4-chloro-6-methylpyrimidine with thiourea in ethanol.[12] This may be probably due to the latter solvent system, because (XXV) was obtained in 80% ethanol and 2-amino-4-mercapto-6-methylpyrimidine (XV) in absolute ethanol in the present investigation. The latter compound was further characterized as 2-amino-4-benzylmercapto-6-methylpyrimidine (XXVI).



(XXV)



(XXVI)

According to Schmid, bromination of benzene and toluene with NBS was catalytically accelerated by 1 mole of aluminium chloride, zinc chloride, ferric chloride, or concentrated sulfuric acid.[5] Such a tendency was also observed in the present work. Though 2-methylthio-6-methyluracil (IV) gave its 5-bromo compound in 21% yield and no catalytic action was observed even when 0.1 mole of aluminium chloride, ferric chloride, or stannic

11) H. Heath, A. Lawson, C. Rimington : J. Chem. Soc., **1951**, 2223.
12) M. Polonovski, H. Schmitt : Bull. soc. chim. France, **1950**, 616.

chloride was used, 1 mole of these catalysts slightly raised the yield. Further curiously, 0.1 mole of picric acid was sufficient to facilitate this reaction. These results are indicated in Table I, which further support an ionic mechanism.

Table I. Yield of 2-Methylthio-5-bromo-6-methyluracil in the Presence of Equimolar Weight of Catalyst to (IV)

Catalyst	Yield (%)
$AlCl_3$	42
$FeCl_3$	31
$SnCl_4$	30
Picric acid	42
None	21

Of course it must be taken into consideration that succinimide radical attacks point of high electron availability.[13] However, bromination of 2-amino-4,6-dimethylpyrimidine (XIV) by NBS was not inhibited or retarded at all by picric acid, *sym*-trinitrobenzene, hydroquinone, or iodine, which are typical inhibitors or retarders for the radical chain reaction. The reason why (XIV) was selected for this purpose consisted in the view that as this pyrimidine was brominated in quantitative yield in chloroform,[*2] retarding or inhibiting action, if any, would clearly been seen. These results are shown in Table II.

Table II. Yield of 2-Amino-5-bromo-4,6-dimethylpyrimidine in the Presence of 0.1 Mole of Radical Retarder or Inhibitor to 1 Mole of (XIV)

Retarder or Inhibitor	Yield (%)
Picric acid	96
sym-Trinitrobenzene	100
Hydroquinone	96
Iodine	97
None	100

In aromatic series, presence of single alkoxyl, alkylthio, or dialkylamino group becomes driving force for the ring-bromination by NBS.[14~16] On nitrosation or diazo-coupling reaction of pyrimidines, Lythogoe, *et al.* demonstrated that the presense of one or two potentially tautomeric substituents was a pre-requisite for this type of reaction.[17] That potentially tautomeric substituents also played a dominant rôle in the bromination of pyrimidines by NBS was further proved by unsuccessful bromination of O- or S-alkylpyrimidines (XIX~XXI), 1,3,4-trimethyluracil (XXIV), and 2,4-dichloro-6-methylpyrimidine (XVIII).

From these observations, the author would like to suggest that electrophilic attack by NBS took place at the 5-position of pyrimidines, although kinetic investigation would be required to prove this.

Experimental[*3]

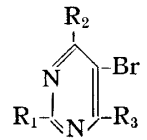
Bromination of Pyrimidines (I~XIV, XVI~XXIV) by NBS; General Method—0.01 mole of the pyrimidine (and 0.01 mole of catalyst when used) was dissolved in 20 cc. of AcOH on a steam bath and to this solution equimolar weight of NBS was added (in the case of 6-methyluracil and uracil, NBS

[*2] Yield of 2-amino-5-bromo-4,6-dimethylpyrimidine was lower in glacial acetic acid than in chloroform. This may be due to partial protonation of (XIV), for electron availability at the 5-position decreases appreciably in protonated pyrimidine.

[*3] Melting points are uncorrected.

13) C. Walling : "Free Radicals in Solution," 381 (1957). John Wiley & Sons, Inc., New York.
14) Ng. Buu-Hoï : Ann., **556**, 1 (1944).
15) W. Groebel : Chem. Ber., **92**, 2887 (1959).
16) Ng. Buu-Hoï : Rec. trav. chim., **73**, 197 (1954).
17) B. Lythogoe, A. Todd, A. Topham : J. Chem. Soc., **1944**, 315.

TABLE III. Melting Point, Yield, and Analytical Data of 5-Bromopyrimidines (catalyst not used)



No.	Substituent R_1	R_2	R_3	m.p. (°C)	Yield (%)	Recrystn. solvent	Mol. formula	Analysis(%) Calcd. C	Calcd. H	Found C	Found H	Ref.
1	OH	OH	H	294 (decomp.)	59	H_2O	——	—	—	—	—	*a*,*b*)
2	〃	〃	Me	248 (〃)	76	AcOH	——	—	—	—	—	10)
3	H	〃	OH	264 (〃)	61	H_2O	——	—	—	—	—	*c*)
4	NH_2	〃	H	275 (〃)	83	AcOH	——	—	—	—	—	*d*)
5	〃	〃	Me	249 (〃)	61	H_2O	——	—	—	—	—	10)
6	〃	H	H	239～240	62[n])	EtOH	——	—	—	—	—	*e*,*f*)
7	〃	Cl	Cl	235～236	63[n])	〃	$C_4H_2N_3BrCl_2$ [o])	19.78	0.83	19.99	1.15	
8	〃	Me	Me	183～184	75[n])	H_2O	——	—	—	—	—	*g*,*h*)
9	〃	Ph	〃	125～128	70[n])	*n*-Heptane	$C_{11}H_{10}N_3Br$ [o])	50.02	3.82	50.10	3.73	
10	Cl	Cl	NH_2	155～157	79[p])	H_2O	$C_4H_2N_3BrCl_2$ [o])	19.78	0.83	19.93	1.12	
11	SMe	OH	H	252	41	EtOH	——	—	—	—	—	*i*)
12	〃	〃	Me	246 (decomp.)	21	〃	——	—	—	—	—	*j*)
13	〃	〃	NH_2	——[m])	60	H_2O	$C_5H_6ON_3BrS$ [o])	25.43	2.56	25.57	2.77	*k*)
14	〃	Cl	〃	164～165	66[n])	〃	——	—	—	—	—	*k*)
15	SEt	OH	H	185～187.5	47	EtOH	——	—	—	—	—	*l*)

a) H. Wheeler, H. Merrian : Am. Chem. J., **29**, 478 (1903).
b) Shih Yi Wang : J. Org. Chem., **24**, 11 (1959).
c) J. Chesterfield, J. McOmie, E. Sayer : J. Chem. Soc., **1955**, 3478.
d) H. Wheeler, T. Johnson : Am. Chem. J., **29**, 492 (1903).
e) J. English, J. Clark, J. Clapp, D. Seeger, R. Ebel : J. Am. Chem. Soc., **68**, 453 (1946).
f) C. Ziegler : U. S. Pat. 2,609,372 (1952).
g) W. Huber, H. Hölscher : Ber., **71B**, 87 (1938).
h) Private communication from Dr. McOmie, Bristol University, to whom warm thanks are due.
i) H. Barrett, I. Goodman, K. Dittmer : J. Am. Chem. Soc., **70**, 1753 (1948).
j) T. Matsukawa, B. Ohta : Yakugaku Zasshi, **70**, 134 (1950).
k) T. Johnson, C. Johns : Am. Chem. J., **34**, 175 (1904).
l) H. Wheeler, T. Johnson : *Ibid.*, **31**, 591 (1904).
m) It began to darken at ca. 220°, but did not melt. Johnson, *et al.* also gave no m.p.[k])
n) Yield was quantitative in chloroform or carbon tetrachloride.
o) Appearances : No. 7, colorless slender needles; No. 9, colorless rods; No. 10, colorless slender needles; No. 13, colorless elongated needles.
p) Carbon tetrachloride being used and after repeated extraction with hexane, 34% yield of pure compound was obtained.

was added to the hot suspension). Reaction took place immediately, with disappearance of NBS in 1 or 2 min. After heating for 1 hr. on a steam bath, precipitate was collected, washed with water, dried, and crystallized from appropriate solvents (when no precipitate was obtained, hot solution was poured into 100 cc. of water and precipitate was treated as before). Yield,*4 melting point, and analytical data are listed in Table III.

Bromination of 2-Amino-4,6-dimethylpyrimidine in Chloroform—Equimolar weight (0.01 mole) of 2-amino-4,6-dimethylpyrimidine, NBS, and 0.001 mole of radical retarder or inhibitor, were refluxed in $CHCl_3$ (20 cc.) on a steam bath. Solvent was distilled off, the residue was heated in water (20 cc.) on a steam bath for 10 min., and warm insoluble product was collected, dried, and recrystallized from a large volume of water.

2-Amino-4-mercapto-6-methylpyrimidine (XV)—2-Amino-4-chloro-6-methylpyrimidine[18] (7.15 g.) and thiourea (3.80 g.) were heated in dehyd. EtOH (150 cc.) on a steam bath for 1.5 hr., and after cool the solid was collected (7.72 g.), which was taken in *N* NaOH (200 cc.), boiled for 1 hr., filtered, and acidified with AcOH. Precipitate was collected, washed with water (3.83 g., 54%), and recrystallized from water to 2-amino-4-mercapto-6-methylpyrimidine as light yellow rods. It began to redden at ca. 240°, but did not melt. *Anal.* Calcd. for $C_5H_7N_3S$: C, 42.53; H, 5.00. Found : C, 42.40; H, 4.84. Gabriel, *et al.* gave no m.p. for this compound, which they prepared by the action of KSH.[18]

2-Amino-4-benzylthio-6-methylpyrimidine(XXVI)—2-Amino-4-mercapto-6-methylpyrimidine (0.42 g.) was dissolved in *N* NaOH (5 cc.) and to this solution, EtOH (10 cc.) and BzCl (1 cc.) were added. After heating for 1 hr., mixture was diluted with water (20 cc.) and precipitate was collected, washed with water (0.41 g., 61%) and crystallized from petr. ether (b.p. 30~60°) to 2-amino-4-benzylthio-6-methylpyrimidine as colorless needles, m.p. 118~120°. *Anal.* Calcd. for $C_{12}H_{13}N_3S$: C, 62.30; H, 5.66. Found : C, 62.07; H, 5.34.

Bis(2-amino-6-methyl-4-pyrimidinyl) Sulfide (XXV)–2-Amino-4-chloro-6-methylpyrimidine (1.43 g.) and thiourea (0.76 g.) were heated in 80% EtOH under reflux for 5 hr. The solvent was evaporated and yellow residue (0.70 g.) was crystallized twice from water to bis(2-amino-6-methyl-4-pyrimidinyl) sulfide hydrate as bright yellow prisms, m.p. 226° (decomp.). Polonovski, *et al.* gave m.p. 224° (decomp.).[12] *Anal.* Calcd. for $C_{10}H_{12}N_6S \cdot H_2O$: C, 45.09; H, 5.30. Found : C, 44.69; H, 5.00.

2-Amino-4-mercapto-5-bromo-6-methylpyrimidine—a) To a hot mixture of 2-amino-4-mercapto-6-methylpyrimidine (1.41 g.) and AcOH (20 cc.), NBS (1.78 g.) was added and heated for 10 min. on a steam bath with occasional shaking and cooled in an ice bath. Solid was collected (0.46 g., 19%), which was dissolved in warm 2*N* NaOH (30 cc.), filtered, and acidified with AcOH. After initially precipitated amorphous solid was removed, yellow needles were obtained, which were crystallized from water to 2-amino-4-mercapto-5-bromo-6-methylpyrimidine. It reddened at ca. 195° and decomposed at 202~204°. Melting point did not depress on admixture with authentic sample prepared as in (b). *Anal.* Calcd. for $C_5H_6N_3BrS$: Br, 36.31. Found : Br, 35.95.

b) 2-Amino-4-chloro-5-bromo-6-methylpyrimidine[19] (1.11 g.) and thiourea (0.38 g.) were heated in dehyd. EtOH (20 cc.) under reflux for 3 hr. The solid was collected, which was boiled in *N* NaOH (30 cc.) for 1 hr., filtered, and acidified with AcOH. The precipitate (0.60 g, 55%) was crystallized twice from water to 2-amino-4-mercapto-5-bromo-6-methylpyrimidine, m.p. 205° (decomp.).

The author is indebted to Mr. Haruo Homma of the Scientific Research Institute for microanalysis.

Summary

Pyrimidines having one or two potentially tautomeric groups at the 2–, 4–, or 6–position were brominated preferentially at the 5–position with N–bromosuccinimide in acetic acid. Mechanism for these reactions was considered to be ionic one on the ground of their experimental conditions.

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*4 Yields were calculated on crude products, for these were practically pure.

18) S. Gabriel, J. Colmann : Ber., **32**, 2921(1900).
19) C. Price, N. Leonard, R. Reitsema : J. Am. Chem. Soc., **68**, 766 (1946).