UDC 615.853.07

164. Tarozaemon Nishiwaki*1 : Bromination of Pyrimidines by N-Bromosuccinimide. III.[1] Bromination of Anilino- and Phenoxypyrimidines.

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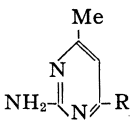
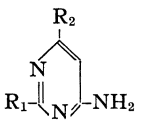
In his originating works on the chemistry of N-halogenoamide, Wohl obtained *p*-bromophenol in undisclosed yield through the reaction of phenol with N-bromoacetamide in ether.[2] The chemistry of N-halogenoamides, especially of N-bromosuccinimide (NBS), however, was extensively developed by virtue of the brilliant work of Ziegler and his fellows,[3] and the further intensive research which ensured had made it possible to use NBS for the ring-bromination of phenols, phenol ethers, phenol thioethers, and aromatic amines.[4]

Two previous papers of the author showed the successful brominations of pyrimidines having one or two potentially tautomeric substituents, preferably amino or hydroxyl groups, with NBS at their C_5-positions.[1] However, consideration of Buu-Hoi,[5] Royer,[6] Abd El-Wahab,[7] Groebel,[8] or Imoto's[9] observations, from which probable conclusion might be drawn that in aromatic compounds preferential bromination occurred at *para* position to an electron-donating group by NBS, if this position was available, would attract the interest to the possible site of attack by NBS on aminopyrimidines having an anilino-, haloanilino-, or phenoxy-group, which is the target point of the present communication, fraught with other observations.

Initially, brominations of 2-amino-4-methyl-6-anilinopyrimidine (I) and 2-amino-4-methyl-6-phenoxypyrimidine (II) were investigated. Although exclusive bromination at the pyrimidine ring was observed in (II), complicated mixture was obtained from (I), from which 2-amino-4-methyl-5-bromo-6-anilinopyrimidine (XIV) could be isolated in poor yield after many abortive attempts, suggesting the possibility of the competitive brominations between the benzene ring and the pyrimidine ring, even though no attempt was made to isolate other product than (XIV).





(I) R=NHPh
(II) R=OPh
(III) R=*o*-NHC_6H_4Cl
(IV) R=*m*-NHC_6H_4Cl
(V) R=*p*-NHC_6H_4Cl
(VI) R=*p*-NHC_6H_4Br
(VII) R=Cl
(VIII) R=H
(IX) R=$C_5H_{10}N$
(X) R_1=SMe R_2=OMe
(XI) R_1=R_2=Me
(XII) R_1=SEt R_2=Me
(XIII) R_1=H R_2=Me

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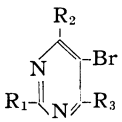
1) T. Nishiwaki : Bull. Chem. Soc. Japan, **33**, 26 (1960) and *Idem* : This Bulletin, **9**, 38 (1961) are designated as Part I and II of this series, respectively.
2) A. Wohl : Ber., **52**, 51 (1919).
3) K. Ziegler, A. Späth, E. Schaaf, W. Schumann, E. Winkelmann : Ann., **551**, 80 (1942).
4) E. Müller : "Methoden der organischen Chemie," Band V/4, 29, 268, 274, 297 (1960). Georg Thiene Verlag, Stuttgart.
5) Ng. Buu-Hoi : Rec. trav. chim., **73**, 197 (1954).
6) R. Royer : Ann. chim., (12) **1**, 418 (1946).
7) M. Abd El-Wahab, M. Barakat : Monatsh., 88, 698 (1957).
8) W. Groebel : Chem. Ber., **92**, 2887 (1959).
9) S. Okawara, H. Sato, E. Imoto : Kogyo Kagaku Zasshi, **58**, 924 (1955).

TABLE I. Melting Point, Yield and Analytical Data of 5-Bromopyrimidines prepared from (II～VIII, X～XIII) and NBS



No.	R_1	R_2	R_3	M.p. (°C)	Yield (%)	Reaction time (min.)	Appearance
XV	NH_2	Me	OPh	170.5～171	89	45	Plates
XVI	〃	〃	o-NHC_6H_4Cl	172 ～173	89	40	Needles
XVII	〃	〃	m-NHC_6H_4Cl	210 ～212	96	40	Rods
XVIII	〃	〃	p-NHC_6H_4Cl	195 ～197	90	60	Needles
XIX	〃	〃	p-NHC_6H_4Br	202 ～204[e]	90	60	
XX	〃	〃	Cl	207 ～208	94	60	Plates
XXI	〃	H	〃	194	81	60	Prisms
XXIII	SMe	OMe	NH_2	138 ～140	88	90	Rods
XXIV	Me	Me	〃	142 ～143.5	87	60	Needles
XXV	SEt	〃	〃	113 ～114.5	44	90	Plates
XXVI	H	〃	〃	194	83	90	Rods

No.	Recrystn. solvent	Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H	Ref.
XV	aq. Me_2CO	$C_{11}H_{10}ON_3Br$	47.16	3.60	47.04	3.70	
XVI	EtOH	$C_{11}H_{10}N_4BrCl$	42.13	3.21	42.42	3.29	
XVII	MeOH	$C_{11}H_{10}N_4BrCl$	42.13	3.21	41.99	3.41	
XVIII	〃	$C_{11}H_{10}N_4BrCl$	42.13	3.21	42.32	3.63	
XIX	〃	$C_{11}H_{10}N_4Br_2$	36.90	2.82	37.18	2.92	
XX	EtOH	$C_5H_5N_3BrCl$	26.99	2.26	26.93	2.22	a)
XXI	〃	$C_5H_6N_3Br$	Br, 42.50		Br, 42.56		b)
XXIII	MeOH	$C_6H_8ON_3BrS$	28.81	3.22	28.95	3.23	c)
XXIV	H_2O	$C_6H_8N_3Br \cdot \frac{1}{4}H_2O$[f]	34.88	4.14	34.86	4.06	
XXV	aq. EtOH	$C_7H_{10}N_3BrS$	33.87	4.06	33.87	4.05	
XXVI	H_2O	—	—	—	—	—	d)

a) C. Price, N. Leonard, R. Reitsema : J. Am. Chem. Soc., **68**, 766 (1946).
b) E. Benary : Ber., **63**, 2601 (1930).
c) T. Ulbricht, C, Price : J. Org. Chem,. **21**, 567 (1956).
d) S. Gabriel, J. Colman : Ber., **34**, 1234 (1901).
e) This compound begins to melt at ca. 198°
f) This sample was submitted for microanalysis after drying over P_2O_5 under reduced pressure (20 mm. Hg) at 75° for 10 hr.

However, compounds (III～VI), in which a benzene ring has a halogen substituent in various sites, gave their respective 5-bromopyrimidines (XVI～XIX) in excellent yield. The site of bromination in these compounds was further verified by an independent preparation of their corresponding 5-bromopyrimidines from 2-amino-4-methyl-5-bromo-6-chloropyrimidine (XX) and a halogen-substituted aniline, which itself could be prepared by the reaction of 2-amino-4-methyl-6-chloropyrimidine (VII) and NBS. That halogen atoms on a pyrimidine ring were not detrimental to this type of reaction has already been indicated.[1)]

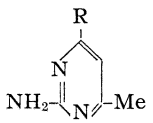
This, along with other similar reactions recorded subsequently, incidentally, justifies the contention of McOmie *et al.*[10)] that a halogen atom at the C_5-position of a pyrimidine ring is unreactive.

In this connection, special attention should be attacked to the report of Phillips and Maggiolo[11)] who recorded the melting point of 2-amino-4-methyl-5-bromo-6-*p*-chloroanilinopyrimidine (XVIII) as 260～261° synthesized by the dropwise addition of bromine to

10) J. Chesterfield, J. McOmie, E. Sayer : J. Chem. Soc., **1955**, 3478.
11) A. Phillips, A. Maggiolo : J. Am. Chem. Soc., **74**, 3922 (1952).

the glacial acetic acid solution of 2-amino-4-methyl-6-*p*-chloroanilinopyrimdine (V). The product obtained had m.p. 195～197°, quite different from that described by Phillips *et al.*, but its authenticity could be confirmed by an elemental analysis and an independent preparation. The check of their method afforded none of their product, the compound having m.p. 196～198° being the sole product. The melting point of 2-amino-4-methyl-5-bromo-6-*p*-bromoanilinopyrimidine (XIX) was somewhat higher than that recorded by Phillips *et al.*

Table II. 2-Amino-4-methyl-5-bromo-6-chloro-(or bromo-)substituted-anilinopyrimidines prepared from XX



R	Yield (%)	M.p. (°C)
o-NHC_6H_4Cl	92	172～174
m-NHC_6H_4Cl	100	210～212
p-NHC_6H_4Cl	100	195～197
p-NHC_6H_4Br	100	203～204.5

As was indicated previously,[1] that the presence of a single amino group at 2-, 4- or 6-position would be sufficient for the ring bromination of pyrimidine compounds at their C_5-position with NBS could be further ascertained by successful bromination of such 2- or 6-aminopyrimidines (VIII～XIII) with NBS, and moreover bromination product of (X) was confirmed by an another method.

During the course of this study, a convenient method for the preparation of 4-methyl-6-aminopyrimidine (XIII) was developed through desulfurization of 4-methyl-6-amino-2-pyrimidinethiol with Raney-nickel, which was the condensation product of thiourea and β-crotonitrile.[12] Gabriel and Colman prepared (XIII) starting from 4-methyluracil via chlorination, amination and subsequent dechlorination with hydrogen iodide and red phosphorous, or with zinc dust.[13]

Experimental*2

2-Amino-4-methyl-6-*o*-chloroanilinopyrimidine (III)——2-Amino-4-methyl-6-chloropyrimidine (4.32 g.) and *o*-chloroaniline (3.9 g.) were heated in boiling water (45 cc.) containing conc. HCl (1 cc.) for 1 hr. The mixture was diluted with water, made alkaline with NH_4OH, and the product (6.72 g.) was crystallized from EtOH to give (III) as colorless needles, m.p. 183～184°. *Anal.* Calcd. for $C_{11}H_{11}N_4Cl$: C, 56.29; H, 4.72. Found: C, 56.13; H, 4.73.

2-Amino-4-methyl-6-*m*-chloroanilinopyrimidine (IV)——2-Amino-4-methyl-6-chloropyrimidine (4.32 g.) and *m*-chloroaniline (3.9 g.) were heated in boiling water (45 cc.) containing conc. HCl (1 cc.) for 1 hr. The reaction mixture was diluted with water, made alkaline with NH_4OH, and the product (4.74 g.) was recrystallized several times from benzene to give (IV) as colorless needles, m.p. 164～166°. *Anal.* Calcd. for $C_{11}H_{11}N_4Cl$: C, 56.29; H, 4.72. Found: C, 56.32; H, 5.03.

2-Amino-4-methyl-5-bromo-6-anilinopyrimidine (XIV)——2-Amino-4-methyl-6-anilinopyrimidine (2.00 g.) and NBS (1.78 g.) were heated in refluxing CCl_4 (20 cc.) for 45 min. After removing succinimide, the filtrate was cooled in an ice bath to give the product, which was heated in boiling water (50 cc.) for 30 min. After cooling, the product was collected and crystallized from benzene-*n*-hexane (charcoal) to give colorless crystals, m.p. 140～145°, (0.90 g.). Further recrystallization from 50% Me_2CO gave (XIV) as colorless needles (0.20 g.), m.p. 151～153°. Melting point did not depress on admixture with the sample prepared by the method of Phillips *et al.*, which had m.p. 151～153°.

2-Amino-4-methyl-5-bromo-6-piperidinopyrimidine (XXII)——2-Amino-4-methyl-6-piperidinopyrimidine (IX) (1.65 g.) and NBS (1.53 g.) were heated in CCl_4 (20 cc.) for 30 min. Succinimide was filtered off, the filtrate was evaporated, 50% EtOH was added to the residue and left for several days.

*2 All melting points were uncorrected.

12) M. Polonovski, M. Pesson, H. Schmitt: Bull. soc. chim. France, **1948**, 392.

13) S. Gabriel, J. Colman: Ber., **32**, 2921 (1899).

Precipitated sticky solid was pressed on the porous plate (1.20 g.) and crystallized from aq. Me_2CO (charcoal) to give (XXII) as colorless needles, m.p. 97~100°. *Anal.* Calcd. for $C_{10}H_{15}N_4Br$: N, 20.67. Found : N, 20.66.

Its picrate was crystallized from 2-butanone as bright yellow needles, m.p. 192.5°. *Anal.* Calcd. for $C_{16}H_{18}O_7N_7Br$: N, 19.60. Found : N, 19.74.

Bromination of Pyrimidines (II~VIII, X~XIII) with NBS——Respective pyrimidine (0.01 mole) and NBS (0.01 mole) were heated in CCl_4 (20 cc.) for the specified period. Solvent was evaporated and the residue, after being treated with water (20 cc.) on a steam bath for 10 min., was crystallized from an appropriate solvent. Reaction time, yield, melting point and analytical data are shown in Table I.

2-Amino-6-methylpyrimidine (XIII)——4-Methyl-6-amino-2-pyrimidinethiol (10.00 g.) and Raney-Ni sludge prepared from 30 g. of alloy under the direction of Mozingo[14] were heated in boiling water (150 cc.) for 2 hr. and Ni was filtered and washed with water. Filtrate was combined with the washings and evaporated under reduced pressure. The residue was pressed on the porous plate (7.45 g., 97%) and crystallized from water (15 cc.) to give the compound (XIII) as colorless plates, m.p. 194~195°. Gabriel and Colman noted m.p. 194~195° for this pyrimidine.[13]

Independent Preparations of Several 5-Bromopyrimidines (XVI~XIX)——2-Amino-4-methyl-5-bromo-6-chloropyrimidine (0.64 g.) and an appropriate chloro- or bromo-aniline (0.4 g.) were heated in water (8 cc.) and conc. HCl (0.5 cc.) for 30 min. The reaction mixture was diluted with water and made alkaline with NH_4OH. Precipitate was crystallized from EtOH or MeOH.

2-Methylthio-4-amino-5-bromo-6-methoxypyrimidine (XXIII)——2-Methylthio-4-chloro-5-bromo-6-aminopyrimidine (1.70 g.) was boiled with MeONa solution prepared from Na (0.20 g.) and MeOH (20 cc.) for 40 min. After the solvent was evaporated, water was added to the residue and the collected product (1.63 g.) was crystallized from MeOH, m.p. 138~140°.

Summary

2-Aminopyrimidines were brominated at their C_5-positions predominantly with NBS in carbon tetrachloride in spite of the presence of an anilino-, haloanilino-, or phenoxy-group at their c_6-positions as substituents.

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14) R. Mozingo : Org. Syntheses, **21**, 15 (1941).

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165. Koichi Nakazawa : Syntheses of Nuclear-substituted Flavonoids and Allied Compounds. IX.[1] Syntheses of Tetramethyl Ether and Dimethyl Ether of Ginkgetin.

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In 1941, the author gave a formula $C_{32}H_{22}O_{10}$ for ginkgetin, a flavone compound isolated from the leaves of maidenhair trees (*Ginkgo biloba*), and suggested a structure of biflavonyl (I),[2] two 4′,5,7-trimethoxyflavone skeletones coupled with each other between positions 3 and 8″.

In order to confirm this structure, this author synthesized afterwards a ketonic compound (ketoflavone) (II) derivable from the structure (I) as an alkaline degradation product, and its 6-substituted isomer, both as trimethyl ethers,[3] which differed from

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1) Part VIII : Yakugaku Zasshi, **76**, 1204 (1956).
2) K. Nakazawa : *Ibid.*, **61**, 174, 228 (1941).
3) K. Nakazawa : S. Matsuura : *Ibid.*, **74**, 40 (1954), **75**, 68, 467, 716 (1955).