623. *Pyrimidines. Part VI.** 5-*Bromopyrimidine.*

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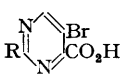
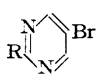
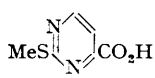
5-Bromopyrimidine has been synthesised from 5-bromo-2-methylpyrimidine-4-carboxylic acid. Raney nickel desulphurisation of 5-bromo-2-methylthiopyrimidine-4-carboxylic acid yields pyrimidine-4-carboxylic acid and 2-methylthiopyrimidine-4-carboxylic acid; that of 5-bromo-2-methylthiopyrimidine yields pyrimidine.

5-Bromopyrimidine was required in connection with studies on the ultra-violet light absorption of pyrimidines (Boarland and McOmie, *J.*, 1952, 3716, 3722). Although many 5-bromopyrimidines are known the parent substance has not previously been prepared. An attempted preparation (Whittaker, *J.*, 1953, 1646) by catalytic dechlorination of 5-bromo-2 : 4-dichloropyrimidine gave only pyrimidine in unspecified yield.

The compound has now been synthesised from 5-bromo-2-methylpyrimidine-4-carboxylic acid (I; R = Me) which was obtained by condensation of acetamidine with mucobromic acid (Budešínský, *Coll. Czech. Chem. Comm.*, 1949, **14**, 223). The pyrimidine acid was smoothly decarboxylated by heat to 5-bromo-2-methylpyrimidine (II; R = Me) which with benzaldehyde in the presence of zinc chloride gave 5-bromo-2-styrylpyrimidine (II; R = Ph·CH:CH·). The same compound was obtained directly, but in poorer yield, from the pyrimidine acid (I; R = Me). The styryl compound was oxidised to the corresponding 5-bromopyrimidine-2-carboxylic acid (II; R = CO_2H) whence thermal decarboxylation gave 5-bromopyrimidine. Budešínský (*loc. cit.*) reported the oxidation of 5-chloro-2-methylpyrimidine-4-carboxylic acid by nitric acid to 5-chloropyrimidine-2 : 4-dicarboxylic acid. However, we were unable to oxidise the bromo-acid (I; R = Me) by nitric acid or potassium permanganate to the corresponding dicarboxylic acid (I; R = CO_2H), which might have been decarboxylated to the required 5-bromopyrimidine.

(I)   (II)  (III)

The synthesis of 5-bromopyrimidine was first attempted starting from 5-bromo-2-methylthiopyrimidine-4-carboxylic acid (I; R = MeS). The preparation of this compound from mucobromic acid and *S*-methylthiuronium sulphate was studied in detail. The highest yields (37%) were obtained by using 1-ethylpiperidine or triethylamine as condensing agent. Even so it was not possible to prepare more than *ca.* 1 gram of the methylthio-acid in each experiment without serious decrease in yield. Raney nickel

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desulphurisation of this acid (I; R = MeS) unexpectedly gave pyrimidine-4-carboxylic acid. Evidently the bromine atom is more labile than the methylthio-group since under milder conditions 2-methylthiopyrimidine-4-carboxylic acid (III) was produced. Simultaneous dehalogenation and desulphurisation also occurred when 5-bromo-2-methylthiopyrimidine (II; R = MeS) was treated with Raney nickel, thereby yielding pyrimidine, whereas similar treatment of 5-bromopyrimidine-2-carboxylic acid resulted in complete degradation or recovery of starting material. Catalytic dehalogenation of pyrimidines in presence of palladium is, of course, well known, but the only recorded use of Raney nickel (with or without added hydrogen) appears to be the dechlorination of 5-chloro-2-(*N*-*m*-aminobenzenesulphonyl-*N*-methylamino)pyrimidine by Raney nickel alloy in methanolic potassium hydroxide (English *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1039).

5-Bromo-2-methylpyrimidine was decomposed when heated with aqueous barium hydroxide. Under the same conditions 2-amino-5-bromo-4 : 6-dimethylpyrimidine was hydrolysed to the corresponding 5-hydroxypyrimidine (Bray, Lake, and Thorpe, *Biochem. J.*, 1951, **48**, 400).

The ultra-violet absorption spectra of 5-bromopyrimidine and of pyrimidine-4-carboxylic acid have already been published (Boarland and McOmie, *loc. cit.*). Data for the other compounds described in this paper are recorded in the Table.

Substituents							
2	4	5	Solvent	λ (mμ)	$\log_{10} \varepsilon_{max.}$	λ (mμ)	$\log_{10} \varepsilon_{max.}$
Ph·CH:CH·	—	Br	EtOH	228	4·11	235	4·04
						308	4·57
CO_2H	—	Br	0·1N-HCl	242	4·33	—	—
			0·1N-NaOH	231	3·97	—	—
Me	CO_2H	Br	0·1N-NaOH	222	3·98	271	3·62
MeS	CO_2H	—	0·1N-NaOH	253·5	4·19	303	3·29
MeS	CO_2H	Br	0·1N-NaOH	262·5	4·37	300 infl.	3·41

Experimental

5-Bromo-2-styrylpyrimidine.—5-Bromo-2-methylpyrimidine (Budešínský, *loc. cit.*) (5·6 g.), benzaldehyde (11·2 g.), and anhydrous zinc chloride (4·3 g.) were heated at 155—160° for 5—6 hr. After steam-distillation to remove benzaldehyde the product was collected in chloroform and purified by recrystallisation from light petroleum (b. p. 60—80°) (charcoal). *5-Bromo-2-styrylpyrimidine* (3·7 g., 44%) formed needles, m. p. 138—140° (Found: C, 55·3; H, 3·2; N, 10·8; Br, 31·2. $C_{12}H_9N_2Br$ requires C, 55·2; H, 3·5; N, 10·7; Br, 30·6%).

5-Bromopyrimidine-2-carboxylic Acid.—Finely powdered potassium permanganate (5·3 g.) and water (11 c.c.) were added separately during 1 hr. to a stirred solution of 5-bromo-2-styrylpyrimidine (3·0 g.) in pyridine (60 c.c.) and water (3 c.c.) at 14—15° (cooling). After being stirred for a further ½ hr. the solution was filtered through a thin bed of Filtercel, and the filter-cake washed with water. The filtrate was diluted with water, then concentrated to *ca.* 30 c.c. and acidified with concentrated hydrochloric acid. The solid was collected, washed with ether, and recrystallised from benzene (charcoal). The *bromo-acid* was obtained in 71% yield as the hemi-hydrate, m. p. 192—193° (Found: C, 28·5; H, 2·1; N, 13·0; Br, 37·6. $C_5H_3O_2N_2Br,\frac{1}{2}H_2O$ requires C, 28·3; H, 1·9; N, 13·2; Br, 37·7%).

5-Bromopyrimidine.—An evacuated sealed tube of 20-c.c. capacity containing the above bromo-acid (0·5 g.) was heated for 1½ hr. in an oil-bath at 250°. The product was sublimed at 80—90° (bath)/20 mm., giving *5-bromopyrimidine* (0·33 g., 85%) as prisms, m. p. 75—76° (Found: C, 29·8; H, 1·9; N, 17·5; Br, 49·8. $C_4H_3N_2Br$ requires C, 30·2; H, 1·9; N, 17·6; Br, 50·3%), slightly soluble in water and readily soluble in chloroform, ethanol, and ether It forms a crystalline complex with mercuric chloride.

5-Bromo-2-methylthiopyrimidine-4-carboxylic Acid.—*S*-Methylthiuronium sulphate (3·0 g.) was dissolved in a warm solution of mucobromic acid (2·8 g.) in water (43 c.c.), and then cooled to 18°. Triethylamine (3·3 g.) was added during 1 hr., with mechanical stirring. Next day a little concentrated hydrochloric acid was added to the solution, and the resulting tar removed by filtration. Further acidification gave a buff solid (1·0 g., 37%), m. p. 173—175°. Recrystallisation from water (charcoal) gave *5-bromo-2-methylthiopyrimidine-4-carboxylic acid* as pale yellow prisms, m. p. 176—177° (decomp.) (Found: C, 29·3; H, 2·0; N, 11·3; S, 12·8; Br, 31·5. $C_6H_5O_2N_2SBr$ requires C, 28·9; H, 2·0; N, 11·3; S, 12·9; Br, 32·1%).

Desulphurisation of 5-Bromo-2-methylthiopyrimidine-4-carboxylic Acid.—(*a*) The bromo-acid

(2 g.) in water (200 c.c.) was heated under reflux for 1¾ hr. with Raney nickel sludge (10 g.) (prepared by Brown's method, *J. Soc. Chem. Ind.*, 1950, **69**, 353), with mechanical stirring. The hot solution was filtered, and the solid washed with hot water (2 × 40 c.c.). The filtrate was concentrated to *ca.* 20 c.c. and set aside overnight. The yield of blue-green prisms of *nickel pyrimidine-4-carboxylate* was 0·65 g. (47·5%) (Found: C, 35·4; H, 2·9; N, 16·8; Ni, 16·7. $C_{10}H_6O_4N_4Ni,2H_2O$ requires C, 35·2; H, 3·0; N, 16·4; Ni, 17·2%). Pyrimidine-4-carboxylic acid (0·3 g.), obtained by the action of hydrogen sulphide on a solution of the nickel salt (0·65 g.), had m. p. 236—237° (decomp.; sealed capillary) (Found: C, 48·1; H, 3·5; N, 22·0. Calc. for $C_5H_4O_2N_2$: C, 48·4; H, 3·3; N, 22·6%). Gabriel and Colman (*Ber.*, 1899, **32**, 1535) give m. p. 240° (decomp.).

(*b*) The bromo-acid (1·0 g.) in water (100 c.c.) was desulphurised as above with Raney nickel sludge (3 g.) during 1¼ hr. The filtered solution yielded green prisms (0·31 g.) of a nickel salt, which was converted by hydrogen sulphide into the free acid (0·09 g.), m. p. 211—213° (decomp.). After three recrystallisations from benzene *2-methylthiopyrimidine-4-carboxylic acid* was obtained as needles (0·048 g.), m. p. 214—215° (decomp.) (Found: C, 42·6; H, 3·4; N, 16·6. $C_6H_6O_2N_2S$ requires C, 42·4; H, 3·6; N, 16·5%).

5-Bromo-2-methylthiopyrimidine.—5-Bromo-2-methylthiopyrimidine-4-carboxylic acid (2·0 g.) (unrecrystallised) was heated just above its m. p. until effervescence ceased. The 5-bromo-2-methylthiopyrimidine was sublimed and recrystallised from aqueous ethanol (charcoal), giving pale yellow leaflets (1·3 g.), m. p. 67°. A second crop (0·1 g.) m. p. 62—65°, was obtained from the mother-liquor, the total yield being 85%. A freshly sublimed sample was colourless and had m. p. 67—68° (Found: C, 29·6; H, 2·8; N, 13·5. Calc. for $C_5H_5N_2SBr$: C, 29·3; H, 2·5; N, 13·2%). Johnson and Joyce (*J. Amer. Chem. Soc.*, 1916, **38**, 1562) record m. p. 64—67° for the compound prepared by bromination of 2-methylthiopyrimidine.

Desulphurisation of 5-Bromo-2-methylthiopyrimidine.—5-Bromo-2-methylthiopyrimidine (1·0 g.) in ethanol (60 c.c.) and ammonia (1·0 c.c.; *d* 0·88) was heated under reflux with Raney nickel sludge (5·0 g.) for 2½ hr. To the filtered solution, after cooling, saturated aqueous mercuric chloride solution was added. The colourless crystals (0·65 g., 38%) had m. p. 230—237° depending on the rate of heating and were identified as pyrimidine mercurichloride by an *X*-ray powder photograph.

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