Pyrimidines. Part VIII. Halogeno- and Hydrazino-pyrimidines.*

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The only three previously unknown chloropyrimidines, namely 4 : 5-dichloro-, 2 : 4 : 5-trichloro-, and 4 : 5 : 6-trichloro-pyrimidine, have now been prepared together with 5-bromo-4 : 6-dichloropyrimidine. 5-Bromo-4-chloropyrimidine has been made by a new route.

Some reactions of these compounds with nucleophilic reagents including hydrazine are recorded and the results of bacteriological tests on the hydrazinopyrimidines are mentioned.

EIGHT of the possible eleven mono- and poly-chloropyrimidines have already been described and this paper records the synthesis of the remaining three, namely 4 : 5-dichloro-, 2 : 4 : 5-trichloro-, and 4 : 5 : 6-trichloro-pyrimidine. In addition, 5-bromo-4 : 6-dichloropyrimidine has been made and 5-bromo-4-chloropyrimidine (Cherbuliez and Stavritch, *Helv. Chim. Acta*, 1922, **5**, 273) prepared by a new route. Apparently, 5-bromopyrimidine (McOmie and White, *J.*, 1953, 3129) and 5-bromo-2 : 4-dichloropyrimidine (Wheeler and Bristol, *Amer. Chem. J.*, 1905, **32**, 437; Whittaker, *J.*, 1953, **1646**) are the only other halogenopyrimidines previously known without other substituents present. The compounds now described were prepared in order to study their ultraviolet spectra (forthcoming publication; cf. Boarland and McOmie, *J.*, 1952, 3716, 3722) and their reactions with nucleophilic reagents.

4-Hydroxypyrimidine in glacial acetic acid, but not in aqueous solution, reacted with chlorine and with bromine to give 5-chloro- and 5-bromo-4-hydroxypyrimidine, respectively. The latter has already been prepared by the action of sodium hypobromite on *N*-methyleneasparagine followed by decarboxylation of the resulting 5-bromo-6-hydroxypyrimidine-4-carboxylic acid (Cherbuliez and Stavritch, *loc. cit.*). 5-Bromo-2-hydroxypyrimidine was obtained from 2-amino-5-bromopyrimidine by treatment with nitrous acid. 4 : 5-Dichloro- and 5-bromo-4-chloro-pyrimidine were prepared from the corresponding 4-hydroxy-compounds by reaction with phosphoryl chloride in presence of dimethylaniline (method of Baddiley and Topham, *J.*, 1944, 679).

Johnson (*Amer. Chem. J.*, 1908, **40**, 19) showed that the chlorination of uracil in aqueous suspension gave a mixture of 5 : 5-dichloro-5 : 6-dihydro-6-hydroxyuracil and 5-chlorouracil, but recorded no yields. By suitable choice of conditions, the former (70%) or the latter (55%) can be obtained as the main product, but the yields are not always reproducible. Conversion of 5-chlorouracil into 2 : 4 : 5-trichloropyrimidine was best effected by using a mixture of phosphoryl chloride and phosphorus pentachloride. An attempt to convert uracil directly into 2 : 4 : 5-trichloropyrimidine by heating it with a large excess of phosphorus pentachloride and phosphoryl chloride (2 : 1) gave only the known 2 : 4-dichloropyrimidine, whereas Childress and McKee (*J. Amer. Chem. Soc.*, 1950, **72**, 4271) obtained 2 : 4 : 5 : 6-tetrachloropyrimidine from barbituric acid under these conditions. Likewise, 5 : 5-dichloro-5 : 6-dihydro-6-hydroxyuracil could not be directly converted into the desired trichloro-compound.

Bromination of 4 : 6-dihydroxypyrimidine in warm water or, better, in acetic acid readily gave the 5-bromo-derivative, but chlorination proved surprisingly difficult. Chlorination at various temperatures in water, aqueous hydrochloric acid, or glacial acetic acid caused degradation of the pyrimidine, and ammonium chloride was the only isolable product. The required 5-chloro-compound was unexpectedly obtained when equimolecular amounts of chlorine and iodine (or more conveniently preformed iodine chloride) were used in warm glacial acetic acid. Iodine chloride normally behaves as an iodinating reagent and, for example, converts 4-amino- into 4-amino-5-iodo-pyrimidine under similar

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conditions (D. J. Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353). The hydroxyl groups of the 5-bromo- and 5-chloro-4 : 6-dihydroxypyrimidines were replaced by chlorine by using phosphoryl chloride and dimethylaniline. Childress and McKee's method (*loc. cit.*) with 4 : 6-dihydroxypyrimidine gave only 4 : 6-dichloropyrimidine, instead of the desired 4 : 5 : 6-trichloro-compound.

The new halogeno-pyrimidines, like those previously described, all have a characteristic smell rather similar to that of acetamidine; they are lachrymatory, and must be handled with care. Some reactions of the compounds were studied; in all cases the halogen atom in position 5 was unreactive. Thus 4 : 5-dichloro- and 5-bromo-4-chloro-pyrimidine with ammonia gave the corresponding 4-amino-5-halogenopyrimidines which have also been prepared by Yanai (*J. Pharm. Soc. Japan*, 1942, **62**, 95) by direct halogenation of 4-amino-pyrimidine. 4 : 5-Dichloropyrimidine with thiourea gave 5-chloro-4-mercaptopyrimidine (cf. Boarland and McOmie, *J.*, 1951, 1218); 2 : 4 : 5-trichloropyrimidine with sodium methoxide gave 5-chloro-2 : 4-dimethoxypyrimidine, and other reactions are given below.

Hydrazinopyrimidines.—In a previous paper (Boarland, McOmie, and Timms, *J.*, 1952, 4691) the results of bacteriological tests on some pyrimidines were recorded. 2-Hydrazino-4 : 6-dimethyl- and 2 : 4-dihydrazino-pyrimidine gave encouraging results and further hydrazino-compounds have been prepared and tested. 5-Chloro-, 5-bromo-, 5-phenyl-, 6-chloro-, and 2 : 5-dichloro-4-hydrazinopyrimidine and also 2-hydrazino-4-phenylpyrimidine were obtained from the corresponding chloropyrimidines by the action of hydrazine hydrate. Similarly, 2- and 4-hydrazinopyrimidine were prepared from the corresponding methoxypyrimidines. 2-Hydrazinopyrimidine has also been prepared from 2-chloropyrimidine (Sirakawa, Ban, and Yoneda, *J. Pharm. Soc. Japan*, 1953, **73**, 598).

The above-mentioned hydrazinopyrimidines (0·1—0·5% solutions in M/15 phosphate buffer of pH 7·38) were tested as before by the agar-cup diffusion method against *Staph. Mayo, Staph. H., Str. viridans, Mycobact. butyricum* Sonne, *Proteus, B. coli, and B. pyocyaneus.* None of the compounds was active against *Str. viridans* or *B. pyocyaneus*, and 2-hydrazinopyrimidine and 2 : 5-dichloro-4-hydrazinopyrimidine were inactive against all the bacteria tested. Since the other hydrazino-compounds were inactive or at best less active than the two hydrazino-compounds previously tested, no details are given here.

Experimental

5-Chloro-4-hydroxypyrimidine.—Chlorine (1·5 g.) was bubbled into 4-hydroxypyrimidine (2·0 g.) in glacial acetic acid (15 ml.). After cooling, the fine, white hydrochloride (2·6 g.) was collected and dissolved in the minimum of cold water, and sodium hydrogen carbonate added until the solution became faintly alkaline. *5-Chloro-4-hydroxypyrimidine* (0·8 g.) slowly separated; recrystallised from water it formed prisms, m. p. 177—179° (Found: C, 36·7; H, 2·1; N, 21·3. $C_4H_3ON_2Cl$ requires C, 36·8; H, 2·3; N, 21·5%).

5-Bromo-4-hydroxypyrimidine.—Bromine (4·4 ml.) in glacial acetic acid was added gradually to 4-hydroxypyrimidine (8 g.) in acetic acid (200 ml.). After several hours, the product (17·2 g.) was recrystallised from ethanol giving *5-bromo-4-hydroxypyrimidine hydrobromide* as needles, m. p. 243—246° (decomp.) (Found: C, 19·6; H, 1·9; N, 10·9; Br, 61·3. $C_4H_3ON_2Br,HBr$ requires C, 18·8; H, 1·6; N, 10·9; Br, 62·5%). Recrystallisation of the hydrobromide from water gave 5-bromo-4-hydroxypyrimidine (6 g.) as leaflets (rapid cooling of a strong solution) or as needles (slow crystallisation from a dilute solution), m. p. 199—200° (Found: C, 27·1; H, 1·5; N, 15·9. Calc. for $C_4H_3ON_2Br$: C, 27·4; H, 1·7; N, 16·0%). Cherbuliez and Stavritch (*loc. cit.*) give m. p. 197°.

5-Bromo-2-hydroxypyrimidine.—2-Amino-5-bromopyrimidine (2 g.) was dissolved in hot concentrated sulphuric acid (2 ml.) and water (8 ml.), then the mixture was cooled rapidly. Aqueous sodium nitrite (1·5 g. in 10 ml.) was added with shaking during ½ hr., the temperature being kept at 5—10°. Next day, the solution was warmed to 75—85°, ammonia (*d* 0·88; 8 ml.) was added, and the solution was cooled. The product was dissolved in hot water (10 ml.) and acidified with glacial acetic acid (2 ml.). The precipitated *5-bromo-2-hydroxypyrimidine* was recrystallised from water, and then had m. p. 241—243° (0·5 g.) (Found: C, 27·8; H, 1·8; N, 15·9; Br, 45·3. $C_4H_3ON_2Br$ requires C, 27·4; H, 1·7; N, 16·0; Br, 45·7%).

5-Bromo-4-chloropyrimidine.—5-Bromo-4-hydroxypyrimidine (3 g.), phosphoryl chloride (22 ml.), and dimethylaniline (0·7 ml.) were heated for 3 hr., and then the mixture was cooled, poured on to ice, and extracted with ether (1 × 100, 6 × 15 ml.). The ethereal solution was shaken with saturated sodium hydrogen carbonate solution, dried, and then distilled. 5-Bromo-4-chloropyrimidine (1·6 g., 50%) was collected as a pale yellow oil, b. p. 87°/16 mm. (Found : C, 25·1; H, 1·1. Calc. for $C_4H_2N_2ClBr$: C, 24·8; H, 1·0%). Cherbuliez and Stavritch (*loc. cit.*) record b. p. 95·5°/26 mm.

4 : 5-*Dichloropyrimidine.*—5-Chloro-4-hydroxypyrimidine hydrochloride (18 g.), phosphoryl chloride (120 ml.), and dimethylaniline (2 ml.) were heated for 3 hr., then the product was isolated as in the preceding experiment. 4 : 5-*Dichloropyrimidine* (7·7 g.; 48%) was obtained as a pale yellow oil, b. p. 82°/34 mm. (Found : C, 32·4; H, 1·3. $C_4H_2N_2Cl_2$ requires C, 32·2; H, 1·3%). After a month the dichloro-compound had changed to a bright yellow solid.

5-Chlorouracil.—Chlorine was bubbled into a suspension of uracil (5·6 g.) in water (100 ml.) at 80—85° until practically all the solid had dissolved, and another solid was beginning to separate. The mixture was cooled and the 5-chlorouracil (4·0 g.) collected. After recrystallisation from water it had m. p. 314—318° (decomp.). Concentration of the mother liquor from the chlorination gave 5 : 5-dichloro-5 : 6-dihydro-6-hydroxyuracil (1·5 g.) as prisms, m. p. 212° (decomp.) after recrystallisation.

5 : 5-*Dichloro*-5 : 6-*dihydro*-6-*hydroxyuracil.*—Chlorine was bubbled into a well-stirred suspension of uracil (5·0 g.) in water (40 ml.) on a boiling-water bath, until the solid had dissolved. On cooling, the 5 : 5-dichloro-compound separated as the monohydrate (6·9 g.). A portion of the material once crystallised from water had m. p. 216—218° (slight decomp.). Johnson (*loc. cit.*) recorded m. p. 212—215°.

2 : 4 : 5-*Trichloropyrimidine.*—5-Chlorouracil (10 g.), phosphoryl chloride (60 ml.), and phosphorus pentachloride (16 g.) were heated on a steam-bath for 1½ hr. then in an oil-bath (bath temp. 135—140°) for 24 hr. Distillation of the mixture gave 2 : 4 : 5-*trichloropyrimidine* (7·6 g.) as a lachrymatory oil, b. p. 73—74°/3 mm. (Found : C, 26·4; H, 0·4; N, 15·6. $C_4HN_2Cl_3$ requires C, 26·2; H, 0·5; N, 15·3%).

5-Bromo-4 : 6-dihydroxypyrimidine.—Bromine (6 ml.) in acetic acid (60 ml.) was added gradually, with shaking, to a suspension of 4 : 6-dihydroxypyrimidine (12 g.) in acetic acid (60 ml.) at 70°. Next day, the crystalline hydrobromide was collected and recrystallised from water giving 5-*bromo*-4 : 6-*dihydroxypyrimidine* (10·5 g.) as pale yellow microprisms, m. p. 263—264° (decomp.) (Found : C, 25·4; H, 1·6. $C_4H_3O_2N_2Br$ requires C, 25·1; H, 1·6%).

5-*Chloro*-4 : 6-*dihydroxypyrimidine.*—Iodine chloride (16·3 g.) in acetic acid (100 ml.) was added to a suspension of 4 : 6-dihydroxypyrimidine (5·6 g.) in the same solvent (100 ml.). The mixture was heated on the steam-bath for 2½ hr. and then cooled. Crystallisation of the product from the minimum of hot water (*ca.* 500 ml.; charcoal) gave pale yellow 5-*chloro*-4 : 6-*dihydroxypyrimidine* (3·8 g.), which decomposes without melting above about 230° (Found : C, 32·7; H, 1·9; N, 19·2. $C_4H_3O_2N_2Cl$ requires C, 32·7; H, 2·0; N, 19·1%).

5-*Bromo*-4 : 6-*dichloropyrimidine.*—5-Bromo-4 : 6-dihydroxypyrimidine (2 g.), phosphoryl chloride (28 ml.), and dimethylaniline (1 ml.) were boiled for 3 hr. The product (1·1 g., 46%), isolated in the usual way, was purified by sublimation, giving the *bromo-compound* as plates, m. p. 75—76° (Found : C, 21·3; H, 0·4; N, 12·0. $C_4HN_2Cl_2Br$ requires C, 21·0; H, 0·4; N, 12·3%).

4 : 5 : 6-*Trichloropyrimidine.*—This was made from 5-chloro-4 : 6-dihydroxypyrimidine and purified as in the preceding experiment. The *trichloro-compound* (77%) formed needles, m. p. 49—51° (Found : C, 26·0; H, 0·4; N, 15·4. $C_4HN_2Cl_3$ requires C, 26·2; H, 0·5; N, 15·3%).

4-*Amino*-5-*bromopyrimidine.*—Ethanol was added to 5-bromo-4-chloropyrimidine (3 g.) and ammonia (*d* 0·88; 15 ml.) to give a homogeneous solution. After 48 hr., the solid was collected; evaporation of the mother liquor gave a further small crop. The total product was twice recrystallised from water giving 4-amino-5-bromopyrimidine (1·1 g., 41%) as yellowish needles, m. p. 208—210° (decomp.) (Found : C, 27·4; H, 2·2. Calc. for $C_4H_4N_3Br$: C, 27·6; H, 2·3%). Yanai (*loc. cit.*) gives m. p. 206—207°.

4-*Amino*-5-*chloropyrimidine.*—In the same way as that above, 4 : 5-dichloropyrimidine gave 4-amino-5-chloropyrimidine (65%) as leaflets, m. p. 192—194° (Found : C, 36·8; H, 2·9; N, 33·0. Calc. for $C_4H_4N_3Cl$: C, 37·1; H, 3·1; N, 32·5%). Yanai (*loc. cit.*) gives m. p. 191—192°.

5-*Chloro*-4-*mercaptopyrimidine.*—A solution of 4 : 5-dichloropyrimidine (0·6 g.) and thiourea (0·4 g.) in ethanol (25 ml.) was boiled for 1 hr., then concentrated to about 12 ml. and cooled.

The product was crystallised from ethanol giving the *mercapto-compound* (0·4 g., 68%) as pale greenish-yellow leaflets, m. p. 212° (slight decomp.) (Found: C, 32·7; H, 2·0. $C_4H_3N_2ClS$ requires C, 32·8; H, 2·1%).

5-Chloro-2 : 4-dimethoxypyrimidine.—2 : 4 : 5-Trichloropyrimidine (5·8 g.) was added very slowly and with thorough mixing to a solution of sodium methoxide [from sodium (5 g.) and methanol (100 ml.)]. After the initial strongly exothermic reaction, the mixture was boiled for 15 min., then cooled and filtered. The filtrate was saturated with dry carbon dioxide, and filtered again. Both residues were extracted with ether, and the extracts combined with the methanolic solution. Removal of the solvent and sublimation of the crystalline residue at 100°/11 mm. (bath temp.) gave *5-chloro-2 : 4-dimethoxypyrimidine* as needles (4 g., 74%), m. p. 72—73° (Found: C, 41·5; H, 4·1; N, 16·1. $C_6H_7O_2N_2Cl$ requires C, 41·3; H, 4·0; 16·1%.

2-Hydrazinopyrimidine.—2-Methoxypyrimidine (Boarland and McOmie, *J.*, 1952, 3716) (2·4 g.), hydrazine hydrate (100%; 1·6 ml.), and methanol (12 ml.) were heated for 2 hr. The methanol was removed by distillation, and after a few days the solid (0·5 g.) was collected. Recrystallisation from benzene–methanol gave 2-hydrazinopyrimidine as hygroscopic needles, m. p. 108—110° after thorough drying (Found: C, 44·0; H, 5·6; N, 50·6. Calc. for $C_4H_6N_4$: C, 43·6; H, 5·5; N, 50·9%). Sirakawa *et al.* (*loc. cit.*) record m. p. 86—88°.

4-Hydrazinopyrimidine.—This was prepared from 4-methoxypyrimidine (Brown and Short, *J.*, 1953, 331) as above. The *compound*, obtained in 55% yield, had m. p. 132—134° (decomp.) (Found: C, 43·8; H, 5·4; N, 50·4%).

Preparation of Hydrazino- from Chloro-pyrimidines. E.g., *5-Chloro-4-hydrazinopyrimidine.*—Hydrazine hydrate (100%; 4 ml.) was added gradually (vigorous reaction) to 4 : 5-dichloropyrimidine (3 g.) in ethanol (15 ml.). After a few hours, the solid *product* was collected and recrystallised from water, giving needles (1·1 g., 38%), m. p. 190—192° (Found: C, 33·2; H, 3·5; N, 38·9. $C_4H_5N_4Cl$ requires C, 33·2; H, 3·5; N, 38·8%).

Similarly 5-bromo-4-chloro- yielded *5-bromo-4-hydrazinopyrimidine* (48% yield), needles, m. p. 185—187° (decomp.) (Found: C, 25·7; H, 2·9. $C_4H_5N_4Br$ requires C, 25·4; H, 2·6%). 4-Chloro-5-phenyl- yielded slowly *4-hydrazino-5-phenyl-pyrimidine* (54% yield), needles, m. p. 140—141° (Found: C, 64·4; H, 5·7; N, 30·3. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1%). 4 : 6-Dichloro- yielded *6-chloro-4-hydrazino-pyrimidine* (34% yield), needles, m. p. 177° (decomp.) (Found: C, 33·1; H, 3·6; N, 38·8. $C_4H_5N_4Cl$ requires C, 33·2; H, 3·5; N, 38·8%). 2 : 4 : 5-Trichloro- yielded *2 : 5-dichloro-4-hydrazino-pyrimidine* (62% yield), needles, which gradually become yellow then black above 220° (Found: C, 26·8; H, 2·4; N, 31·0. $C_4H_4N_4Cl_2$ requires C, 26·8; H, 2·2; N, 31·3%). 2-Chloro-4-phenyl- gave *2-hydrazino-4-phenyl-pyrimidine* (25% yield), needles, m. p. 115° (Found: C, 64·7; H, 5·7; N, 30·3. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1%) [prepared by M. J. Abercrombie].

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