272. *Monosubstituted Pyrimidines, and the Action of Thiourea on Chloropyrimidines.*

By (Miss) M. P. V. Boarland and J. F. W. McOmie.

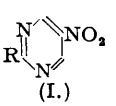
The amide and the methyl ester of pyrimidine-5-carboxylic acid, and the hydrochlorides of 4-chloro- and 4-mercapto-pyrimidine have been prepared. New syntheses of 2-mercapto- and of 5-amino-pyrimidine are also described. The reaction between certain chloropyrimidines and thiourea has been found to give good yields of the corresponding mercapto-compounds directly. Some of these results have been briefly reported elsewhere (*Chem. and Ind.*, 1950, 602).

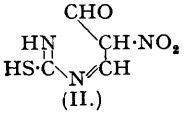
Many polysubstituted pyrimidines have been prepared, mainly because of their relation to biologically important compounds, such as vitamin B_1, the purines, and pteridines (see review by Lythgoe, *Quart. Reviews*, 1949, **3**, 181). Certain compounds are used clinically, *e.g.*, barbiturates as hypnotics, and mercapto-compounds as antithyroid drugs (*Ann. Reports*, 1947, **44**, 247). Comparatively little is known about the parent compound and its monosubstitution products, except for 2-sulphanilamidopyrimidine, which is used in the chemotherapy of bacterial infections (Roblin *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 567).

Recently, attempts have been made to correlate the structure of polysubstituted pyrimidines with their infra-red (Brownlie, *J.*, 1950, 3062) and ultra-violet (Cavalieri and Bendich, *J. Amer. Chem. Soc.*, 1950, **72**, 2587) absorption spectra, but these attempts have been handicapped by the lack of suitable model compounds. We have undertaken the preparation of monosubstituted compounds for fundamental physical, chemical, and biological studies. The results of infra-red investigations on some of these compounds will be reported elsewhere by Dr. L. N. Short.

We have prepared pyrimidine-5-carboxylic acid by Gabriel and Colman's method (*Ber.*, 1904, **37**, 3643) and converted it into the amide and the methyl ester. These compounds are structurally analogous to nicotinic acid and its amide and might show growth-promoting or -inhibiting action on bacteria which require an exogenous source of these vitamins.

5-Aminopyrimidine has been prepared by a new route, involving the condensation of *S*-methylthiuronium sulphate with nitrosodiomalondialdehyde in the presence of 1-ethylpiperidine, giving 2-methylthio-5-nitropyrimidine (I; R = MeS). Other condensing agents such as pyridine, sodium hydroxide, diethylamine, and tetraethylammonium hydroxide were ineffective, while piperidine gave a mixture of the methylthio-compound and 5-nitro-2-


(I.)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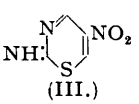
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piperidinopyrimidine (I; R = $C_5H_{10}N$). According to Hale and Brill (*J. Amer. Chem. Soc.*, 1912, **34**, 295) the condensation of thiourea with nitrosodiomalondialdehyde in the presence of small quantities of sodium hydroxide or diethylamine gave the thiourea (II), whereas the 1 : 3-thiazine (III) was obtained when piperidine was employed as condensing agent. We were not able to confirm these observations; in our hands the use of piperidine gave only the piperidino-derivative (I; R = $C_5H_{10}N$) and in no case could we obtain (II) and (III). The reduction of the nitro-group and hydrogenolysis of the methylthio-group of (I; R = MeS) were carried out in one stage by refluxing the compound in alcoholic solution with Raney nickel previously saturated with hydrogen. Another example of simultaneous reduction and desulphurisation is recorded by Cavalieri, Tinker, and Bendich (*J. Amer. Chem. Soc.*, 1949, **71**, 533) who obtained 4 : 5 : 6-triaminopyrimidine from 4 : 6-diamino-2-mercapto-5-nitrosopyrimidine.

In contrast to 3-aminopyridine, the action of nitrous acid on 5-aminopyrimidine does not

give a diazonium compound, nor could we isolate from the reaction mixture the still unknown 5-hydroxypyrimidine. Other routes for the preparation of the latter are being investigated.

In an attempt to prepare pyrimidine by the zinc dust reduction of 2 : 4-dichloropyrimidine in aqueous solution, a monochloropyrimidine was obtained (J. F. W. McOmie, Part II Thesis, Oxford, 1943). The orientation of this compound followed from its conversion into the known 2-anilino-derivative. The same partial reduction has since been reported by Matsukawa and Ohta (*J. Pharm. Soc., Japan*, 1950, **70**, 134). A similar result was obtained by Johnson and Joyce (*J. Amer. Chem. Soc.*, 1915, **37**, 2151), who found that 2 : 4-dichloro-5-ethoxypyrimidine gave the 2-chloro-5-ethoxy-compound with the same reducing agent. 2-Chloropyrimidine has also been prepared by the action of phosphorus oxychloride on 2-hydroxypyrimidine hydrochloride (B.P. Appln. 10,503/1949; Matsukawa and Ohta, *J. Pharm. Soc. Japan*, 1949, **69**, 491) and by the action of sodium nitrite on a solution of 2-aminopyrimidine in hydrochloric acid (U.S.P. 2,477,409/1949).

In contrast to the relatively stable 2-chloro-compound, 4-chloropyrimidine is extremely unstable and decomposes within a few minutes. Its hydrochloride, prepared by the action of phosphorus oxychloride on 4-hydroxypyrimidine, is, however, more stable, but can only be kept for a few days. A previous attempt to convert 4-hydroxy- into 4-chloro-pyrimidine was unsuccessful (Uber and Winters, *J. Amer. Chem. Soc.*, 1941, **63**, 137). Our method is essentially that of Mrs. R. H. Cornforth (private communication), who did not isolate the chloro-compound but converted it at once into 4-mercaptopyrimidine (see Experimental).

Until very recently three methods have been available for the synthesis of mercaptopyrimidines. The first of these, involving the condensation of thiourea with a β-dicarbonyl compound, is obviously limited to 2-mercaptopyrimidines. Again, the reaction of hydroxypyrimidines with phosphorus pentasulphide in inert solvents (Carrington, *J.*, 1944, 124) has only limited application, while the more general method of treating chloropyrimidines with alkali hydrogen sulphides often involves drastic conditions resulting in low yields (Gabriel and Colman, *Ber.*, 1899, **32**, 2921). We have found that some chloropyrimidines react with thiourea in boiling alcohol to give good yields of the corresponding thiols directly, no intermediate products being isolated. Thus 2-chloro- and 2 : 4-dichloro-pyrimidines gave the 2-mercapto- and 2 : 4-dimercapto-compounds in 50 and 90% yields, respectively, while 4-chloropyrimidine hydrochloride gave a 70% yield of 4-mercaptopyrimidine hydrochloride. Since the completion of this work Polonovski and Schmitt (*Bull. Soc. chim.*, 1950, **17**, 616) have described the reaction of polysubstituted chloropyrimidines with thiourea under somewhat milder conditions. In most cases they obtained the corresponding thiuronium salts which they were able to hydrolyse to the mercapto-compounds. From 2-amino-6-chloro-4-methylpyrimidine they could only isolate the dipyrimidyl sulphide.

Reaction of thiourea with 2-chloro-4 : 6-dimethylpyrimidine in hot alcohol gave mainly the corresponding thiuronium chloride, together with an unidentified compound (see Experimental). Alkaline hydrolysis of the former, under conditions similar to those used by Polonovski and Schmitt, yielded the expected mercapto-compound.

From the reaction between 2 : 4 : 6-trichloropyrimidine and thiourea in hot alcohol we obtained intractable products similar to those obtained by Polonovski and Schmitt (*loc. cit.*). Alkaline hydrolysis failed to give 2 : 4 : 6-trimercaptopyrimidine.

The number of heterocyclic halides reported to react with thiourea to give the corresponding mercapto-compounds directly is quite small. Rosenhauer, Hoffmann, and Heuser (*Ber.*, 1929, **62**, 2730) showed that α-chloro-quinoline and -lepidine and their methiodides reacted in boiling alcohol to give the corresponding α-mercapto-derivatives. When the reaction was carried out at room temperature, the intermediate thiuronium salts could be isolated. Scott and Watt (*J. Org. Chem.*, 1937, **2**, 148) obtained theoretical yields of 2-mercapto- and 2-mercapto-6-nitrobenzthiazoles from the corresponding chlorides. They could not isolate thiuronium salts even when the reaction was carried out in the cold. The majority of heterocyclic halides react with thiourea to give thiuronium salts or sulphides (*e.g.*, see Renfrew, *J. Amer. Chem. Soc.*, 1946, **68**, 1433; Surrey and Lindwall, *ibid.*, 1940, **62**, 1697). Sulphides are frequently formed both in the initial reaction and during the hydrolysis of the thiuronium salts. A summary of these reactions and the mechanisms put forward to explain them is given by Polonovski and Schmitt (*loc. cit.*). Although there does not appear to be any obvious connection between the structure of the heterocyclic halide and the reaction product, the experimental conditions seem to have an important bearing on the course of the reaction. In general, prolonged heating favours thiol formation, and sulphides appear to be formed more readily in aqueous media (see, *e.g.*, Watt, *J. Org. Chem.*, 1939, **4**, 436). A further example of the thermal effect is afforded by 2-bromo-

pyridine, which readily gives the thiuronium salt, but on prolonged heating under reflux gives a small yield of 2-mercaptopyridine. The latter has been prepared by Phillips and Shapiro (*J.*, 1942, 584) by the hydrolysis of the thiuronium salt, which they did not isolate. 3-Bromopyridine was recovered unchanged after 24-hours refluxing with thiourea in alcohol.

Experimental.

(M. p.s are uncorrected. Microanalyses are by Mr. W. M. Eno, Bristol, and Drs. Weiler and Strauss, Oxford.)

Methyl Pyrimidine-5-carboxylate.—A solution of pyrimidine-5-carboxylic acid (2·07 g.) (Gabriel and Colman, *Ber.*, 1904, **37**, 3643) in methanol (50 c.c.) saturated with dry hydrogen chloride was kept for 3 days. After removal of the solvent, the residue was made just alkaline by addition of aqueous sodium carbonate, and the solution extracted with ether (4 × 50 c.c.). The combined, dried extracts yielded a brown solid (1·22 g.), m. p. 67—68°, which was sublimed at 60°/20 mm., giving pure *methyl pyrimidine-5-carboxylate* (1·1 g., 48%), m. p. 84—85° (Found: C, 52·3; H, 4·3; N, 20·6. $C_6H_6O_2N_2$ requires C, 52·2; H, 4·35; N, 20·3%). The ester is readily soluble in water, methanol, and ether, and sparingly soluble in ethyl acetate.

Pyrimidine-5-carbonamide.—(*a*) Methyl pyrimidine-5-carboxylate (0·5 g.) and aqueous ammonia (*d*, 0·88; 20 c.c.) were kept for 2 days with occasional shaking. The white crystalline solid (0·2 g.; m. p. 209—213°) was collected and dried on the water-bath. Sublimation at 140°/20 mm. gave the pure *amide* (0·15 g., 34%), m. p. 211—213° (Found: C, 48·9; H, 4·1. $C_5H_5ON_3$ requires C, 48·8; H, 4·1%). (*b*) Methyl pyrimidine-5-carboxylate (0·44 g.) in methanol (10 c.c.) saturated with dry ammonia was kept for 4 days. The crude amide (0·29 g.) was purified by sublimation giving the pure material (0·25 g., 64%), m. p. 210—213°. (*c*) The amide was also prepared in low yield by the action of aqueous ammonia (*d* 0·88) on the acid chloride prepared by treatment of pyrimidine-5-carboxylic acid with thionyl chloride.

2-Methylthio-5-nitropyrimidine.—A mixture of methylthiuronium sulphate (3·6 g.), nitrosodiomalondialdehyde (4·0 g.) (Hill and Torry, *Amer. Chem. J.*, 1899, **22**, 89), and 1-ethylpiperidine (3·0 g.) in water (50 c.c.) was kept at 60° for 15 minutes. Next day, the solid was collected and sublimed at 80°/0·5 mm. (1·15 g., 26·4%). After two further sublimations *2-methylthio-5-nitropyrimidine* was obtained as very pale yellow needles, m. p. 82—83° (Found: C, 35·2; H, 3·0; N, 24·3; S, 17·1, 19·6. $C_5H_5O_2N_3S$ requires C, 35·1; H, 2·9; N, 24·6; S, 18·7%).

5-Aminopyrimidine.—Freshly prepared Raney nickel (40·0 g. of an ethanolic suspension) (Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353) in dry ethanol (50 c.c.) was saturated with hydrogen (*ca.* 35 c.c.) at atmospheric pressure and temperature. 2-Methylthio-5-nitropyrimidine (4·3 g.) in ethanol (150 c.c.) was added and the suspension refluxed for 3 hours with vigorous stirring. After filtration the solution was evaporated to dryness under reduced pressure, leaving a pale brown crystalline product (1·8 g., 75·4%). Several recrystallisations from benzene gave pure 5-aminopyrimidine as fine needles, m. p. 170—171° (Found: C, 50·8; H, 5·1; N, 44·3. Calc. for $C_4H_5N_3$: C, 50·5; H, 5·3; N, 44·2%). Roblin, Winnek, and English (*J. Amer. Chem. Soc.*, 1942, **64**, 567) give m. p. 170—171° (corr.).

5-Nitro-2-piperidinopyrimidine.—A mixture of thiourea (0·24 g.), nitrosodiomalondialdehyde (0·5 g.), and piperidine (0·26 g.) in water (10 c.c.) was kept at 70° for 10 minutes. After 12 hours the yellow crystalline product was collected (0·1 g., 15·3%). *5-Nitro-2-piperidinopyrimidine* crystallised from ethanol in shining yellow plates, m. p. 147—148° (Found: C, 52·4; H, 5·7; N, 26·6. $C_9H_{12}O_2N_4$ requires C, 52·0; H, 5·75; N, 26·9%).

2 : 4-Dichloropyrimidine.—Hilbert and Johnson's method (*J. Amer. Chem. Soc.*, 1930, **52**, 1154) was improved by the use of dimethylaniline (cf. Baddiley and Topham, *J.*, 1944, 678). Uracil (40·0 g.) was added portionwise to a mixture of dimethylaniline (46 c.c.) and phosphorus oxychloride (80·0 g.). The mixture was refluxed for 5 minutes and the dark brown liquid poured on ice (600 g.). The deep purple solution was filtered and extracted with ether (5 × 200 c.c.); the combined, dried extracts gave crystalline 2 : 4-dichloropyrimidine (30·4 g., 57%).

Reduction of 2 : 4-Dichloropyrimidine.—2 : 4-Dichloropyrimidine (14·0 g.), followed by zinc dust (66·6 g.), was added to a vigorously stirred, boiling solution of ammonium chloride (6·6 g.) in water (666 c.c.). After half an hour more zinc dust (13·6 g.) was added and boiling continued for another 1½ hours. After filtration the solution was distilled until *ca.* 500 c.c. of distillate had been collected; this was saturated with sodium chloride and continuously extracted with ether for 16 hours. Removal of the ether from the dried extract gave 2-chloropyrimidine (3·1 g.) as brownish crystals, m. p. 61°. The pure compound was obtained in the form of colourless needles, m. p. 63·5—64°, by sublimation at 50°/18 mm. (Found: C, 42·0; H, 2·8; N, 24·7; Cl, 30·0. Calc. for $C_4H_3N_2Cl$: C, 42·0; H, 2·6; N, 24·5; Cl, 31·0%). The mercuric chloride complex separated as colourless needles.

When 2-chloropyrimidine (0·1 g.) was warmed on a water-bath with excess of aniline (1·0 c.c.) and the mixture left overnight, crystalline 2-anilinopyrimidine separated. After crystallisation from aqueous ethanol and aqueous methanol, the pure compound was obtained as white needles, m. p. 115·5—116° (Found: C, 70·0; H, 5·25. Calc. for $C_{10}H_9N_3$: C, 70·2; H, 5·3%). Johnson and Heyl (*Amer. Chem. J.*, 1907, **38**, 237) give m. p. 116°.

4-Chloropyrimidine Hydrochloride.—4-Hydroxypyrimidine (1·0 g.) [obtained in 80% yield by Brown's method (*J. Soc. Chem. Ind.*, 1950, **69**, 353)] was treated with phosphorus oxychloride (4·0 c.c.) at 100° until dissolution occurred (*ca.* 5 minutes), the reaction being carried out in the test-tube portion of a "cold-finger" sublimation apparatus. The product was washed with light petroleum (b. p. 40—60°), the "cold-finger" condenser inserted, and the pressure slowly reduced. At 90°/20 mm. a white crystalline product began to sublime and sublimation proceeded rapidly at 130°/20 mm. The crude material (0·4 g., 25·4%) melted with decomposition over the range 158—170°. After further sublimation, *4-chloropyrimidine hydrochloride* decomposed when heated to 193—194° in a sealed tube (Found: C, 32·1; H, 3·0; N, 18·3; Cl, 48·4. $C_4H_3N_2Cl,HCl$ requires C, 31·8; H, 2·6; N, 18·5; Cl, 47·0%).

4-Chloropyrimidine hydrochloride was found to be readily soluble in water and ethanol. The mercuric chloride complex separated from an aqueous solution as fine needles. The hydrochloride is, however, unstable, decomposing after a few days to a bright yellow solid; its vapour is lachrymatory and the substance has an irritating effect on the skin.

4-Chloropyrimidine was liberated from the hydrochloride by treatment with aqueous potassium carbonate in the presence of ether. It was obtained as an oil, which decomposed within a few minutes to an orange ether-insoluble solid.

2-*Mercaptopyrimidine.*—A mixture of 2-chloropyrimidine (1·0 g.) and thiourea (0·9 g.) in ethanol (40 c.c.) was refluxed for 10½ hours, the initially colourless solution becoming yellow after about 5 hours. After concentration, 2-mercaptopyrimidine separated in the form of greenish-yellow plates (0·5 g., 50%). The pure compound, m. p. 230° (decomp.; bath preheated to 220°), was obtained by sublimation at 120°/20 mm. (Found: C, 42·8; H, 3·7; N, 24·8; S, 28·2. Calc. for $C_4H_4N_2S$: C, 42·8; H, 3·6; N, 25·0; S, 28·6%). Roblin and Clapp (*J. Amer. Chem. Soc.*, 1950, **72**, 4890) record m. p. 220° (decomp.).

2-Mercaptopyrimidine is soluble in methanol, moderately soluble in water and ethanol, and very sparingly soluble in chloroform.

4-*Mercaptopyrimidine Hydrochloride.*—A mixture of 4-chloropyrimidine hydrochloride (0·1 g.) and thiourea (0·07 g.) in ethanol (20 c.c.) was refluxed for 2 hours. The solution became bright yellow as soon as it was warmed. When the solution was concentrated, bright yellow needles separated (0·07 g., 70%). After sublimation at 130°/20 mm., 4-*mercaptopyrimidine hydrochloride* had m. p. 220° (decomp.) (Found: C, 32·6; H, 3·7; N, 18·4; S, 22·0. $C_4H_4N_2S$,HCl requires C, 32·3; H, 3·4; N, 18·8; S, 21·6%).

4-Mercaptopyrimidine, liberated from the hydrochloride by treatment with aqueous ammonia, was obtained as yellow needles, m. p. 187°. Mrs. Cornforth (private communication) found m. p. 188° for this compound, prepared by the action of sodium hydrogen sulphide on crude 4-chloropyrimidine hydrochloride.

Reactions of Thiourea.—(i) *With* 2 : 4-*dichloropyrimidine.* A mixture of 2 : 4-dichloropyrimidine (2·0 g.) and thiourea (2·5 g.) in ethanol (70 c.c.) was refluxed for 2 hours, the colour gradually becoming bright yellow. Crystalline 2 : 4-dithiouracil (1·8 g., 90%) separated after the solution had been concentrated. Recrystallisation from water gave the pure material as shining yellow needles, m. p. 285° (decomp.) (Found: C, 33·8; H, 2·8; N, 19·5; S, 45·0, 43·7. Calc. for $C_4H_4N_2S_2$: C, 33·4; H, 2·8; N, 19·4; S, 44·5%). The m. p. was not depressed by mixture of the specimen with a sample prepared by the method described by Wheeler and Liddle (*Amer. Chem. J.*, 1908, **40**, 557).

(ii) *With* 2-*chloro*-4 : 6-*dimethylpyrimidine.* A mixture of 2-chloro-4 : 6-dimethylpyrimidine (6·0 g.), prepared by Matsukawa and Ohta's method (*J. Pharm. Soc., Japan*, 1949, **69**, 491), and thiourea (3·2 g.) in ethanol (120 c.c.) was refluxed for 6 hours and the yellow solution slightly concentrated. Next day a small quantity (1·3 g.) of a bright yellow product was collected. After several recrystallisations from ethanol the pure material was obtained as shining, yellow plates, m. p. *ca.* 198° (decomp.) (Found: C, 44·0; H, 5·2; N, 22·1; S, 18·7; Cl, 10·6. $C_{12}H_{15}N_5S_2$,HCl requires C, 43·8; H, 4·9; N, 21·3; S, 19·4; Cl, 10·8%). The structure of this *compound* has not yet been established. The main product of the reaction was obtained after further concentration of the mother liquor, and separated as pale yellow needles (6·3 g.). After recrystallisation from ethanol–ether (4 : 6-*dimethyl-2-pyrimidyl*)*thiuronium chloride* was obtained as almost colourless needles, m. p. *ca.* 191° (decomp.) (Found: C, 38·9; H, 4·9; N, 25·9. $C_7H_{11}N_4SCl$ requires C, 38·5; H, 5·0; N, 25·65%).

Hydrolysis of (4 : 6-*dimethyl-2-pyrimidyl*)*thiuronium chloride.* A solution of the thiuronium salt (2·0 g.) in N-sodium hydroxide (40 c.c.) was refluxed for ¾ hour. After acidification with acetic acid and concentration, the solution deposited 2-mercapto-4 : 6-dimethylpyrimidine as shining, orange needles (0·7 g.), m. p. 208—210°. Sublimation at 140°/0·5 mm. gave the pure compound as pale yellow needles, m. p. and mixed m. p. with an authentic sample 208—210° (Found: C, 51·8; H, 5·65; N, 19·9; S, 22·8. Calc. for $C_6H_8N_2S$: C, 51·5; H, 5·2; N, 20·0; S, 22·8%). Hale and Williams (*J. Amer. Chem. Soc.*, 1915, **37**, 594) give m. p. 210°. Treatment of an ethanolic solution of the mercapto-compound with dilute hydrochloric acid intensified the yellow colour, and addition of ether precipitated a hydrochloride as long, yellow needles, m. p. 260° (decomposing >240°). The m. p. was not depressed by admixture of the hydrochloride with 2-mercapto-4 : 6-dimethylpyrimidine hydrochloride prepared under the same conditions.

(iii) *With* 2-*bromopyridine.* (*a*) A mixture of 2-bromopyridine (3·0 g.) and thiourea (1·5 g.) in ethanol (30 c.c.) was refluxed for 1 hour. After concentration of the yellow solution, pale yellow crystals were obtained (2·4 g.). Recrystallisation from ethanol–ether gave pure 2-*pyridylthiuronium bromide* as needles, m. p. 126—127° (Found: C, 30·6; H, 3·5; N, 17·9. $C_6H_8N_3SBr$ requires C, 30·8; H, 3·4; N, 17·9%).

Hydrolysis of the thiuronium salt with concentrated ammonia solution by the method described by Phillips and Shapiro (*J.*, 1942, 584) gave 2-mercaptopyridine as yellow prisms, m. p. 125° after recrystallisation from benzene. Marckwald, Klemm, and Trabert (*Ber.*, 1900, **33**, 1556) give m. p. 125°.

(*b*) A mixture of 2-bromopyridine (6·0 g.) and thiourea (3·0 g.) in ethanol (80 c.c.) was boiled under reflux for 24 hours. The bright yellow solution was concentrated and the remainder of the ethanol removed under reduced pressure, leaving a yellow syrup. This was dissolved in a little water, and the aqueous solution saturated with sodium chloride and extracted many times with ether. Removal of the ether from the dried extract left an oil which, when triturated with a little cold ether, gave 2-mercaptopyridine (50 mg.) as bright yellow prisms, m. p. 123—125° alone or mixed with the product from the hydrolysis of the thiuronium salt.

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