N-*Methylthiamine.*

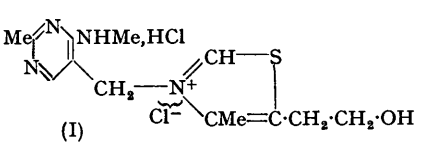
By P. Nesbitt and P. Sykes.

[Reprint Order No. 5399.]

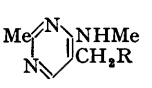
N-Methylthiamine [5-2′-hydroxyethyl-4-methyl-3-(2-methyl-4-methylamino-5-pyrimidyl)methylthiazolium chloride hydrochloride], required as a thiamine analogue, has been prepared in good yield. The effect, on the reactions of a substituted 5-pyrimidylmethyl group, of replacing an amino- by a methylamino-group in the adjacent 4-position is investigated and discussed.

After a study (Sykes and Todd, *J.*, 1951, 534) of the mechanism of the oxidation of thiamine (vitamin B_1) by one-electron oxidising agents and the disproportionation of thiamine disulphide in hot high-boiling hydroxylic solvents, a model compound having certain features was required. Essentially it must be a 5-pyrimidylmethylthiazolium compound containing a modified amino-group in the 4-position of the pyrimidine nucleus that would be unable to undergo a dehydrative ring-closure with the *N*-formyl group liberated by the action of alkali on the thiazole nucleus. *N*-Methylthiamine [5-2′-hydroxyethyl-4-methyl-3-(2-methyl-4-methylamino-5-pyrimidyl)methylthiazolium chloride hydrochloride] (I) was thought to be suitable.

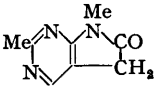
N-Methylthiamine is mentioned in the literature (Schultz, *Z. physiol. Chem.*, 1940, **265**, 113) only in reference to its biological testing, no indication being given of the method of preparation. A potential intermediate in its preparation, 5-aminomethyl-2-methyl-4-methylaminopyrimidine (II; R = NH_2), is mentioned in U.S.P. 2,377,395, being prepared from ethyl 4-chloro-2-methyl-5-pyrimidylacetate (V; R′ = Cl, R″ = CO_2Et) (Cerecedo and Pickel, *J. Amer. Chem. Soc.*, 1937, **59**, 1714) *via* 2-methyl-4-methylamino-5-pyrimidylacetic acid (II; R = CO_2H) and the corresponding ethyl ester and amide; the desired amine (II; R = NH_2) was obtained by Hofmann degradation of the amide. We were, however, unable to repeat this series of reactions outlined: treatment of the chloro-compound (V; R′ = Cl, R″ = CO_2Et) with ethanolic methylamine, followed by hydrolysis of the methylamide (II; R = CO·NHMe), led to the expected acid (II; R = CO_2H), but the subsequent reactions followed a different course. Attempted esterification of this acid yielded, not the expected ethyl ester (II; R = CO_2Et), but the lactam (III). In attempts to convert this lactam into the desired amide (II; R = $CO{\cdot}NH_2$), it was recovered unchanged on treatment with ethanolic or liquid ammonia, and it was reconverted into the



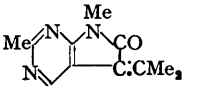
(I)



(II)



(III)



(IV)

acid (II; R = CO_2H) by aqueous ammonia or alkali. On attempting to recrystallise the compound from acetone it was converted into an *iso*propylidene derivative (IV), the reaction being facilitated by the presence of a little dry ammonia; this behaviour, which is not duplicated by the formally similar, *N*-methyl-α-(2-methyl-4-methylamino-5-pyrimidyl)-acetamide (II; R = CO·NHMe), is somewhat surprising but is reminiscent of oxindole which also forms an *iso*propylidene derivative (Wahl and Livovschi, *Bull. Soc. chim.*, 1938, **5**, 653), though with somewhat greater difficulty. No carbonyl condensation compound derived from the more closely analogous *N*-methyloxindole has been recorded.

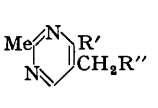
A crude, unstable methyl ester (II; R = CO_2Me) was prepared by means of diazomethane but with ammonia again led to the lactam (III). Nor could the desired amide be obtained by the action of ammonia on the methylamide (II; R = CO·NHMe). Attention was therefore turned to the hydrazide (II; R = $CO{\cdot}NH{\cdot}NH_2$), which was prepared from the methyl ester, lactam, and methylamide.

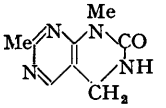
The hydrazide was treated with nitrous acid by Cerecedo and Pickel's method (*loc. cit.*), and with amyl nitrite by the method of Todd *et al.* (*J.*, 1936, 1601). The former gave the

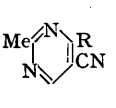
tetra-azanaphthalene derivative (VI) [by cyclisation of the *iso*cyanate (II; R = NCO)] and the latter gave largely the lactam (III) arising because the azide (II; R = CON_3) acts as an acylating agent, under the various conditions employed, on the adjacent methylamino-group. That the methods are satisfactory for hydrazides having an amino-group in the 4-position of the pyrimidine nucleus was demonstrated by the preparation of 4-amino-2-methyl-5-pyrimidylacethydrazide (V; R′ = NH_2, R″ = $CO{\cdot}NH{\cdot}NH_2$) by the action of hydrazine on the corresponding amide, and its conversion into 4-amino-2-methyl-5-ethoxy-(and methoxy)carbonylaminomethylpyrimidine (V; R′ = NH_2, R″ = $NH{\cdot}CO_2Et$ and $NH{\cdot}CO_2Me$, respectively).

The very ready cyclisation to the lactam (III) and the anomalous decompositions of the hydrazide (II; R = $CO{\cdot}NH{\cdot}NH_2$) spring from the increased basicity due to the replacement of an amino- by a methylamino-group in the 4-position of the pyrimidine nucleus; even so, this centre is still only weakly basic and it is surprising that it should be able so to dominate the reactions, though the decreased tendency of the substituted amino-compound to exist in the imino-form may also play a part. A sufficiently strong base can still reverse the reactions, however; thus, while the lactam (III) is unaffected by ammonia, it is cleaved by the stronger bases hydrazine and methylamine, to yield the corresponding hydrazide and methylamide.

As an alternative route to the desired amine (II; R = NH_2), the intermediate 4-chloro-5-cyano-2-methylpyrimidine (VII; R = Cl) (Todd and Bergel, *J.*, 1937, 364) was prepared. It proved possible to introduce several modifications in this synthesis; thus ethyl α-cyano-α-ethoxymethyleneacetate was treated with two mols. of acetamidine instead of one, yielding the condensation product (VIII). This can be cyclised to 5-cyano-4-hydroxy-2-


(V)


(VI)


(VII)

$H_2N{\cdot}CMe{:}N{\cdot}CH{:}C(CN){\cdot}CO{\cdot}NH{\cdot}CMe{:}NH$

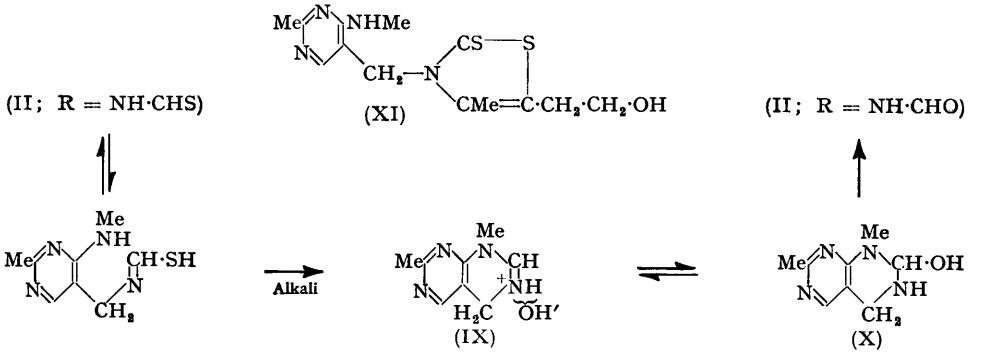
(VIII)

methylpyrimidine (VII; R = OH) which is then converted into the 4-chloro-compound with phosphorus oxychloride. Isolation of the hydroxypyrimidine or even separate cyclisation is unnecessary, however, as the crude condensation product can be converted directly into the chloro-compound in high yield. This is then converted into 5-cyano-2-methyl-4-methylaminopyrimidine (VII; R = NHMe) by adding it to liquid methylamine at −80° (higher temperatures lead to extensive side reactions). Catalytic hydrogenation of the cyano-compound to the amine (II; R = NH_2) proved unexpectedly difficult; the normal safeguards against secondary amine formation were ineffective, or inhibited reduction completely. The primary amine was obtained only if reduction was carried out in very dilute solution (<1%).

Treatment of the amine with sodium dithioformate led to the formyl derivative (II; R = $NH{\cdot}CHO$) instead of the expected thioformyl compound (II; R = $NH{\cdot}CHS$) (though the unstable thioformyl compound was obtained on one occasion only, being rapidly converted into the formyl derivative in solution or on attempted condensation with a chloro-ketone). Such an interconversion in the corresponding 4-amino-series (V; R′ = NH_2, R″ = $NH{\cdot}CHO$ and $NH{\cdot}CHS$, respectively) can be effected only by heating an aqueous solution of the thioformyl compound in a sealed tube for several hours. It seems unlikely that the explanation of this difference is merely the greater basicity of the 4-methylamino-group as, under alkaline conditions, *N*-thioformyl compounds tend to be converted into the parent amine rather than that sulphur should be replaced by oxygen. The extreme readiness with which the 4-methylamino-group takes part in cyclisation reactions makes the formation of a cyclic intermediate such as (IX) not impossible, the corresponding *pseudo*-base (X) being a carbinol-amine corresponding to the formyl compound (II; R = $NH{\cdot}CHO$). Such a cyclisation would certainly be promoted by the alkaline conditions prevailing during thioformylation.

Owing to the inability of this thioformyl compound (II; R = $NH{\cdot}CHS$) to form *N*-methylthiamine (I) by reaction with a chloro-ketone, an alternative route from the amine

to (I) by formation of the 2-thione (XI), and its subsequent oxidation under acid conditions, was considered. Model compounds, such as (II; R = NH·CS·S·CH_2·COMe) were prepared but failed to undergo closure to the corresponding 2-thiones by Sykes's (*J.*, 1951, 2507) or Matsukawa's method (*J. Pharm. Soc. Japan*, 1951, **71**, 455). Here again it seems likely that the 4-methylamino-group is responsible, as a wide variety of 4-aminopyrimidine derivatives have been successfully cyclised by this method.



The desired vitamin analogue (I) was finally obtained in good yield by treatment of the hydrochloride of the formyl derivative (II; R = NH·CHO) with 3-acetoxy-1-chloropropyl methyl ketone in the presence of hydrogen sulphide.

Experimental

2-Methyl-4-methylamino-5-pyrimidylacetic Acid (II; R = CO_2H).—Ethyl 4-chloro-2-methyl-5-pyrimidylacetate (V; R′ = Cl, R″ = CO_2Et) (Cerecedo and Pickel, *J. Amer. Chem. Soc.*, 1937, **59**, 1714) (68 g.) was heated at 120° for 8 hr. with ethanolic methylamine (70 g. in 150 ml.). The ethanol was then removed, the residue dissolved in water (250 ml.), and a concentrated solution of barium hydroxide (100 g.) added. The solution was heated on a water-bath till no more methylamine could be detected, then treated with dilute sulphuric acid till no more barium sulphate was precipitated. The mixture was centrifuged and then evaporated under reduced pressure till crystallisation began. Recrystallisation from acetone–water gave 31 g. (54%) of colourless needles, m. p. 217° (Found: C, 53·0; H, 6·0; N, 23·2. Calc. for $C_8H_{11}O_2N_3$: C, 53·0; H, 6·1; N, 23·2%).

2-Methyl-4-methylaminopyrimidyl-5-acetolactam (1 : 6-*Dimethyl*-2-*oxo*-1 : 5 : 7-*triazaindane*) (III).—The above acid (30·9 g.) in ethanol (300 ml.) was refluxed for 6 hr. while dry hydrogen chloride was passed through the solution. The ethanol was removed, and the residue dissolved in ethanol and again evaporated to remove hydrochloric acid. This was repeated a second time and the residue set aside overnight in a vacuum-desiccator over solid potassium hydroxide. The residue was dissolved in ethanol, and concentrated aqueous sodium hydrogen carbonate (11·2 g., 1 equiv.) added. The solution was evaporated to small bulk and then freeze-dried. The residue was extracted with boiling alcohol, and the solution evaporated to dryness. Recrystallisation of the *lactam* from ethanol gave 15·3 g. (55%) of colourless needles, m. p. 141° (Found: C, 58·5; H, 5·5; N, 25·4. $C_8H_9ON_3$ requires C, 58·8; H, 5·5; N, 25·8%). Treatment of the lactam with ethanolic ammonia at 120° results in its recovery, while aqueous ammonia reconverts it into the acid. When the lactam was heated in acetone to which a little dry ammonia had been added, removal of the solvent and sublimation of the product at 150°/10^{-3} mm. gave the iso*propylidene* derivative (IV) as colourless needles, m. p. 172° (Found: C, 65·3; H, 6·4; N, 20·6%; *M*, 201. $C_{11}H_{13}ON_3$ requires C, 65·1; H, 6·4; N, 20·7%; *M*, 203).

Methyl 2-Methyl-4-methylamino-5-pyrimidylacetate (II; R = CO_2Me).—A suspension of the acid (2·9 g.) was stirred in ethanol (100 ml.) while excess of ethereal diazomethane was added and then until all the acid had passed into solution. Evaporation under reduced pressure at room temperature yielded the extremely unstable (it is converted overnight into a black tar) methyl ester, which decomposed on attempts at crystallisation, sublimation, etc. Reaction with ammonia converted it into the lactam (III).

2-Methyl-4-methylamino-5-pyrimidylacethydrazide (II; R = CO·NH·NH_2).—The above crude

methyl ester (freshly prepared from 3·76 g. of acid) was heated at 100° for 20 min. in aqueous hydrazine hydrate (50%; 20 ml.). Colourless crystals separated on cooling. Recrystallisation from ethanol gave 3·7 g. (92%) of colourless needles, m. p. 220° (Found: C, 49·5; H, 6·4; N, 35·8. $C_8H_{13}ON_5$ requires C, 49·2; H, 6·7; N, 35·9%). The *hydrazide* may also be obtained from the lactam (III) (79%) and the methylamide (II; R = CO·NHMe) (70%); it is unaffected by ammonia under any conditions tried.

1 : 2 : 3 : 4-*Tetrahydro*-1 : 7-*dimethyl*-2-*oxo*-1 : 3 : 6 : 8-*tetra-azanaphthalene* (VI).—A solution of the above hydrazide (7·5 g.) in N-hydrochloric acid (92 ml.) was cooled to −2° and stirred while a solution of sodium nitrite (2·7 g., 1·05 equivs.) was added dropwise and for 15 min. thereafter. The solution was heated on a water-bath until the evolution of gas ceased, then cooled and adjusted to pH 8 by addition of sodium hydrogen carbonate; it was then repeatedly extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated. The solid residue was extracted with boiling anhydrous acteone, and the solution evaporated till crystallisation began. Recrystallisation of the *compound* from ethanol gave 4·7 g. (69%) of colourless needles, m. p. 222° (Found: C, 53·6; H, 5·5; N, 32·7. $C_8H_{10}ON_4$ requires C, 53·9; H, 5·6; N, 32·4%).

4-*Amino*-2-*methyl*-5-*pyrimidylacethydrazide* (V; R′ = NH_2, R″ = CO·NH·NH_2).—4-Amino-2-methyl-5-pyrimidylacetamide (Andersag and Westphal, *Ber.*, 1937, **70**, 2035) (4·1 g.) was heated at 100° for 30 min. with hydrazine hydrate (100%; 15 ml.); crystals separated from the cold solution. Recrystallisation of the *hydrazide* from ethanol gave 4·0 g. (89%) of colourless needles, m. p. 235° (Found: C, 46·6; H, 5·9; N, 38·7. $C_7H_{11}ON_5$ requires C, 46·4; H, 6·1; N, 38·7%).

4-*Amino*-5-*ethoxycarbonylaminomethyl*-2-*methylpyrimidine* (V; R′ = NH_2, R″ = NH·CO_2Et).—A suspension of the above hydrazide (1·025 g.) in ethanol (17 ml.), containing dry hydrogen chloride (0·413 g., 2 equivs.) and amyl nitrite (1·16 ml., 1 equiv.), was heated to 60° till gas evolution was complete. The solution was cooled and a large volume of ether added to precipitate the urethane hydrochloride, which was filtered off and dissolved in ethanol, and alcoholic sodium ethoxide solution (1·59N; 7·1 ml., 2 equivs.) was added. The mixture was then centrifuged to remove sodium chloride, and the resultant solution evaporated to crystallisation. Sublimation at 140°/10^{-4} mm. of the *ethylurethane* gave 0·28 g. (22%) of colourless needles, m. p. 214° (decomp.) (Found: C, 51·4; H, 6·9; N, 26·3. $C_9H_{14}O_2N_4$ requires C, 51·5; H, 6·7; N, 26·7%).

In methanol there was more rapid formation of the *methylurethane* (also purified by vacuum-sublimation) in 67% yield, m. p. 206° (Found: C, 49·2; H, 5·8; N, 28·4. $C_8H_{12}O_2N_4$ requires C, 48·9; H, 6·1; N, 28·5%).

N-(β-1-*Aminoethylideneamino*-α-*cyanoacryloyl*)*acetamidine* (VIII).—Acetamidine hydrochloride (166 g., 2·1 equivs.) was added to ethanolic sodium ethoxide (2·26N; 815 ml., 2·2 equivs.) at 0°, and the mixture shaken until all the acetamidine hydrochloride had dissolved, and then centrifuged to remove the precipitated sodium chloride. Ethyl α-cyano-α-ethoxymethyleneacetate (de Bollemont, *Bull. Soc. chim.*, 1901, **25**, 20) (141 g., 1 equiv.) at 60° was then added. The temperature rose rapidly to *ca.* 40°. The solution, which had become bright red, was left overnight at room temperature and then kept at 0° for 48 hr. The product separated as pale pink needles (more was obtained by concentraion of the mother-liquors, after filtration, and addition of ether). Recrystallisation of the *product* from ethanol gave 133 g. (83%) of colourless needles, m. p. 180° (Found: C, 48·3; H, 5·9; N, 34·7. $C_8H_{11}ON_5$,$\frac{1}{2}H_2O$ requires C, 48·5; H, 6·0; N, 34·7%).

5-*Cyano*-4-*hydroxy*-2-*methylpyrimidine* (VII; R = OH).—The foregoing compound (1·46 g.) in ethanol (10 ml.) and hydrochloric acid (0·5N; 15 ml., 1 equiv.) was heated to 100° for 10 min.; on cooling, crystals of the hydroxypyrimidine separated. This crystallised from water as colourless needles (0·69 g., 68%), m. p. 235° (Found: C, 52·9; H, 3·6; N, 31·0. Calc. for $C_6H_5ON_3$: C, 53·3; H, 3·7; N, 31·1%).

4-*Chloro*-5-*cyano*-2-*methylpyrimidine* (VII; R = Cl).—The crude amidine (VIII) (63 g.) was heated at 130°/4 mm. for 4 hr., the solid being shaken from time to time to prevent charring. After cooling, it was powdered and added to phosphorus oxychloride (1500 g.). The mixture was refluxed for 30 min. (air-bath), during which the amidine dissolved and the solution became dark red. The excess of phosphorus oxychloride was then removed under reduced pressure (it is extremely difficult to remove the last *ca.* 10%), and the warm flask then rotated so that the product solidified as a thin layer over the surface of the flask. The residue was then extracted with successive portions (300 ml. each) of ether, each portion being washed, as obtained, with potassium carbonate solution till neutral. These aqueous washings were then cooled

to 0° and added to the residue in the flask. The aqueous solution so obtained was neutralised with potassium carbonate and repeatedly ether-extracted. The ether extracts were combined with the original ether-washings and dried (Na_2SO_4) (*ca.* 4 l. of ether is required). The solvent was removed and the residue distilled, b. p. 79—81°/6 × 10^{-3} mm. The chloropyrimidine forms colourless needles (31 g., 62%), m. p. 64—65° (Found: C, 47·1; H, 3·0; N, 27·4. Calc. for $C_6H_4N_3Cl$: C, 46·9; H, 2·6; N, 27·4%).

5-Cyano-2-methyl-4-methylaminopyrimidine (VII; R = NHMe).—The above chloro-compound (32·3 g.) was finely powdered and added in 1-g. portions to liquid methylamine (250 ml.) cooled to −80°. The temperature, which rose to *ca.* −40° after each addition, was reduced to −80° again before the next addition. The excess of methylamine was then distilled off and the residue sublimed at 130°/10^{-3} mm. The *methylamino*-compound (20·6 g., 61%) was obtained as colourless needles, m. p. 151—152° (Found: C, 56·7; H, 5·3; N, 38·1. $C_7H_8N_4$ requires C, 56·7; H, 5·4; N, 37·8%).

Reduction of 5-Cyano-2-methyl-4-methylaminopyrimidine (VII; R = NHMe).—(*a*) The above methylaminocyano-compound (1·46 g.) in glacial acetic acid (200 ml.), saturated with hydrogen chloride, was hydrogenated at room temperature with 10% palladised charcoal as catalyst, the theoretical volume of hydrogen being absorbed in 2 hr. The mixture was diluted with water (200 ml.), filtered, and evaporated under reduced pressure. The residue was dissolved in water (10 ml.), the pH of the solution brought to 7 by the addition of sodium carbonate solution, and sodium dithioformate solution (2·1 g., 1 equiv.; in 10 ml.) added. No precipitate had formed after 3 days at room temperature, so the solution was extracted with chloroform, the extract dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue sublimed at 140°/10^{-4} mm. Colourless needles (1·14 g., 64%) were obtained of 5-formamidomethyl-2-methyl-4-methylaminopyrimidine (II; R = NH·CHO), m. p. 152—153° (Found: C, 53·3; H, 6·6; N, 31·2. $C_8H_{12}ON_4$ requires C, 53·3; H, 6·7; N, 31·1%). Numerous attempts to repeat this reduction were unsuccessful.

(*b*) A solution of the methylaminocyanopyrimidine (0·78 g.) in acetic anhydride (100 ml.) containing triethylamine (0·74 ml., 1 equiv.) was hydrogenated at 35°/50 atm. with 10% palladised charcoal (0·3 g.). The mixture was filtered and then evaporated to dryness under reduced pressure. Triethylamine acetate was removed at room temperature at 10^{-4} mm. and the residue then sublimed at 10^{-4} mm., leading to recovery of starting material (0·113 g.) up to 100°, and from 120—140° sublimation of *5-acetamidomethyl-2-methyl-4-methylaminopyrimidine* (II; R = NHAc) (0·493 g., 52%), m. p. 213—214° (Found: C, 55·4; H, 7·3; N, 28·6. $C_9H_{14}ON_4$ requires C, 55·7; H, 7·2; N, 28·8%). Subsequent attempts resulted in the almost complete recovery of starting material. In the absence of triethylamine, a small amount of the acetamidomethyl compound is obtained, but the product is largely a mixture of acetamide and 5-acetoxymethyl-2-methyl-4-methylaminopyrimidine (II; R = OAc) arising from the decomposition of the secondary amine which is then the major product of the reduction of the cyanide.

Hydrolysis of 4-Amino-2-methyl-5-thioformamidomethylpyrimidine (V; R′ = NH_2, R″ = NH·CHS).—A solution of 4-amino-2-methyl-5-thioformamidomethylpyrimidine (Todd and Bergel, *J.*, 1937, 364) (0·19 g.) in water (15 ml.) was heated at 120° in a sealed tube for 2 hr. The solution, which had an odour of hydrogen sulphide, was freeze-dried and the residue sublimed at 140°/10^{-4} mm. The product (0·10 g., 60%) had m. p. 227—228°, undepressed on admixture with an authentic sample of 4-amino-5-formamidomethyl-2-methylpyrimidine (Andersag and Westphal, *Ber.*, 1937, **70**, 2035).

5-Aminomethyl-2-methyl-4-methylaminopyrimidine (II; R = NH_2).—A solution of the methylaminocyano-compound (1·00 g.) in *iso*propyl alcohol (200 ml.) was hydrogenated at room temperature and 6 atm. with freshly prepared W-7 Raney nickel (6 g.), the theoretical volume being absorbed in 1·5 hr. The mixture was then filtered through " Hyflo Supercel " and evaporated to dryness under reduced pressure. The yield of crude material was 0·75 g. (73%). Conversion into the acetyl compound with acetic anhydride–triethylamine, for characterisation, is almost quantitative.

2-Methyl-4-methylamino-5-thioformamidomethylpyrimidine (II; R = NH·CHS).—The above crude aminomethyl compound (0·89 g.) was dissolved in the minimum amount of methanol, and water (2 ml.) was added, followed by aqueous sodium dithioformate (1·34 g., 1·1 equivs.; in 10 ml.). After 2 days at room temperature the solution was concentrated to *ca.* 5 ml. under reduced pressure at room temperature. The *thioformyl* compound (0·68 g., 59%) separated as pale green needles, m. p. 132° (Found: C, 49·6; H, 6·2; N, 28·3. $C_8H_{12}N_4S$ requires C, 49·0; H, 6·2; N, 28·6%). Attempted recrystallisation gave the corresponding formyl compound, and other thioformylations of the aminomethyl compound also gave this as the major product.

Attempted condensation of the thioformyl compound with chloro-ketones resulted only in the formation of the hydrochloride, m. p. 234—235°, of the formyl compound.

5-Formamidomethyl-2-methyl-4-methylaminopyrimidine Hydrochloride (II; R = NH·CHO).—The crude aminomethylmethylaminopyrimidine (from 4·06 g. of the cyano-compound) was refluxed in formic acid (98%; 20 ml.) for 6 hr. The solution was evaporated to dryness, the residue dissolved in water, and the pH of the solution brought to 7 by the addition of aqueous potassium carbonate solution. The solution was extracted with butanol, and the butanol extract dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was dissolved in acetone, and ethanolic hydrogen chloride (10%) added, followed by a trace of ether. After being kept overnight at 0° the colourless crystals were filtered off. Recrystallisation from ethanol–ether yielded colourless needles (3·23 g., 54%) of the *hydrochloride*, m. p. 234—235°, of the formyl compound (Found: C, 44·3; H, 5·9; N, 25·8. $C_8H_{12}ON_4$,HCl requires C, 44·3; H, 6·0; N, 25·8%).

S-Acetonyl N-(2-Methyl-4-methylamino-5-pyrimidylmethyl) Dithiocarbamate (II; R = NH·CS·S·CH_2·COMe).—A solution of the crude aminomethyl compound (from 0·97 g. of the cyano-compound) in methanol (10 ml.) and water (3 ml.) was treated with potassium hydroxide (0·37 g.) in methanol (6 ml.) and water (2 ml.), followed by carbon disulphide (0·40 ml.). The mixture was vigorously shaken for 15 min.; chloroacetone (0·52 ml.) was then added and shaking continued for a further 30 min. The precipitated potassium chloride (0·28 g., 57%) was then filtered off and the solution diluted with water (10 ml.). Crystals were deposited from the solution at 0°. Recrystallisation from methanol followed by sublimation at 140°/10^{-4} mm. led to colourless needles (0·51 g., 27%) of the *dithiocarbamate*, m. p. 242—243° (Found: C, 46·7; H, 5·4; N, 20·0. $C_{11}H_{16}ON_4S_2$ requires C, 46·4; H, 5·6; N, 19·7%). Heating the solid to 100°, or refluxing a solution of the compound in hydrochloric acid (10%), failed to effect the desired cyclisation (cf. Sykes, *J.*, 1951, 2507), the starting material being recovered.

5-2′-Hydroxyethyl-4-methyl-3-(2-methyl-4-methylamino-5-pyrimidylmethyl)thiazolium Chloride Hydrochloride (N-*Methylthiamine Chloride Hydrochloride*) (I).—5-Formamidomethyl-2-methyl-4-methylaminopyrimidine hydrochloride (13·8 g.) was added to a mixture of formic acid (16·5 ml.), activated charcoal (2 g.), and 3-acetoxy-1-chloropropyl methyl ketone (12 g.), and hydrogen sulphide was passed through the mixture at 115—120° for 5 hr. The solution was then evaporated to dryness under reduced pressure and kept over solid potassium hydroxide (pellets) in a vacuum-desiccator overnight. The residue was then extracted with boiling methanol, decolorised with activated charcoal, filtered, and diluted with ether. Crystals separated when the solution was left at 0°. A further crop was obtained on concentration of the mother liquors and treatment with more ether. Recrystallisation from methanol–ether yielded colourless needles (10·7 g., 48%) of *N*-methylthiamine chloride hydrochloride, m. p. 253—254° (Found: C, 44·7; H, 5·7; N, 16·0. Calc. for $C_{13}H_{20}ON_4SCl_2$: C, 44·5; H, 5·7; N, 16·0%).

One of us (P. N.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant, and we also make grateful acknowledgment to Roche Products Ltd. for gifts of material.

University Chemical Laboratory, Cambridge. [*Received, May 21st*, 1954.]