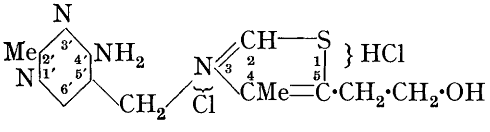
310. *Aneurin. Part VIII. Some Analogues of Aneurin.*

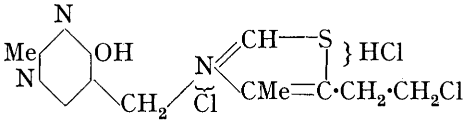
By F. Bergel and A. R. Todd.

Five analogues of aneurin (vitamin-B_1) are described. Four of these were prepared by methods analogous to that used in the synthesis of aneurin (Part VII, this vol., p. 364), and the fifth by addition of 2 : 4-dichloro-5-chloromethyl-6-methylpyrimidine to 4-methyl-5-β-hydroxyethylthiazole, followed by partial amination of the product. None of these compounds showed measurable vitamin activity. The results suggest that vitamin activity is unlikely in a 3-(pyrimidyl-5′-methyl)thiazolium salt unless it contains (*a*) a 4′-amino-group, (*b*) a 5-hydroxyalkyl group, and (*c*) a free 2-position in the thiazole ring. It is also probable that the nature of the substituents in positions 2′ and 6′ in the pyrimidine ring influences vitamin activity.

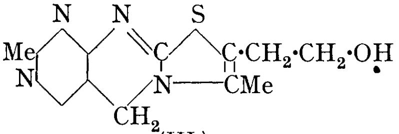
The question as to how far vitamin activity is associated with details of structure has been investigated in the cases of ascorbic acid (vitamin-*C*) and lactoflavin (vitamin-B_2) by the synthesis of compounds of related constitution. The results obtained in such work indicate clearly that any structural alteration in the vitamin molecule causes a marked diminution in activity, and indeed, often causes its complete disappearance. The structure of aneurin (vitamin-B_1) (I) has been established by complete synthesis (Cline and Williams, *J. Amer. Chem. Soc.*, 1936, **58**, 1504; Todd and Bergel, Part VII, *loc. cit.*; Cline, Williams, and Finkelstein, *J. Amer. Chem. Soc.*, 1937, **59**, 1052), and it is of importance to determine in this case also the structural features essential for vitamin activity. Observations bearing on this point have hitherto been few. The " oxychlorovitamin " (II) of Buchman and Williams (*J. Amer. Chem. Soc.*, 1935, **57**, 1751) has no vitamin activity, which suggests that either, or both, the 4′-amino-group and the hydroxyl in the thiazole side chain are essential.



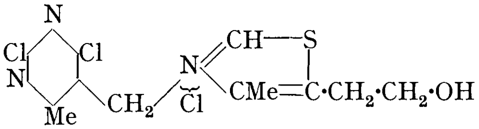
(I.)



(II.)



(III.)



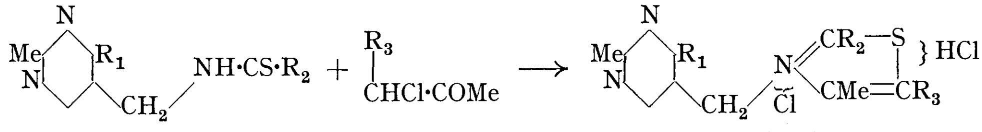
(IV.)

Thiochrome (III) also is inactive (Barger, Bergel, and Todd, Part 1, *Ber.*, 1935, **68**, 2257), but here the presence of the additional ring makes it difficult to draw any valid conclusions. That the methylene bridge between the pyrimidine nucleus and the thiazole nitrogen is necessary, is suggested by the biological inactivity of synthetic 3-pyrimidylthiazolium salts (Todd and Bergel, Part V, J., 1936, 1560). The only other evidence is provided by Bowman (this vol., p. 494), who reported that the substance (IV) was inactive; in this case also the 4′-amino-group is missing.

In the hope of throwing further light on the problem, we have synthesised several analogues of aneurin having the general formula (VII), by application of the synthetic method described in Part VII (*loc. cit.*). The compounds were tested for vitamin-B_1 activity on rats, Birch and Harris's electrocardiagraphic method (*Biochem. J.*, 1934, **28**, 602) being used, but in no case could measurable activity be detected. The behaviour of each substance in the formaldehyde–azo-test (Kinnersley and Peters, *ibid.*, p. 667) and the thiochrome test (Part I, *loc. cit.*) was noted. The scheme of synthesis and particulars of the individual analogues are indicated on p. 1505.

The synthesis of analogue B (" oxyaneurin ") proved rather difficult. Unsatisfactory results were obtained on condensing 4-hydroxy-5-thioformamidomethyl-2-methylpyrimidine (V; R_1 = OH, R_2 = H) with methyl α-chloro-γ-hydroxypropyl ketone (VI; R_3 =

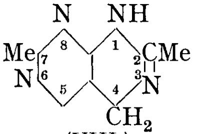
$CH_2\cdot CH_2\cdot OH$) or its acetyl derivative. The use of methyl α-bromo-γ-acetoxypropyl ketone and addition of glacial acetic acid to the reaction mixture was more successful.

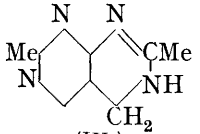

(V.) (VI.) (VII.)

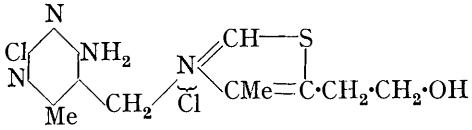
Substance.	R_1.	R_2.	R_3.	Azo-test.	Thiochrome test.
Aneurin	NH_2	H	$CH_2\cdot CH_2\cdot OH$	+	+
A	NH_2	H	H	–	+
B	OH	H	$CH_2\cdot CH_2\cdot OH$	+	–
C	OH	H	H	–	–
D	NH_2	Me	$CH_2\cdot CH_2\cdot OH$	–	–

In the synthesis of analogue D ("2-*methylaneurin*") the necessary 4-*amino*-5-*thioacetamidomethyl*-2-*methylpyrimidine* (V; $R_1 = NH_2$, $R_2 = Me$) was prepared in good yield from the corresponding 5-aminomethyl compound by allowing it to react in aqueous solution with potassium dithioacetate; this method was more satisfactory than heating the amine with dithioacetic acid. On heating the thioacetamido-compound with methyl α-chloro-γ-acetoxypropyl ketone or the corresponding bromo-ketone at a temperature of *ca.* 130°, the chief product was a crystalline sulphur-free compound considered to be a 2 : 7-*dimethyldihydro*-1 : 3 : 6 : 8-*benztetrazine* of structure (VIII) or (IX). At temperatures below 100° mainly unchanged thioacetamido-compound was isolated. The benztetrazine base was characterised as its *hydrochloride, hydrobromide,* and *picrate*; its formation from the thioacetamido-compound is exactly analogous to the production of purines from 4-amino-5-thioformamidopyrimidines by intramolecular loss of hydrogen sulphide (Part V, *loc. cit.*).

When condensation of the thioacetamido-compound and the bromo-ketone was carried out at 120° in presence of glacial acetic acid, *acetylmethylaneurin* could be isolated in moderately good yield after separation of the above benztetrazine. Decomposition of the *picrate* with hydrochloric acid caused removal of the acetyl group, yielding the *chloride* of *methylaneurin,* whose isolation, like that of its acetyl derivative, was complicated by its great solubility in alcohol. As expected, methylaneurin, which bears a substituent in position 2 of the thiazole nucleus, gave no response in the azo-test or the thiochrome test.


(VIII.)


(IX.)


(X.)

In the course of model experiments preliminary to the synthesis of aneurin (*Nature,* 1936, **138**, 76), we condensed 2 : 4-dichloro-5-chloromethyl-6-methylpyrimidine with 4-methyl-5-β-hydroxyethylthiazole and obtained the salt (IV); this compound has also been prepared by Bowman (*loc. cit.*) by a similar method. The corresponding iodide was prepared in similar fashion from 2 : 4-*dichloro*-5-*iodomethyl*-6-*methylpyrimidine.* In order to obtain a compound more closely related to the vitamin, (IV) was treated with cold alcoholic ammonia. By analogy with the behaviour of 2 : 4-dihalogenated pyrimidines (cf. Gabriel and Colman, *Ber.*, 1901, **34**, 1254), it was expected that the chlorine atom in position 4′ would be replaced by an amino-group, and that the resulting compound (as chloride) would have structure (X). This view appeared to be confirmed by the fact that oxidation of the product with alkaline potassium ferricyanide gave solutions with a blue fluorescence similar to that of thiochrome; furthermore, a biological test carried out on the crude amination product showed that it possessed some vitamin activity.

We have recently subjected this material to further examination, but have been unable to confirm the earlier observation of biological activity. The substance has certain properties which are not readily explained on the basis of structure (X). It appears to be a monochloride and yields a monopicrate, which is unexpected in a thiazolium salt of this type. On oxidation with potassium ferricyanide, blue fluorescence develops only in presence of strong alkali, and then rather slowly. Similarly, the response to the azo-test is feeble and much delayed; addition of alkali causes an increase in intensity of colour, but not in rate of its development. We are unable to offer an adequate explanation of these facts, although it might be that the compound exists normally as a derivative of the pseudo-base, formed by migration of the ionic chlorine to the 2-position of the thiazole ring. Attempts to synthesise (X) by the general method used for other aneurin analogues were unsuccessful, as partial amination of 2 : 4-dichloro-5-chloromethyl-6-methylpyrimidine to produce a 5-aminomethyl compound could not be effected.

Although the number of analogues so far prepared is small, it seems probable that any significant alteration in the aneurin molecule will cause almost complete loss of activity. Our results suggest that vitamin activity will be exceedingly feeble, if not entirely absent, in any analogue which does not contain (*a*) an amino-group in position 4′, (*b*) a 5-β-hydroxyethyl group, (*c*) a hydrogen atom in position 2, and (*d*) a methylene group between the pyrimidine nucleus and the thiazole nitrogen. With regard to condition (*b*), it may be that other hydroxyalkyl groups could be substituted for the hydroxyethyl group without loss of activity. The necessity for the presence of a hydroxylated side-chain on the thiazole ring may also be inferred from the results of Lohmann and Schuster (*Naturwiss.*, 1937, **25**, 26; *Ned. Tijd. Geneesk.*, 1937, 2793), who consider the pyrophosphoric ester of aneurin to be identical with co-carboxylase (cf. Stern and Hofer, *Science*, 1937, **85**, 483; v. Euler and Vestin, *Naturwiss.*, 1937, **25**, 416); phosphorylation of the vitamin can only occur at this point in the molecule—the possibility that it might take place at the 4-amino-group is ruled out by the fact that co-carboxylase gives on oxidation a thiochromine which still contains phosphorus.

As far as chemical tests for aneurin are concerned, it seems as though any thiazolium salt containing a 5-β-hydroxyethyl group and a free 2-position will give a positive azo-test. The thiochrome test will give a positive result with any 3-(pyrimidyl-5′-methyl)thiazolium salt with a free 2-position and a 4′-amino-group, since blue fluorescence is a general property of thiochromines (Part VI; J., 1936, 1601).

EXPERIMENTAL.

3-(4′-*Amino-2′-methylpyrimidyl-5′-methyl*)-4-*methylthiazolium Chloride Hydrochloride* (*Analogue* A).—4-Amino-5-thioformamidomethyl-2-methylpyrimidine (0·3 g.) (Part VII, *loc. cit.*) was heated at 115° with chloroacetone (0·2 g.) for about 5 minutes; the mixture liquefied and then became solid again. The cooled product was washed with absolute ether to remove unchanged chloroacetone, and triturated with warm absolute alcohol containing a little hydrogen chloride. The residue was collected and recrystallised from methanol–acetone, forming colourless crystals (0·12 g.), sparingly soluble in absolute alcohol. On heating, the *salt* sintered and blackened at 261—262° but did not liquefy completely below 300° (Found, in material dried at 30°: N, 17·9; S, 10·2; Cl, 22·7. $C_{10}H_{13}N_4ClS,HCl,H_2O$ requires N, 18·0; S, 10·3; Cl, 22·8%). The thiochrome test was positive though weaker than with aneurin, and the azo-test negative. In a biological test 8 mg. showed no aneurin activity.

3-(4′-*Hydroxy-2′-methylpyrimidyl-5′-methyl*)-4-*methyl*-5-β-*hydroxyethylthiazolium Chloride Hydrochloride* (*Analogue* B).—Three methods were tried, in which 4-hydroxy-5-thioformamidomethyl-2-methylpyrimidine (Part VI, *loc. cit.*) was condensed severally with methyl α-chloro-γ-hydroxypropyl ketone (Part III, J., 1936, 1555), methyl α-chloro-γ-acetoxypropyl ketone (*ibid.*), and methyl α-bromo-γ-acetoxypropyl ketone (Research Corporation, E. P. Appln. 1936, No. 7927). Of these, only the third proved satisfactory.

The thioformamido-compound (0·5 g.) and methyl α-bromo-γ-acetoxypropyl ketone (0·6 g.) were heated with glacial acetic acid (2 g.) at 80—100° during 10 minutes. On addition of ether to the resulting solution, an oil was precipitated, which was dissolved in water, and excess of saturated aqueous picric acid added. The oily picrate was washed, decomposed by dissolution in hydrochloric acid (10%), and the picric acid extracted with ether. The aqueous solution was evaporated to dryness in a vacuum, and the residue, which could not be readily recrystallised, was purified by repeated dissolution in absolute alcohol and precipitation with dioxan. In this way a hygroscopic crystalline product was obtained which, on heating, frothed somewhat at

170° and became completely molten at 195—197°. The azo-test was positive, and the thiochrome test negative. In a dosage of 1 mg. the *substance* had no vitamin activity (Found, in material dried at 40° in a high vacuum : C, 42·7; H, 5·1; Cl, 20·3. $C_{12}H_{16}O_2N_3ClS,HCl$ requires C, 42·6; H, 5·0; Cl, 21·0%).

3-(4'-*Hydroxy*-2'-*methylpyrimidyl*-5'-*methyl*)-4'-*methylthiazolium Chloride Hydrochloride* (*Analogue* C).—When 4-hydroxy-5-thioformamidomethyl-2-methylpyrimidine (0·5 g.) and chloroacetone (0·4 g.) were heated together at 105—115° for 5 minutes, the initially liquid mixture suddenly solidified. After being washed with ether, the product was dissolved in absolute alcohol (30—40 c.c.), and acetone added till a turbidity appeared. On standing, colourless crystals separated, which, when recrystallised from a mixture of methyl and ethyl alcohol (1 : 1) to which a little acetone was added, formed prisms (0·35 g.) which had no definite m. p. but shrank and softened at about 220° [Found, (*a*) in material dried at 30° in a high vacuum : C, 38·3; H, 4·6. $C_{10}H_{12}ON_3ClS,HCl,H_2O$ requires C, 38·2; H, 4·8%; (*b*) in material dried at 40° in a high vacuum : N, 14·2; Cl, 24·8. $C_{10}H_{12}ON_3ClS,HCl$ requires N, 14·3; Cl, 24·2%]. The azo-test and the thiochrome test were both negative, and in a dosage of 8 mg. no vitamin activity could be detected.

4-*Amino*-5-*thioacetamidomethyl*-2-*methylpyrimidine* (V; $R_1 = NH_2$, $R_2 = Me$).—Crude 4-amino-5-aminomethyl-2-methylpyrimidine (0·55 g.) (prepared from its hydrochloride by saturating a cold aqueous solution with potassium hydroxide) was heated under reflux for 4 hours with a solution of dithioacetic acid (0·55 g.) in dioxan (15 c.c.). After addition of excess of light petroleum, the brownish precipitate was collected, triturated with a little water, and recrystallised from hot water, affording colourless, stout needles, m. p. 228—229° (Found : N, 28·5. $C_8H_{12}N_4S$ requires N, 28·6%).

The *compound* is more conveniently obtained by dissolving the diamine hydrochloride in water, neutralising it with potassium carbonate, and adding a solution of potassium dithioacetate; on standing, the thioacetamido-compound separates in practically pure condition. This method avoids the preparation of pure dithoacetic acid : the solution of the crude potassium salt obtained in an intermediate stage of its preparation (Pohl, *Ber.*, 1907, **40**, 1304) may be used directly for thioacetylation purposes.

Condensation of 4-*Amino*-5-*thioacetamidomethyl*-2-*methylpyrimidine with Methyl* α-*Bromo*-γ-*acetoxypropyl Ketone*.—When the above thioacetamido-compound (0·5 g.) was heated with methyl α-bromo-γ-acetoxypropyl ketone (0·75 g.) and glacial acetic acid (5 drops) to 120° during 20 minutes, the mixture, initially liquid, set to a semicrystalline mass. The product was thoroughly washed with absolute ether, heated with absolute alcohol (5 c.c.) for a few minutes, and cooled, and the sparingly soluble crystalline material (A) (0·3 g.) collected and washed with absolute alcohol (2·5 c.c.).

2 : 7-*Dimethyldihydro*-1 : 3 : 6 : 8-*benztetrazine* (VIII *or* IX).—The solid (A) (above), recrystallised from absolute alcohol, formed colourless needles (0·25 g.), m. p. 283—284°. It contained no sulphur and is evidently the *hydrobromide* of 2 : 7-dimethyldihydro-1 : 3 : 6 : 8-benztetrazine (Found: C, 39·9; H, 4·5; Br, 33·3. $C_8H_{10}N_4,HBr$ requires C, 39·6; H, 4·5; Br, 33·3%). With aqueous picric acid it gave a picrate, forming broad yellow needles, m. p. 198—199°. Decomposition of the picrate in the usual manner with 10% hydrochloric acid furnished the hydrochloride, which crystallised from absolute alcohol containing light petroleum in needles, m. p. 269—270° with partial sublimation. The free *base* crystallised on addition of a slight excess of potassium hydroxide solution (15%) to the hydrobromide dissolved in a little water. Recrystallised from hot water, it formed woolly needles, m. p. 169—170° (picrate, m. p. 198—199°) (Found, in material dried at 30° : C, 59·2; H, 6·4; N, 34·4. $C_8H_{10}N_4$ requires C, 59·2; H, 6·2; N, 34·6%). Aqueous solutions of the base show no fluorescence in ordinary light.

3-(4'-*Amino*-2'-*methylpyrimidyl*-5'-*methyl*)-2 : 4-*dimethyl*-5-β-*hydroxyethylthiazolium Chloride Hydrochloride* (*Methylaneurin*).—The alcoholic mother-liquor from the above condensation, after removal of the solid (A), was diluted with light petroleum, and the precipitated brownish oil (0·47 g.) dissolved in a small quantity of absolute alcohol (2·5 c.c.). After 2 days, the solution deposited a crystalline solid (0·15 g.); this was collected, purified by dissolution in alcohol and reprecipitation with light petroleum, and recrystallised from butyl alcohol at — 5°. It formed colourless crystals, m. p. 193—194° (Found, in material dried at 30° : C, 36·5; H, 4·8; Br, 32·2. $C_{15}H_{21}O_2N_4BrS,HBr,H_2O$ requires C, 36·0; H, 4·8; Br, 32·0%), and is evidently the *bromide hydrobromide* of O-*acetyl*-2-*methylaneurin*. The picrate crystallised from water in yellow needles, m. p. 188—189°, and on decomposition with hydrochloric acid (10%) in the usual manner, it afforded 2-methylaneurin chloride. Recrystallised from absolute alcohol containing light petroleum, this formed broad, colourless needles, m. p. 199° (Found, in material dried at 30° :

C, 43·0; H, 6·0; Cl, 18·5. $C_{13}H_{19}ON_4ClS,HCl,H_2O$ requires C, 42·4; H, 6·0; Cl, 19·2%). The picrate crystallised from water in yellow needles, m. p. 218—219°.

The 2-methylaneurin gave no thiochrome test, and only a slight orange coloration in the azo-test. It had no vitamin activity in a dosage of 100γ; similar inactivity was shown by the acetyl derivative.

Other Condensation Experiments.—(*a*) On heating a mixture of the above thioacetamido-compound (1 g.), methyl α-bromo-γ-acetoxypropyl ketone (1·3 g.), and glacial acetic acid (1·2 g.) at 80° for 5 minutes, a solution was formed which on cooling deposited the *hydrobromide* of the original thioacetamido-compound; it crystallised from alcohol in colourless needles, m. p. 198—200° (Found : C, 34·8; H, 4·6. $C_8H_{12}N_4S,HBr$ requires C, 34·7; H, 4·7%). The picrate had m. p. 165°, not depressed by admixture with the picrate (m. p. 165°) prepared directly from the free thioacetamido-compound.

Decomposition of the above picrates with hydrochloric acid gave the *hydrochloride*, m. p. 197—199° (Found : Cl, 14·1; S, 12·6. $C_8H_{12}N_4S,HCl,H_2O$ requires Cl, 14·2; S, 12·8%). By addition of ether to the acetic acid mother-liquors from the above experiment, 2 : 7-dimethyldihydrobenztetrazine hydrobromide, m. p. 283—284° (picrate, m. p. 198—199°), was obtained.

(*b*) By carrying out the condensation of the thioacetamido-compound with the chloro- or the bromo-ketone at 130°, 2 : 7-dimethyldihydrobenztetrazine was formed almost exclusively.

3-(2′ : 4′-*Dichloro*-6′-*methylpyrimidyl*-5′-*methyl*)-4-*methyl*-5-β-*hydroxyethylthiazolium Chloride* (IV).—2 : 4-Dichloro-5-chloromethyl-6-methylpyrimidine (2·8 g.) (Part VI, *loc. cit.*; Bowman, *loc. cit.*) was heated to 105° with 4-methyl-5-β-hydroxyethylthiazole (1·75 g.) (Part III, *loc. cit.*; Buchman, *J. Amer. Chem. Soc.*, **1936**, **58**, 1803) during 30 minutes. The melt had then solidified, and, after cooling, it was washed thoroughly with absolute ether and recrystallised from absolute alcohol (30—40 c.c.), forming faintly yellowish platelets (1·15 g.), m. p. 206° (Bowman gives m. p. 203—204°) (Found : C, 40·7; H, 3·8; N, 11·7; S, 8·5. Calc. for $C_{12}H_{14}ON_3Cl_3S$: C, 40·6; H, 4·0; N, 11·8; S, 9·0%). The azo-test was positive, but weaker and more delayed than with aneurin; addition of sodium hydroxide increased the intensity of colour. The thiochrome test was negative. The corresponding picrate had m. p. 142°.

2 : 4-*Dichloro*-5-*iodomethyl*-6-*methylpyrimidine*.—To 2 : 4-dichloro-5-chloromethyl-6-methylpyrimidine (3·2 g.), dissolved in the minimum amount of acetone, a *N*-solution of sodium iodide in acetone (20 c.c.) was added. The sodium chloride which was immediately precipitated was filtered off, and the *iodo*-compound precipitated by addition of water. It crystallised from light petroleum (b. p. 60—80°) in large, colourless prisms (3 g.), m. p. 93·5—94·5° (Found : C, 23·9; H, 1·8; N, 9·3. $C_6H_5N_2Cl_2I$ requires C, 23·8; H, 1·7; N, 9·3%).

3-(2′ : 4′-*Dichloro*-6′-*methylpyrimidyl*-5′-*methyl*)-4-*methyl*-5-β-*hydroxyethylthiazolium Iodide*.—The above iodo-compound (2·1 g.), when heated at 60—70° with 4-methyl-5-β-hydroxyethylthiazole (1 g.) for 5 minutes, yielded a crystalline *iodide*, which was washed with ether and recrystallised from absolute alcohol, forming glistening leaflets, m. p. 181—182° (Found : C, 32·6; H, 3·1; N, 9·2; S, 6·9. $C_{12}H_{14}ON_3Cl_2IS$ requires C, 32·2; H, 3·1; N, 9·4; S, 7·2%). It was similar in properties to the corresponding chloride (above), and gave the same picrate, m. p. 142°.

Amination of the Salt (*IV*).—The chloride (IV) (0·27 g.) was dissolved in 4*N*-alcoholic ammonia (10 c.c.), and the bright yellow solution was kept for 1 hour at room temperature, then evaporated to dryness. The residue was stirred with absolute alcohol containing hydrogen chloride, whereupon most of it dissolved, leaving ammonium chloride. Addition of 2 vols. of acetone to the solution precipitated a small amount of amorphous material, which was filtered off, and the filtrate precipitated with light petroleum. The rather sticky precipitate was collected and spread on a porous plate, which was left for several hours at room temperature in a closed vessel over methanol–acetone (1 : 1); gummy material was thus removed. The crystalline residue was recrystallised from absolute alcohol containing light petroleum. It formed colourless needles which, on heating, shrank at 135° (probably owing to loss of water) and melted at 200—205°. Analysis indicates that it has the composition of the expected 3-(2′-*chloro*-4′-*amino*-6′-*methylpyrimidyl*-5′-*methyl*)-4-*methyl*-5-β-*hydroxyethylthiazolium chloride* (X) (Found, in material dried at 30° : C, 40·9; H, 5·1; N, 15·5; Cl, 21·1; S, 9·1. $C_{12}H_{16}ON_4Cl_2S,H_2O$ requires C, 40·9; H, 5·1; N, 15·9; Cl, 20·1; S, 9·1%). The compound gave positive results in the thiochrome and the azo-test, but the response was feebler than with aneurin and much delayed. The positive thiochrome test is evidence for the presence of a 4′-amino-group. In biological tests no measurable vitamin activity could be detected in doses of 0·5 and 1 mg. The *picrate* had m. p. 214—215° (Found : Cl, 7·2. $C_{18}H_{19}O_8N_7ClS$ requires Cl, 6·7%).

The corresponding iodide was prepared in similar fashion from the iodide corresponding to

(IV); crystallised from absolute alcohol containing light petroleum, it had m. p. 228° (decomp.), and gave the same picrate, m. p. 214—215°, as was obtained from the chloride; it showed no vitamin activity, and gave the same delayed colour tests as the chloride.

Experiments on the Amination of 2 : 4-*Dichloro*-5-*chloromethyl*-6-*methylpyrimidine.*—(i) To a solution of the trichloro-compound (4 g.) in absolute alcohol (5 c.c.) was added 4*N*-alcoholic ammonia (20 c.c.), and the mixture left at room temperature for 3 hours. The crystalline precipitate was collected, washed with water to remove ammonium chloride, and recrystallised from alcohol, affording colourless needles (0·5 g.), m. p. 162—163° after slight sintering at 153°. The compound was practically insoluble in water, and this, together with the analytical values, suggests that it is the secondary base *bis*-(2 : 4-*dichloro*-6-*methylpyrimidyl*-5-*methyl*)*amine* (Found : C, 39·5; H, 2·9; N, 18·9; Cl, 38·4. $C_{12}H_{11}N_5Cl_4$ requires C, 39·3; H, 3·0; N, 19·0; Cl, 38·7%).

On addition of water to the ammoniacal alcoholic solution remaining after separation of the above compound, an amorphous ether-soluble base (1·9 g.) was precipitated. The mother-liquors contained nothing which would react with potassium dithioformate. Similar results were obtained when amination was carried out under various conditions with aqueous or alcoholic ammonia, or liquid ammonia.

(ii) Attempts were made to replace the chloromethyl group in the trichloro-compound by an aminomethyl group by addition of hexamine and subsequent hydrolysis of the crystalline product. The oil obtained in this way would not react with potassium dithioformate.

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