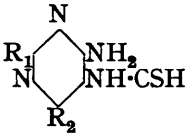
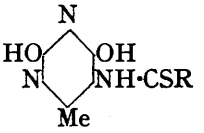
343. *Aneurin. Part IV. 5-Thioformamidopyrimidines.*

By A. R. Todd, F. Bergel, and Karimullah.

For the synthesis of 3-pyrimidylthiazolium salts according to the scheme indicated in the preceding paper it is necessary to synthesise 5-thioformamidopyrimidine derivatives including those of type (I). It is known that an amino-group in position 5 of the pyrimidine nucleus is unique in that it is readily acylated; amino-groups in other positions are not. Thus, formylation of a 5 : 6-diaminopyrimidine leads to the formation of the corresponding 6-amino-5-formamidopyrimidine and not to a diformyl derivative (Gabriel and Colman, *Ber.*, 1901, **34**, 1246; Johns, *Amer. Chem. J.*, 1908, **41**, 58). Thioacylamidopyrimidines are not described in the literature, and we were unable to prepare them by the action of phosphorus pentasulphide on the corresponding acyl derivatives. A similar lack of success was encountered on attempting to replace the 5-amino-group by an *iso*nitrile group with a view to subsequent addition of hydrogen sulphide according to Hofmann (*Ber.*, 1878, **11**, 339).

(I.)  (II.) 

Thioacetic acid reacts readily with primary amines to give the corresponding acetyl derivatives (Pawlewski, *Ber.*, 1898, **31**, 661; 1902, **35**, 110); accordingly we next tried direct thioacylation by heating amines with dithio-acids (R·CS·SH). With dithioacetic acid, this was completely successful and *5-thioacetamido-4-methyluracil* (II; R = Me) was readily obtained from 5-amino-4-methyluracil. Dithioformic acid acts in a similar way,* but the yield is not good and the product is difficult to purify. It was, however, found that the thioformylation can be readily effected by mixing aqueous solutions of 5-amino-pyrimidines and potassium dithioformate; at room temperature in an atmosphere of carbon dioxide the thioformyl derivatives normally separate in almost pure condition, the yield being nearly quantitative. Amino-groups in positions 2, 4 and 6 of the pyrimidine nucleus did not react under these conditions.

In this way *6-amino-5-thioformamido-4-methylpyrimidine* (I; $R_1 = H$, $R_2 = Me$), *6-amino-5-thioformamido-4-ethylpyrimidine* (I; $R_1 = H$, $R_2 = Et$), and *2 : 6-diamino-5-thioformamido-4-methylpyrimidine* (I; $R_1 = NH_2$, $R_2 = Me$) were prepared from the corresponding 5-amino-compounds; they are crystalline substances which evolve hydrogen sulphide above the melting point and yield the corresponding purines. On heating with chloroacetone, they yield the corresponding 3-pyrimidylthiazolium salts.

In the course of this work a considerable number of aminopyrimidines were prepared; most of these are known compounds, but *2-amino-6-hydroxy-4-ethylpyrimidine* and *2 : 6-diamino-4-ethylpyrimidine* have not hitherto been described. Neither could be thioformylated with potassium dithioformate.

Experimental.

5-Thioacetamido-4-methyluracil (II; R = Me).—5-Amino-4-methyluracil (1 g.) (Behrend, *Annalen*, 1885, **231**, 250), dissolved in dioxan (50 c.c.), was heated on the water-bath with di-

* Experiments by Miss A. Jacob.

thioacetic acid (0·9 g.) (Pohl, *Ber.*, 1907, **40**, 1304) during 4 hours. The mixture was cooled and diluted with light petroleum. The yellowish precipitate crystallised from hot water in colourless needles, m. p. 265—267° (Found: C, 42·4; H, 4·8; N, 21·1. $C_7H_9O_2N_3S$ requires C, 42·2; H, 4·6; N, 21·2%). Yield, quantitative.

5-*Thioformamido*-4-*methyluracil* (II; R = H).—5-Amino-4-methyluracil (1 g.) in dioxan (50 c.c.) was heated under reflux with dithioformic acid (0·7 g.) (Levi, *Atti R. Accad. Lincei*, 1923, **32**, I, 569). The crude *thioformyl* derivative precipitated with light petroleum was difficult to purify. After recrystallisation from water it had m. p. 260—262° (Found: N, 21·0. $C_6H_7O_2N_3S$ requires N, 22·7%. $C_6H_7O_2N_3S,H_2O$ requires N, 20·7%).

3-(2′: 6′-*Dihydroxy*-4′-*methylpyrimidyl*-5′)-4-*methylthiazolium Chloride*.—The above thioformyl compound (1 mol.), mixed with chloroacetone (4—5 mols.), was heated carefully over a free flame. Vigorous reaction occurred, and after 10—15 minutes the mixture was cooled, and the *product* precipitated as a gum by addition of ether. It crystallised from alcohol–acetone in colourless needles, m. p. 306° (decomp.) (Found: C, 40·9; H, 4·6; N, 15·6; Cl, 13·6. $C_9H_{11}O_2N_3ClS$ requires C, 41·4; H, 4·3; N, 16·1; Cl, 13·6%).

6-*Amino*-5-*thioformamido*-4-*methylpyrimidine* (I; R_1 = H, R_2 = Me).—To 5: 6-diamino-4-methylpyrimidine (1·5 g.) (Gabriel and Colman, *Ber.*, 1901, **34**, 1254), dissolved in water (10 c.c.), potassium dithioformate (2 g.) was added; traces of crystalline material, m. p. above 300°, soon separated. The solution was filtered and kept over sulphuric acid in a desiccator filled with carbon dioxide. After 12 hours the crystalline precipitate was collected (the filtrate may be treated with a further quantity of potassium dithioformate and the process repeated until the yield is nearly quantitative). The *thioformyl* compound crystallised from water in colourless needles (Found: C, 43·0; H, 5·2; S, 18·6. $C_6H_8N_4S$ requires C, 42·9; H, 4·8; S, 19·0%). It melted sharply at 168° with evolution of hydrogen sulphide; the melt resolidified and on further heating melted at 230°. Gabriel (*Ber.*, 1901, **34**, 1247) gives m. p. 235° for 4-methylpurine. Conversion into 4-methylpurine occurs slowly above 100°. The substance is very soluble in alcohol, less so in methyl alcohol, acetone and water, and insoluble in ether.

2-*Amino*-6-*hydroxy*-4-*ethylpyrimidine*.—A mixture of ethyl propionylacetate (13·3 g.) (Willstätter and Clarke, *Ber.*, 1914, **47**, 298), guanidine carbonate (8 g.), and absolute alcohol (25 c.c.) was heated under reflux for 4 hours, cooled, and the *product* filtered off and recrystallised from hot water; it formed colourless prisms (7 g.), m. p. 247—248° (Found: C, 51·6; H, 6·2; N, 29·6. $C_6H_9ON_3$ requires C, 51·8; H, 6·2; N, 30·2%). When it (1 g.) was heated with concentrated hydrochloric acid (6 c.c.) for 20 hours at 160°, 4-ethyluracil, m. p. 205°, was obtained (yield, 60%).

6-*Chloro*-2-*amino*-4-*ethylpyrimidine*.—A mixture of the above compound (3·5 g.) and phosphoryl chloride (10 c.c.) was heated under reflux for 2 hours. The resulting brownish solution was poured on ice and made alkaline with ammonia, and the precipitated *chloro*-compound collected. It crystallised from alcohol in colourless needles, m. p. 120—121° (yield, 60%) (Found: C, 45·2; H, 4·9; N, 26·1. $C_6H_8N_3Cl$ requires C, 45·7; H, 5·1; N, 26·7%).

2: 6-*Diamino*-4-*ethylpyrimidine*.—The above *chloro*-compound (0·6 g.) was heated with saturated alcoholic ammonia (20 c.c.) in a sealed tube at 180° during 6 hours. The alcohol was removed, the residue dissolved in a little water, and solid potassium hydroxide added. The precipitated *diamine* was collected and recrystallised from ethyl acetate containing a little light petroleum; it formed colourless needles, m. p. 160—161° (yield, 80%) (Found: N, 40·0. $C_6H_{10}N_4$ requires N, 40·6%).

6-*Amino*-5-*thioformamido*-4-*ethylpyrimidine* (I; R_1 = H, R_2 = Et).—5: 6-Diamino-4-ethylpyrimidine was prepared from 4-ethyluracil by a slight modification of Robinson and Tomlinson's method (J., 1935, 1283). The following process for isolating the diamine is simpler and gives much improved yields: The reaction mixture obtained on reduction of 2-chloro-5: 6-diamino-4-ethylpyrimidine is filtered, concentrated to remove alcohol, and diluted somewhat with water, and solid potassium hydroxide added. The precipitated diamine crystallises from ethyl acetate in large yellowish prisms, m. p. 164—165°; Robinson and Tomlinson (*loc. cit.*) give m. p. 159—161°. A further quantity may be obtained by extracting the alkaline mother-liquor with ethyl acetate (total yield, 60% or more).

The diamine (100 mg.), thioformylated in aqueous solution with potassium dithioformate in the manner described above, gave a *product* crystallising from water in colourless needles, m. p. 178° with evolution of hydrogen sulphide (yield, theoretical) (Found: C, 45·5; H, 6·0; S, 17·1. $C_7H_{10}N_4S$ requires C, 46·1; H, 5·5; S, 17·6%).

2: 6-*Diamino*-5-*thioformamido*-4-*methylpyrimidine* (I; R_1 = NH_2, R_2 = Me).—2: 5: 6-Triamino-4-methylpyrimidine (Gabriel and Colman, *loc. cit.*) on treatment with potassium

dithioformate as above gave colourless needles (from water), m. p. 255° with evolution of hydrogen sulphide (Found : S, 17·2. $C_6H_9N_5S$ requires S, 17·5%).

3-(2′ : 6′-*Diamino*-4′-*methylpyrimidyl*-5′)-4-*methylthiazolium Chloride Hydrochloride*.—To a solution of the above thioformyl compound (1 mol.) in acetone, chloroacetone (2 mols.) was added. The mixture was left for 3 days at room temperature, then diluted with an equal volume of alcohol, and refluxed for 4 hours. The colourless needles that separated were collected after cooling and recrystallised from alcohol–acetone containing hydrogen chloride; needles, m. p. 315° (decomp.), were obtained containing water of crystallisation, which was only expelled with difficulty (Found : C, 31·2; H, 5·4; N, 19·9; S, 9·0; Cl, 20·4. $C_9H_{13}N_5Cl_2S,3H_2O$ requires C, 31·0; H, 5·5; N, 20·1; S, 9·2; Cl, 20·4%). The corresponding picrate has m. p. 255°. On shaking with alkaline potassium ferricyanide, a substance is produced which, though non-fluorescent in visible light, is blue-fluorescent in ultra-violet light; the fluorescence disappears when the liquid is made acid, but reappears when it is made alkaline again.

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