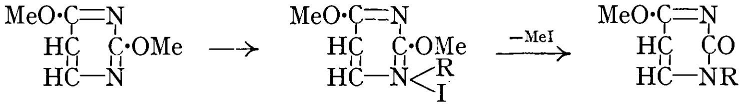
217. *Rearrangement of Methoxy-pyrimidines and -purines.*

By Ernst Bergmann and Heinz Heimhold.

For the synthesis of pyrimidine glucosides, there is an unambiguous method based on the observation (Hilbert and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 4491) that the quaternary ammonium iodides of 2 : 6-dimethoxypyrimidine lose methyl iodide when heated and are converted into 6-methoxy-3-alkyl-2-pyrimidones :



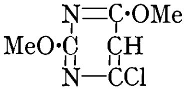
If R is methyl, the reaction consists formally in an intramolecular rearrangement; this in fact occurs with both methoxyls when 2 : 6-dimethoxypyrimidine is heated, 1 : 3-dimethyluracil being formed.

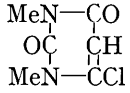
In the course of synthetic experiments on the nucleic acids, we investigated the applicability of the above reaction, especially in the purine series.

(1) 4-Chloro-2 : 6-dimethoxypyrimidine (I) is stable when heated, but the interaction with methyl iodide causes rearrangement into 4-*chloro*-1 : 3-*dimethyluracil* (II).

(2) 2 : 6-*Dimethoxy*-7-*methylpurine* (III), which is readily accessible from 2 : 6-dichloro-7-methylpurine, is converted, when heated alone or by interaction with methyl iodide, into caffeine (IV), the latter method giving the better yield. The rearrangement by heat is accompanied by side reactions, which produce the characteristic odour of methylamine. The new synthesis of caffeine may easily compete with the known methods starting with uric acid (Boehringer and Soehne, *Chem. Zentr.*, 1904, I, 1430) or theophylline and theobromine (Kassel, *Ber.*, 1888, **21**, 2164; *Z. physiol. Chem.*, 1889, **13**, 298; E. Fischer, *Ber.*, 1897, **30**, 1839).

(3) 2-*Chloro*-6-*methoxy*-7-*methylpurine* (V) possesses marked thermal stability [compare (I), which also contains chlorine], but when it is heated with methyl iodide, the methiodide of 2-chloro-1 : 7-dimethylhypoxanthine (VI) is formed.


(I.)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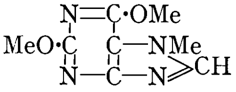
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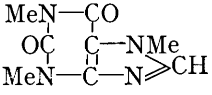
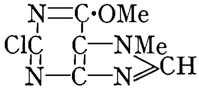
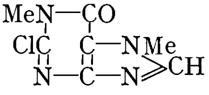

(IV.)

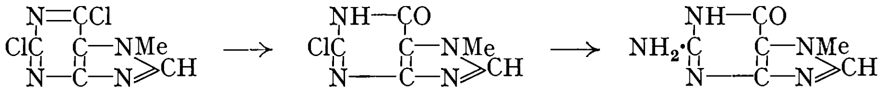

(V.)


(VI.)

In the rearrangement (III) ⟶ (IV), too, the caffeine was partly isolated in the form of its methiodide (Schmidt, *Annalen*, 1883, **217**, 226). Both methiodides (of IV and VI) have the characteristic property of fixing one molecule of iodine. The violet derivative of caffeine has been described by Gulland and Macrae (J., 1933, 663). We are unable to explain how these periodides can be formed in the above reactions (we always used iodine-free methyl iodide). The methoperiodide of (VI) has also been obtained in experiments carried out in an atmosphere of nitrogen.

(4) In addition to the allyl derivatives, only the methylpurine compounds seem to be capable of rearrangement by heat : 2 : 6-dipropoxy-7-methylpurine, however, is stable at 150°. In the thiocyanate series also, only the allyl and the methyl derivatives undergo intramolecular rearrangement.

That the compound (V) is formed from 2 : 6-dichloro-7-methylpurine and sodium methoxide (1 mol.) by replacement of the chlorine atom in position 6 follows from the fact that, by the action of cold alkali hydroxide solution also, this chlorine atom is replaced by hydroxyl, the product being converted by ammonia into 7-methylguanine (E. Fischer, *Ber.*, 1897, **30**, 2400; 1898, **31**, 104, 431) :



EXPERIMENTAL.

Rearrangement of 4-*Chloro*-2 : 6-*dimethoxypyrimidine* (I).—The compound (Fisher and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 730) (2·2 g.) and methyl iodide (4 g.) were heated for 8 hours at 90° in a sealed tube. The mass crystallised on cooling, and recrystallisation from benzene–light petroleum (1 : 1) gave prismatic crystals, m. p. 113°. They are very volatile in a vacuum, sublimation taking place even at 80°. The analysis and the lack of methoxy-groups showed that the substance was 4-*chloro*-1 : 3-*dimethyluracil* (II) (Found : C, 41·3; H, 4·1. $C_6H_7O_2N_2Cl$ requires C, 41·4; H, 4·0%).

2 : 6-*Dimethoxy*-7-*methylpurine* (III).—2 : 6-Dichloro-7-methylpurine (E. Fischer, *loc. cit.*) (4·4 g.) was heated at 100° in a sealed tube for 2 hours with a solution of sodium (1 g.) in methyl alcohol (20 c.c.). After cooling, the solid was collected, washed with water, and recrystallised from xylene, yielding colourless prisms (2·4 g.), m. p. 199° (Found : C, 50·3; H, 4·9; OMe, 34·7. $C_8H_{10}O_2N_4$ requires C, 49·5; H, 5·0; OMe, 32·0%).

Rearrangement. (a) The compound (III) (1 g.) was heated at 210° for 15 minutes. After reaching the m. p., the mass suddenly boiled and turned into a cake of needles, the odour of methylamine being very noticeable. Repeated crystallisation from propyl alcohol gave caffeine (IV) (0·54 g.) in long silky needles, m. p. and mixed m. p. 234—236° (Found : N, 28·3. Calc. for $C_8H_{10}O_2N_4$: N, 28·9%).

(b) 2 : 6-Dimethoxy-7-methylpurine (0·44 g.) was heated at 100° in a sealed tube with methyl iodide (3·5 g.) for 24 hours. The methyl iodide was evaporated, and the solid residue, consisting of caffeine and its methiodide, sublimed in a vacuum, initially at 180° and finally at 270°. The sublimate (0·2 g.) was identified as caffeine by mixed m. p. The colourless reaction product was often contaminated with violet needles, m. p. 159—160°, of caffeine methoperiodide (see Gulland and Macrae, *loc. cit.*) : this was synthesised by heating caffeine methiodide (Schmidt, *Annalen*, 1913, **217**, 226) (0·37 g.) and iodine (0·27 g.) in alcohol (50 c.c.) for 1 hour on the water-bath; the violet-black shiny needles, m. p. 159—160° (sealed tube), formed could not be purified by recrystallisation (Found : I, 64·5. Calc. for $C_9H_{13}O_2N_4I_3$: I, 64·6%).

2-*Chloro*-6-*methoxy*-7-*methylpurine* (V).—2 : 6-Dichloro-7-methylpurine (3·5 g.) was boiled with a solution of sodium (0·49 g.) in methyl alcohol (100 c.c.) for 2 hours, and the liquid filtered while boiling; on cooling, silky needles separated. Recrystallisation from propyl alcohol gave 1·22 g., m. p. 219° (decomp.) (Found : C, 42·5; H, 3·6; N, 28·0; OMe, 15·6. $C_7H_7ON_4Cl$ requires C, 42·4; H, 3·5; N, 28·3; OMe 15·6%).

2-*Chloro*-1 : 7-*dimethylhypoxanthine Methiodide*.—The substance (V) (0·75 g.) was heated with methyl iodide (4 g.) in a sealed tube at 100° for 5 hours. The excess of methyl iodide was evaporated, and the residue triturated with acetone, collected (0·75 g.), and recrystallised from propyl alcohol. Besides dark-violet thin prisms of a periodide, m. p. 158—160°, which were much the more soluble, colourless thick prisms were obtained. The latter were easily isolated by fractional crystallisation, and had m. p. 228° (decomp.) after repeated crystallisation from the same solvent (Found : C, 28·4; H, 3·0; N, 16·0; Cl + I, 47·1. $C_8H_{10}ON_4ClI$ requires C, 28·2; H, 2·9; N, 16·5; Cl + I, 47·6%).

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