61. *The Application of the Hofmann Reaction to the Synthesis of Heterocyclic Compounds. Part II. Synthesis of Xanthine from Glyoxaline-4 : 5-dicarboxyamide and of 9-Methylxanthine from 1-Methylglyoxaline-4 : 5-dicarboxyamide.*

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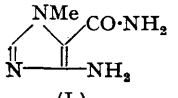
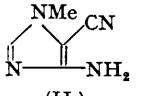
Glyoxaline-4 : 5-dicarboxylic acid is converted into *methyl glyoxaline-4 : 5-dicarboxylate* and thence into *glyoxaline-4 : 5-dicarboxyamide* (IV). Treatment of the last compound with alkaline potassium hypobromite solution gives xanthine (V), characterised by conversion into caffeine. When methyl glyoxaline-4 : 5-dicarboxylate reacts with sodium methoxide and methyl iodide, and the product is treated with alcoholic ammonia, *1-methylglyoxaline-4 : 5-dicarboxyamide* (VI) is obtained. The latter amide was also obtained by treatment of glyoxaline-4 : 5-dicarboxylic acid with diazomethane, followed by heating the product with alcoholic ammonia. By reaction with alkaline potassium hypobromite solution, 1-methylglyoxaline-4 : 5-dicarboxyamide (VI) yields 9-methylxanthine (VIII) (characterised by conversion into *iso*caffeine). This new synthesis of 9-methylxanthine is remarkable for the facility with which it proceeds, simple shaking of the diamide (VI) with alkaline hypobromite solution for 5 minutes at 0° leading to a separation of the potassium salt of 9-methylxanthine in a minimum yield of 60%. It is intended to apply this new purine synthesis to the preparation of a nucleoside of the xanthosine type.

Three different syntheses of purine derivatives have been accomplished starting from a glyoxaline derivative. Sarasin and Wegmann (*Helv. Chim. Acta*, 1924, **7**, 713) obtained 7-methylxanthine (heteroxanthine) in poor yield by treatment of 4-amino-1-methylglyoxaline-5-carboxyamide (I) (itself obtained by a four-stage route from 5-chloro-1-methylglyoxaline) with ethyl carbonate. Allsebrook, Gulland, and Story (J., 1942, 232) have shown that this method is probably applicable to the synthesis of 9-methylxanthine by the preparation of the intermediate 5-nitro-1-methylglyoxaline-4-carboxyamide. Montequi (*Anal. Soc. Fís. Quím.*, 1927, **25**, 182) obtained heteroxanthine in poor yield by treatment of 4-amino-5-cyano-1-methylglyoxaline (II) with urethane, followed by treatment of the product with hydrochloric acid. Finally, Allsebrook, Gulland, and Story (*loc. cit.*) obtained xanthine from 4(5)-ureidoglyoxaline-5(4)-carboxylic acid (III). These methods have the common feature that the correctly oriented glyoxaline derivative subjected to (pyrimidine) ring closure is in each case difficult of access.

It appeared probable that application of the Hofmann reaction to the diamide of the readily available glyoxaline-4 : 5-dicarboxylic acid would give xanthine. This proved to be the case.



(I.)



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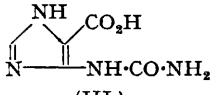


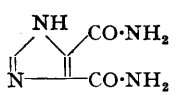
(III.)

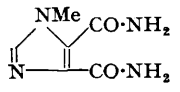
It is reported (*Chem. Abs.*, 1934, **28**, 150) that Tamamushi prepared the ester (presumably the diethyl ester) and the acid chloride of glyoxaline-4 : 5-dicarboxylic acid. We have not had access to the original paper by Tamamushi and the abstract cited does not record the experimental conditions employed or the physical constants of the two derivatives. The same author has described ethyl 2-methylglyoxaline-4 : 5-dicarboxylate and ethyl 2-ethylglyoxaline-4 : 5-dicarboxylate and the two corresponding diamides (*J. Pharm. Soc. Japan*, 1935, **55**, 1053; 1937, **57**, 1023; 1938, **58**, 1).

Preliminary experiments showed that glyoxaline-4 : 5-dicarboxylic acid gave intractable resinous material when treated with thionyl chloride, and esterification of the acid could not be accomplished under normal Fischer–Speier conditions. *Methyl glyoxaline-4 : 5-dicarboxylate* was, however, readily obtained in very high yield either by dissolving the acid in 100% sulphuric acid and pouring the solution into methanol (Newman, *J. Amer. Chem. Soc.*, 1941, **63**, 2431) or by refluxing a suspension of the acid in methanol saturated with hydrogen chloride. Methyl glyoxaline-4 : 5-dicarboxylate was readily converted into the corresponding *diamide* (IV), again in nearly quantitative yield. Treatment of glyoxaline-4 : 5-dicarboxyamide (IV) with potassium hypobromite in alkaline solution gave xanthine (V), characterised by conversion into caffeine. The course of this reaction does not appear to vary according as one or two molecular proportions of hypobromite are used, although in the former case the yield of xanthine is lower than in the latter.

Having established that the Hofmann reaction is applicable to glyoxaline-4 : 5-dicarboxyamide, a natural development was to apply the reaction to a 1-substituted glyoxaline-4 : 5-dicarboxyamide, which would be expected to yield either a 7- or a 9-substituted xanthine. To this end *1-methylglyoxaline-4 : 5-dicarboxyamide* (VI) was prepared by the reaction of methyl glyoxaline-4 : 5-dicarboxylate with sodium methoxide and methyl iodide, followed by treatment of the product with alcoholic ammonia. The diamide (VI) was also obtained by the action of diazomethane upon glyoxaline-4 : 5-dicarboxylic acid, followed by treatment of the product with alcoholic ammonia at 120°. If the product obtained by the action of diazomethane upon glyoxaline-4 : 5-dicarboxylic acid is treated with alcoholic ammonia at 0°, a *compound*, $C_7H_9O_3N_3$, m. p. 231° (decomp.), btained which is freely soluble in water but very sparingly soluble in alcohol. This compound, which is

probably either the betaine-amide (VII) or an amide-ester (*e.g.*, VII*a*), gives 1-methylglyoxaline-4 : 5-dicarboxyamide (VI) when heated with alcoholic ammonia at 120°.

(IV.)  (V.)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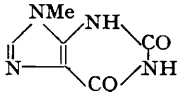
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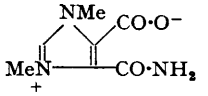
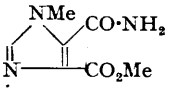

(VII.)


(VII*a*.)

Treatment of the diamide (VI) with potassium hypobromite in alkaline solution gave 9-methylxanthine (VIII). The formation of 9-methylxanthine from 1-methylglyoxaline-4 : 5-dicarboxyamide is a remarkably facile reaction, simple shaking with potassium hypobromite solution for 5 minutes at 0° leading to the separation of the potassium salt of 9-methylxanthine in a minimum yield of 60%. The yield of 9-methylxanthine is greater than is the yield of xanthine from glyoxaline-1 : 2-dicarboxyamide, a fact which is probably attributable to the instability of xanthine in the presence of hypohalite solution (Biltz and Beck, *J. pr. Chem.*, 1928, **118**, 196), and to the relative insolubility of the potassium salt of 9-methylxanthine. 9-Methylxanthine was characterised by conversion into *iso*caffeine, m. p. 284—286°, which exhibited the characteristic absorption bands in the ultra-violet region of the spectrum with maxima at 2400 A. and 2675 A. (Gulland, Holiday, and Macrae, J., 1934, 1643).

This relatively simple preparation of a 9-substituted xanthine suggests a possible method for the synthesis of purine nucleosides of the xanthosine type, the successful development of which will require a method for the introduction of a suitable oriented glycosidic group at position 1 in glyoxaline-4 : 5-dicarboxyamide and, secondly, a sufficient degree of stability of this group under the alkaline conditions employed in the Hofmann reaction. Experiments designed to test this route are in progress.

Experimental.

Methyl Glyoxaline-4 : 5-dicarboxylate.—(*a*) Glyoxaline-4 : 5-dicarboxylic acid (*Org. Syn.*, **22**, 45) (2 g.) was dissolved in sulphuric acid (100%; 12 c.c.) with cooling, and the solution poured into dry methanol (50 c.c.). The mixture was refluxed for 15 minutes, solution then being complete. The alcohol was removed (reduced pressure), and the residue carefully diluted with water (200 c.c.). The solution was neutralised with calcium carbonate, filtered, and concentrated until crystallisation started. *Methyl glyoxaline-4 : 5-dicarboxylate* separated as rosettes of needles (1·7 g.), m. p. 198—200°, which after two recrystallisations from water had m. p. 200—203° (Found : C, 45·8; H, 4·4; N, 15·3. $C_7H_8O_4N_2$ requires C, 45·65; H, 4·3; N, 15·2%).

(*b*) Dry hydrogen chloride was passed into a suspension of glyoxaline-4 : 5-dicarboxylic acid (10 g.) in boiling methanol (100 c.c.) for 3 hours; solution was then complete. The solution was concentrated (reduced pressure) to 20 c.c. and poured into saturated aqueous sodium carbonate solution (50 c.c.). The separated solid was collected, washed with water, and recrystallised from water to give methyl glyoxaline-4 : 5-dicarboxylate as needles (9·8 g.), m. p. 200—202°, identical with the specimen obtained by method (*a*).

Glyoxaline-4 : 5-dicarboxyamide.—A solution of methyl glyoxaline-4 : 5-dicarboxylate (5 g.) in aqueous ammonia (*d* 0·88; 100 c.c.) was set aside at 20° for 14 hours. The *diamide* (4·2 g.) separated as needles which did not melt below 360°. It was but slightly soluble in water and alcohol. For analysis a specimen was recrystallised from much water (Found : C, 39·0; H, 3·9; N, 36·3. $C_5H_6O_2N_4$ requires C, 39·0; H, 3·9; N, 36·4%).

1-Methylglyoxaline-4 : 5-dicarboxyamide.—(*a*) A suspension of glyoxaline-4 : 5-dicarboxylic acid (3 g.) in ether (100 c.c.) was treated with an ethereal solution of diazomethane (from 10 c.c. of nitrosomethylurethane), nitrogen being evolved vigorously. After standing overnight, the ether was removed. The residual gum, which was very soluble in water and alcohol and insoluble in ether and benzene, could not be crystallised. It was dissolved in dry methanol (30 c.c.), a small quantity of unchanged acid removed by filtration, and the solution saturated with dry ammonia at 0°. This solution was heated at 120° in a sealed tube for 6 hours and evaporated to dryness. The residue crystallised from aqueous alcohol (charcoal) to give *1-methylglyoxaline-4 : 5-dicarboxyamide* as prisms (0·3 g.), m. p. 263—266° (decomp.) (Found : C, 42·5; H, 4·6; N, 33·8. $C_6H_8O_2N_4$ requires C, 42·9; H, 4·8; N, 33·3%).

The product obtained by treatment of glyoxaline-4 : 5-dicarboxylic acid (3 g.) with diazomethane as described above was dissolved in methanol, saturated with dry ammonia at 0°, and the solution left for 16 hours at room temperature. The crystalline product was collected and recrystallised from aqueous alcohol, from which the *compound* separated as needles (1·3 g.), m. p. 231° (decomp.) (Found : N, 23·4. $C_7H_9O_3N_3$ requires N_1 23·0%). It was freely soluble in water and insoluble in alcohol and other common organic solvents. When heated with methanolic ammonia in a sealed tube at 120° for 6 hours, the compound $C_7H_9O_3N_3$ was converted into 1-methylglyoxaline-4 : 5-dicarboxyamide, m. p. and mixed m. p. 263—266°.

(*b*) A solution of methyl glyoxaline-4 : 5-dicarboxylate (4·6 g.) in dry methanol (200 c.c.) containing sodium methoxide (from 0·6 g. of sodium) was treated with methyl iodide (4·0 g.), and the mixture refluxed for 4 hours. The mixture was evaporated to half bulk, filtered, and the filtrate saturated with dry ammonia at 0°. On standing overnight, 1-methylglyoxaline-4 : 5-dicarboxyamide separated as prismatic needles (3·5 g.), m. p. 264—266° (decomp.), not depressed by the specimen described above.

Xanthine.—A solution of glyoxaline-4 : 5-dicarboxyamide (0·77 g.) in alkaline potassium hypobromite solution (28 c.c.; prepared as described on p. 231) was kept at 0° for 16 hours. The solution was heated on the steam-bath for 1 hour, cooled, and carefully acidified with acetic acid. The yellow precipitate was collected, washed with water, and digested with dilute aqueous ammonia (5·0 c.c., *d* 0·88, diluted with 20 c.c. of water). After removal of unchanged diamide (0·25 g.), the filtrate was heated to remove ammonia. On cooling, xanthine (0·15 g.) was deposited as flakes, not melting below 360°. A smaller yield of xanthine was obtained when the diamide was treated with one molecular

proportion of alkaline hypobromite solution. Analyses of xanthine prepared by this method were not satisfactory, since it was not possible completely to free it from inorganic material. Methylation of this product (100 mg.) by methyl sulphate and potassium hydroxide (Biltz and Beck, *J. pr. Chem.*, 1928, **118**, 198) gave caffeine (50 mg.), which separated from alcohol as feathery needles, m. p. 230—232°. After sublimation at 140°/10^{-3} mm., this had m. p. 231—232°, not depressed by an authentic specimen (m. p. 231—232°) (Found: C, 49·8; H, 5·3; N, 28·5. Calc. for $C_8H_{10}O_2N_4$: C, 49·5; H, 5·2; N, 28·9%).

9-*Methylxanthine.*—1-Methylglyoxaline-4 : 5-dicarboxyamide (0·85 g.) was shaken with alkaline potassium hypobromite solution (28 c.c., prepared as described on p. 231) at 0° for 5 minutes, a solid rapidly separating. The potassium salt was collected, washed with ice-water, and dissolved in the minimum volume of hot water. Acidification of this solution with acetic acid gave 9-methylxanthine (0·5 g.), m. p. 375—378°. After recrystallisation from much water, it was obtained as needles, m. p. 380° (decomp.) (Found: C, 43·7; H, 3·5; N, 33·6. Calc. for $C_6H_6O_2N_4$: C, 43·4; H, 3·6; N, 33·7%).

Light absorption. (*a*) In N/10-sodium hydroxide. Maxima at 2470 A., $\varepsilon = 8000$, and 2800 A., $\varepsilon = 8000$. Using a solution (pH, 10·0) of 9-methylxanthine in sodium hydroxide, Gulland, Holiday, and Macrae (*loc. cit.*) observed absorption maxima at 2470 A., $\varepsilon = 9300$, and at 2780 A., $\varepsilon = 9300$.

(*b*) In N/10-hydrochloric acid. Maxima at 2365 A., $\varepsilon = 6000$, and 2630 A., $\varepsilon = 8000$. Using a solution (pH, 5·0) of 9-methylxanthine in hydrochloric acid, Gulland, Holiday, and Macrae (*loc. cit.*) observed maxima at 2350 A., $\varepsilon = 7300$, and 2640 A., $\varepsilon = 9300$.

iso*Caffeine.*—9-Methylxanthine (100 mg.), prepared as described above, was suspended in dry ether (50 c.c.) and treated with an ethereal solution of diazomethane (from 2 c.c. of nitrosomethylurethane). Nitrogen was slowly evolved. After 3 days the mixture was evaporated, and the residue crystallised from alcohol, from which the product separated as small needles (55 mg.), m. p. 265—270°. After sublimation at 220°/10^{-3} mm., *iso*caffeine was obtained as a crystalline mass, m. p. 284—286°.* Biltz and Strufe (*Annalen*, 1921, **423**, 223) give m. p. 285—287° (corr.) for *iso*caffeine (Found: C, 49·7; H, 5·4; N, 28·4. Calc. for $C_8H_{10}O_2N_4$: C, 49·5; H, 5·2; N, 28·9%). *Light absorption in alcohol:* Maxima at 2400 A., $\varepsilon = 8400$, and 2675 A., $\varepsilon = 8300$. Gulland, Holiday, and Macrae (*loc. cit.*) observed maxima at 2400 A., $\varepsilon = 7600$, and 2690 A., $\varepsilon = 9000$ for a solution (pH, 10·0) of *iso*caffeine in sodium hydroxide.

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