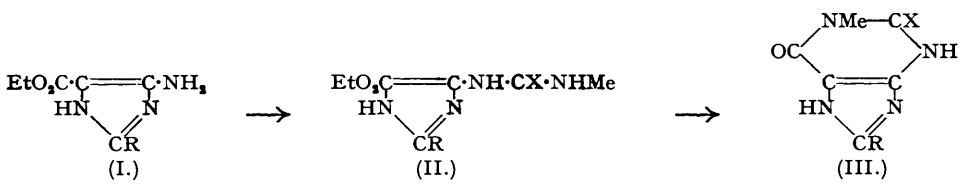
384. *Studies in the Azole Series. Part XXIX. The Preparation of Some Natural Xanthines and Related Purines.*

By A. H. Cook and G. H. Thomas.

Ethyl 4-aminoglyoxaline-5-carboxylate on reaction with methyl *iso*cyanate followed by treatment with alkali affords 1-methylxanthine. Methylation of the glyoxaline with diazomethane yields a monomethyl derivative orientated so as to give paraxanthine and caffeine by the usual pyrimidine cyclisation. Ethyl 4-amino-2-phenyl- and -2-benzyl-glyoxaline-5-carboxylate likewise form monomethyl derivatives from which, ultimately, are obtained 8-*phenyl*- and 8-*benzyl-caffeine*. Reaction of aminoglyoxalines with urea yields, with some difficulty, xanthines substituted only at $C_{(8)}$. Thiourea reacts only very slowly with aminoglyoxalines but acetyl *iso*thiocyanate is an excellent substitute.

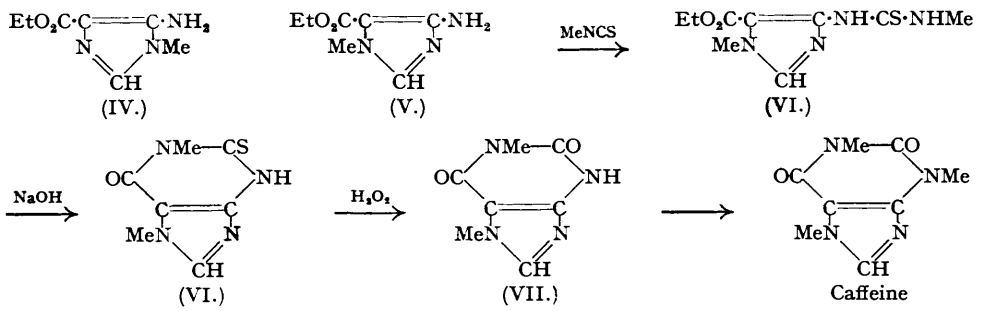
Cook, Davis, Heilbron, and Thomas (Part XIV of this series, *J.*, 1949, 1071) described a synthesis of xanthines whereby ethyl 4-aminoglyoxaline-5-carboxylates (I; R = H, Me, Ph, and CH_2Ph) reacted with methyl *iso*thiocyanate, and the resulting 4-*N*-methylthioureido-compounds (II) were cyclised to 2-thio-1-methylxanthines (III; R = H, Me, Ph, and CH_2Ph; X = S). The 1-methylxanthines (III; R = Me and Ph; X = O) were obtained by a similar route, using methyl *iso*cyanate in the place of methyl *iso*thiocyanate. The present paper describes the extension of this work to include some natural purines and further homologues thereof.



Attention was first directed to the synthesis of 1-methylxanthine (III; R = H, X = O) which, although itself of no known outstanding importance, is of interest as an intermediate in the synthesis of caffeine. Ethyl 4-aminoglyoxaline-5-carboxylate (I; R = H) afforded ethyl 4-*N'*-methylureidoglyoxaline-5-carboxylate (II; R = H, X = O) on treatment with excess of methyl *iso*cyanate in warm pyridine. The ureido-compound readily dissolved in aqueous sodium hydroxide and acidification of the solution resulted in the precipitation of 1-methylxanthine, but the yield was low (50%), the alkaline filtrate containing some diazotisable base. It appears, therefore, that alkali caused partial reversion of the 4-*N'*-methylureido-compound to an aminoglyoxaline; no such decomposition was observed in the related cyclisation of the 4-*N'*-methylthioureido-analogue described in the earlier paper. Apart from analytical evidence and the murexide reaction, the formulation of the product as 1-methylxanthine was confirmed by methylation to caffeine by methyl sulphate (cf. Englemann, *Ber.*, 1909, **42**, 177).

The synthesis of a dimethylxanthine, either paraxanthine or 1 : 9-dimethylxanthine, required preliminary methylation of the glyoxaline ring of (I). Pyman and his co-workers, after an extensive study of the methylation of substituted glyoxalines, concluded that an electron-attracting substituent at $C_{(5)}$ favours the formation of 1- rather than of 3-methyl derivatives, whereas electron-donating groups act in the opposite manner (*J.*, 1910, 1814; 1922, 2616; 1924, 1431; 1925, 577). That more than this mere inductive effect of a 4(5)-substituent was concerned was shown by the more complicated example (Gulland and Story, *J.*, 1942, 232) of the methylation of methyl 4-nitroglyoxaline-5-carboxylate to methyl 4-nitro-1-methylglyoxaline-5-carboxylate despite the fact that of the 4- and the 5-substituent the latter was the less

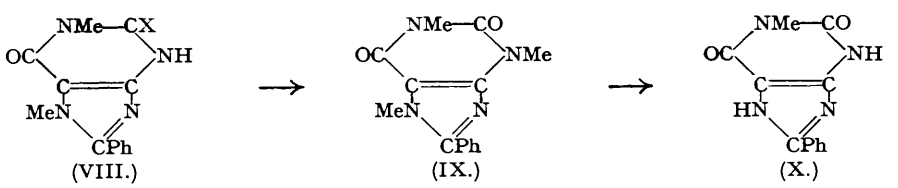
electropositive. No work was done on the methylation of aminoglyoxalines, mainly because of the difficulty of access of these compounds at that time so that it was of some additional interest to see how (I) behaved. With diazomethane, which had been successfully employed by Forsythe and Pyman (*J.*, 1925, 573) for the methylation of several glyoxalines, (I) yielded a diazotisable monomethyl derivative, necessarily therefore ethyl 4-amino-1-methylglyoxaline-5-carboxylate (V) or 5-amino-1-methylglyoxaline-4-carboxylate (IV). Of these two, one was known as the hydrochloride (Mann and Porter, *J.*, 1945, 751), and the other as the hydrochloride and free base (Cook, Downer, and Heilbron, *J.*, 1948, 2028). The product under discussion was the hitherto unknown 4-amino-compound (V). The methylation of the imino-group adjacent to the carbethoxy-substituent might be correlated with the obvious structural analogy between (I) and xanthine which is methylated in the 7- rather than the 9-position. The structure of the diazomethane methylation product was indeed confirmed by its conversion into caffeine: reaction of the methylated glyoxaline with methyl *iso*thiocyanate in boiling pyridine yielded 4-*N'*-methylthioureido-5-carbethoxyglyoxaline, dissolution of which in hot aqueous sodium hydroxide yielded a sparingly soluble sodium salt whence acid precipitated



2-thio-1 : 7-dimethylxanthine (VI); paraxanthine (VII) was obtained by treating the thiopurine in alkali with hydrogen peroxide, and converted into caffeine by methylation. This synthesis, apart from establishing beyond all doubt the structure of the monomethylation product, also proved to be a more satisfactory route to caffeine than the previous synthesis using 1-methylxanthine as an intermediate, although involving more stages.

The preparation of paraxanthine and caffeine derivatives containing hydrocarbon substituents situated at $C_{(8)}$ has not been extensively studied despite the pharmaceutical importance of caffeine. 8-Methyl- and 8-ethyl-caffeine have been prepared by treatment of the corresponding 8-alkyl ethers of caffeine with acetic anhydride (Huston and Allen, *J. Amer. Chem. Soc.*, 1934, **56**, 1793). This method, which is essentially an application of the preparation of 8-methylxanthines by reaction of uric acid and acetic anhydride (Boehringer and Son, *Chem. Zentr.*, 1901, II, 71; Golovchinskaya, *Chem. Abs.*, 1948, **42**, 2580), is very limited in scope and cannot, for example, be extended to include the syntheses of 8-propyl- and 8-butyl-caffeine. 8-Methyl-1 : 7-diethylxanthine (Mann and Porter, *loc. cit.*) is possibly the nearest approach to an 8-alkylparaxanthine recorded in the literature. Thus no general method has been established for the preparation of both alkyl- and aryl-caffeines and -paraxanthines, but as ethyl 4-amino-2-alkyl- and -aryl-glyoxaline-5-carboxylates were readily available from ethyl aminocyanoacetate they appeared to offer a useful route.

Ethyl 4-amino-2-phenylglyoxaline-5-carboxylate (I; R = Ph) and diazomethane yielded a diazotisable monomethyl base, formulated, by analogy, as ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate and characterised as its 4-azo-2-naphthol derivative and picrate. This base and methyl *iso*thiocyanate afforded ethyl 4-*N'*-methylthioureido-2-phenyl-1-

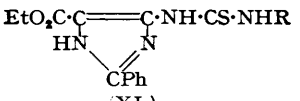


methylglyoxaline-5-carboxylate from which the sparingly soluble sodium salt of 2-thio-8-phenyl-1 : 7-dimethylxanthine was obtained in the usual way; the free xanthine (VIII; X = S)

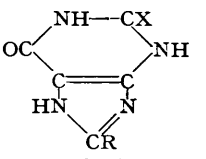
separated on acidification of the sodium salt. 8-Phenyl-1 : 7-dimethylxanthine (VIII; X = O), obtained by keeping the thiopurine in alkali with hydrogen peroxide, yielded 8-phenylcaffeine (IX) on methylation. 8-Phenylcaffeine was obtained in better overall yield from ethyl 4-amino-2-phenylglyoxaline-5-carboxylate, by the methylation of 8-phenyl-1-methylxanthine (X).

Ethyl 4-amino-2-benzyl-1-methylglyoxaline-5-carboxylate, obtained by reaction of ethyl 4-amino-2-benzylglyoxaline-5-carboxylate with diazomethane or methyl sulphate, afforded the 4-*N'*-methylthioureido-ester, 2-thio-8-benzyl-1 : 7-dimethylxanthine, 8-benzyl-1 : 7-dimethylxanthine, and, finally, 8-benzylcaffeine, by a similar route.

The use of urea in the place of the lachrymatory *iso*cyanates for the formation of the pyrimidine ring seemed to present a more economical synthesis of purines from aminoglyoxalines. The results, however, proved disappointing since not only was the condensation of urea and ethyl 4-amino-2-phenyl- and -2-benzyl-glyoxaline-5-carboxylate difficult to effect, but also much decomposition occurred on treatment with alkali and the yields of 8-phenyl- (XII; R = Ph, X = O) and 8-benzyl-xanthine (XII; R = CH_2Ph, X = O) were low. Urea reacted more smoothly with ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate, and 8-phenyl-7-



(XI.)



(XII.)

methylxanthine (8-phenylheteroxanthine) was obtained from the resultant ureide without accompanying decomposition. Reaction of ethyl 4-amino-2-phenylglyoxaline-5-carboxylate with thiourea was unsatisfactory but the desired thiopurine was obtained by a less direct route. The aminoglyoxaline and acetyl *iso*thiocyanate gave the 4-*N'*-acetylthioureido-ester (XI; R = Ac) which in hot concentrated hydrochloric acid afforded ethyl 4-thioureido-2-phenylglyoxaline-5-carboxylate (XI; R = H). Cyclisation of the last gave 2-thio-8-phenylxanthine (XII; R = Ph, X = S).

Experimental.

All the ethyl 4-amino-1-methylglyoxaline-5-carboxylates described below were diazotised in dilute hydrochloric acid and the resulting solutions, when poured into β-naphthol in aqueous sodium hydroxide, yielded red alkali-insoluble azo-dyes. The xanthines and 2-thioxanthines gave strong murexide reactions on oxidation with nitric acid, and potassium chlorate in hydrochloric acid, respectively.

Preparation of Caffeine.—(*a*) Ethyl 4-aminoglyoxaline-5-carboxylate (4·4 g.) in dry pyridine (8 c.c.) was warmed with methyl *iso*cyanate (2 c.c.) for 10 minutes. The solution was cooled, a further quantity of methyl *iso*cyanate (2 c.c.) added, and the solution again warmed; this procedure was repeated twice more. On being kept at 0°, *ethyl 4-N'-methylureidoglyoxaline-5-carboxylate* (4·0 g.) separated and crystallised from ethanol as needles, m. p. 147° (Found: C, 45·4; H, 5·8; N, 26·3. $C_8H_{12}O_3N_4$ requires C, 45·3; H, 5·7; N, 26·4%). The ureido-compound was dissolved in 5% aqueous sodium hydroxide (10 c.c.), and the solution heated at 80° for 20 minutes. On neutralisation of the solution with glacial acetic acid, 1-methylxanthine (0·3 g.) separated as a bluish salt-like solid. The filtrate was treated with sodium nitrite at 0° and poured into excess of alkaline β-naphthol; a red alkali-soluble azo-dye developed, indicating the presence of some aminoglyoxaline. 1-Methylxanthine was obtained as a pale blue microcrystalline solid by repeated acidification of its solution in alkali (Found: C, 43·2; H, 3·4. Calc. for $C_6H_6O_2N_4$: C, 43·4; H, 3·6%). Caffeine was obtained by methylation of 1-methylxanthine with methyl sulphate (cf. Englemann, *Ber.*, 1909, **42**, 177) and its identity confirmed by a mixed melting point with an authentic specimen.

(*b*) Diazomethane (2·8 g.) in ether (100 c.c.) was added to ethyl 4-aminoglyoxaline-5-carboxylate (2·1 g.) in methanol (40 c.c.); a steady evolution of nitrogen occurred for *ca.* 3 hours. The solution was concentrated *in vacuo* (to 40 c.c.) and the crystalline solid which separated at 0° was collected. More solid (0·8 g.) was precipitated on addition of cold light petroleum (b. p. 40—60°) to the filtrate. *Ethyl 4-amino-1-methylglyoxaline-5-carboxylate* was readily soluble in most common organic solvents; it was crystallised best from water or benzene–light petroleum, forming long needles, m. p. 140° (Found: C, 49·5; H, 6·6; N, 24·9. $C_7H_{11}O_2N_3$ requires C, 49·2; H, 6·4; N, 24·9%); ethyl 4-amino-3-methylglyoxaline-5-carboxylate has m. p. 192° (Cook, Downer, and Heilbron, *J.*, 1948, 2028). Addition of ethanolic hydrogen chloride to ethyl 4-amino-1-methylglyoxaline-5-carboxylate in ethanol yielded the hydrochloride, m. p. 195° (Mann and Porter, *J.*, 1945, 751, give m. p. 190°). The methylated glyoxaline (0·7 g.) and methyl *iso*thiocyanate (0·5 g.) in pyridine (2 c.c.) were heated under reflux for 2 hours. The cooled solution was diluted with ice water (10 c.c.), *ethyl 4-N'-methylthioureido-1-methylglyoxaline-5-carboxylate* (0·8 g.) being precipitated. A sample crystallised from ethanol as fine needles, m. p. 136° (Found: C, 45·0; H, 5·6. $C_9H_{14}O_2N_4S$ requires C, 44·6; H, 5·8%). The thioureido-compound (0·5 g.) readily dissolved in hot 5% aqueous sodium hydroxide and on slight cooling the sodium salt of 2-thio-1 : 7-dimethylxanthine separated as a mass of colourless threads, m. p. >360°. Addition of excess of glacial acetic acid to the sodium salt suspended in hot water yielded *2-thio-1 : 7-dimethylxanthine* as

clusters of laths, m. p. 355° (Found: C, 42·8; H, 4·1. $C_7H_8ON_4S$ requires C, 42·9; H, 4·1%). Conversion of ethyl 4-amino-1-methylglyoxaline-5-carboxylate into 2-thio-1 : 7-dimethylxanthine was accomplished in overall yield of 78% when the intermediate thioureido-compound was not recrystallised but dissolved in hot alkali and the solution acidified with glacial acetic acid.

Hydrogen peroxide (80 vol.; 5 c.c.) was added, with stirring, to a suspension of 2-thio-1 : 7-dimethylxanthine (0·9 g.) (as the sodium salt) in sodium hydroxide solution (5%; 25 c.c.). The sodium salt dissolved and, after 1 hour, the clear solution was heated at 80° until effervescence ceased. On acidification of the cooled solution with glacial acetic acid and storage at 0°, paraxanthine (0·7 g.) separated. The purine crystallised from water as needles, m. p. 299° (Found: C, 47·0; H, 4·4; N, 31·1. Calc. for $C_7H_8O_2N_4$: C, 46·7; H, 4·4; N, 31·1%). Finely powdered paraxanthine (0·21 g.) was added to ethereal diazomethane (0·4 g. in 20 c.c.); a brisk evolution of nitrogen ensued which ceased after 2 hours. The caffeine (0·18 g.) was collected and had m. p. 235°, undepressed on admixture with an authentic specimen.

Methylation of Ethyl 4-Amino-2-phenylglyoxaline-5-carboxylate.—Ethereal diazomethane (3·6 g. in 200 c.c.) was added to a suspension of finely powdered ethyl 4-amino-2-phenylglyoxaline-5-carboxylate (10 g.) in methanol (20 c.c.); nitrogen was slowly evolved and the glyoxaline dissolved. After 24 hours some undissolved glyoxaline (1 g.) was filtered off and the filtrate evaporated *in vacuo*, leaving a gum which solidified on trituration under a mixture of light petroleum (b. p. 40—60°; 50 c.c.) and ethanol (5 c.c.). The yellow solid (6·7 g.), *ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate*, was readily soluble in cold acetone, ethanol, or warm chloroform, benzene, or ethyl acetate, soluble in warm water, and insoluble in light petroleum; a sample crystallised from benzene–light petroleum as large colourless needles, m. p. 141° (Found: C, 63·5; H, 6·3; N, 17·1. $C_{13}H_{15}O_2N_3$ requires C, 63·7; N, 6·1; N, 17·1%). The *picrate*, prepared in ethanol, crystallised from this solvent as yellow needles, m. p. 157° (Found: N, 17·8. $C_{19}H_{18}O_9N_6$ requires N, 17·7%). Ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate (0·5 g.) in 2N-hydrochloric acid (8 c.c.) was diluted with an equal volume of water and cooled to 0°. Sodium nitrite (0·2 g.) in water (3 c.c.) was dripped into the acid solution at $\not>5°$. The diazotised solution was poured into a cold solution of β-naphthol (0·5 g.) in 5% sodium hydroxide (20 c.c.); *ethyl 4-(2′-hydroxynaphthalene-1′-azo)-2-phenyl-1-methylglyoxaline-5-carboxylate* (0·4 g.) separated and was crystallised from glacial acetic acid as deep-red laths, m. p. 202—203° (Found: N, 14·5. $C_{23}H_{20}O_3N_4$ requires N, 14·0%).

A solution of ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate (3 g.) and methyl *iso*thiocyanate (3 g.) in pyridine (5 c.c.) was heated under reflux for 2 hours. The cooled pyridine solution was diluted with water (20 c.c.) whereupon *ethyl 4-N′-methylthioureido-2-phenyl-1-methylglyoxaline-5-carboxylate* (4·1 g.) was precipitated; this crystallised from ethyl acetate as needles, m. p. 191° (Found: N, 17·3. $C_{15}H_{18}O_2N_4S$ requires N, 17·6%). The thioureido-compound (3·4 g.) rapidly dissolved in hot 5% sodium hydroxide solution (30 c.c.) and on slight cooling the *sodium* salt of 2-thio-8-phenyl-1 : 7-dimethylxanthine separated as a mass of threads. A sample of the salt crystallised from a large volume of hot water as threads melting indefinitely above 360° (Found: N, 18·5. $C_{13}H_{11}ON_4SNa$ requires N, 19·0%). Glacial acetic acid was added to the above suspension of the sodium salt, whereby *2-thio-8-phenyl-1 : 7-dimethylxanthine* was precipitated as a gelatinous solid, m. p. 342° (Found: C, 57·0; H, 4·2; N, 20·9. $C_{13}H_{12}ON_4S$ requires C, 57·3; H, 4·4; N, 20·6%). The thiopurine (2·4 g.) was added to 5% sodium hydroxide (30 c.c.), and the solution, from which some of the sodium salt had separated, was stirred whilst 80-vol. hydrogen peroxide (10 c.c.) was added. The reaction was exothermic and when all the sodium salt had re-dissolved the solution was heated to 80° and acidified with acetic acid; *8-phenyl-1 : 7-dimethylxanthine* separated as very small plates, m. p. 326° (Found: C, 60·5; H, 5·0; N, 21·8. $C_{13}H_{12}O_2N_4$ requires C, 60·9; H, 4·7; N, 21·9%).

8-Phenylcaffeine.—(*a*) A solution of 8-phenyl-1 : 7-dimethylxanthine (0·7 g.) in sodium hydroxide solution (5%; 10 c.c.) was shaken with methyl sulphate (1·0 c.c.), and the precipitated solid (0·7 g.) collected. *8-Phenylcaffeine* crystallised from ethanol as needles, m. p. 187° (Found: C, 62·5; H, 5·2; N, 21·0. $C_{14}H_{14}O_2N_4$ requires C, 62·2; H, 5·1; N, 20·7%). (*b*) 8-Phenyl-1-methylxanthine (1 g.) (*J.*, 1949, 1071) in 5% sodium hydroxide (10 c.c.) was shaken with methyl sulphate (2·0 c.c.). On cooling of the clear solution to 0°, 8-phenylcaffeine (0·9 g.) separated, identical with the compound prepared as above.

Methylation of Ethyl 4-Amino-2-benzylglyoxaline-5-carboxylate.—(*a*) Ethereal diazomethane (2 g. in 80 c.c.) was added to ethyl 4-amino-2-benzylglyoxaline-5-carboxylate (5 g.) in methanol (100 c.c.). After 24 hours the solution was evaporated *in vacuo* and the yellow residue (5·10 g.) crystallised from ethanol, *ethyl 4-amino-2-benzyl-1-methylglyoxaline-5-carboxylate* being obtained as clusters of needles, m. p. 155° (Found: C, 64·5; H, 6·3; N, 16·6. $C_{14}H_{17}O_2N_3$ requires C, 64·9; N, 6·7; N, 16·2%). The glyoxaline was readily soluble in cold chloroform, soluble in warm ethyl acetate or benzene, and insoluble in water or ether.

(*b*) Ethyl 4-amino-2-benzylglyoxaline-5-carboxylate (0·5 g.), dissolved in the minimum quantity of dilute hydrochloric acid, was poured into 5% sodium hydroxide (20 c.c.) at 60° with stirring. The clear solution was rapidly cooled and shaken mechanically with methyl sulphate (0·4 c.c.) for 5 minutes; the 1-methylglyoxaline (0·4 g.) separated as a granular solid, m. p. 146°. After crystallisation from ethanol the compound proved to be identical with the former product.

(*c*) Shaking an alkaline solution of ethyl 4-amino-2-benzylglyoxaline-5-carboxylate (0·5 g.) with methyl iodide (0·3 g.) for 12 hours gave the same methylated glyoxaline (0·38 g.) in an impure state.

8-Benzylcaffeine.—Ethyl 4-amino-2-benzyl-1-methylglyoxaline-5-carboxylate (2·5 g.) and methyl *iso*thiocyanate (2·0 g.) were heated in pyridine (2 c.c.) under reflux for 2 hours. On dilution of the cooled pyridine solution with water, *ethyl 4-N′-methylthioureido-2-benzyl-1-methylglyoxaline-5-carboxylate* (3·2 g.) separated. This was readily soluble in cold chloroform or warm benzene, soluble in ethanol, acetic acid, or hot ethyl acetate; a sample crystallised from ethanol as hexagonal prisms, m. p. 124° (Found: C, 47·5; H, 6·0; N, 16·7. $C_{16}H_{20}O_2N_4S$ requires C, 47·8; H, 6·0; N, 16·9%). On alkali treatment of the thioureido-compound (2 g.) in the usual way, followed by acidification, *2-thio-8-benzyl-1 : 7-dimethylxanthine* (1·6 g.) was obtained as small needles, m. p. 295° (Found: C, 58·9; H, 4·9; N, 19·6.

$C_{14}H_{14}ON_4S$ requires C, 58·7; H, 4·9; N, 19·6%). 80-Vol. hydrogen peroxide (7 c.c.) was added to 2-thio-8-benzyl-1 : 7-dimethylxanthine (1 g.) in 5% sodium hydroxide (15 c.c.); heat was evolved and the solution was set aside until all the solid had dissolved. On acidification of the solution at 80°, *8-benzyl-1 : 7-dimethylxanthine* (0·8 g.) was obtained as small needles, m. p. 252° (Found: C, 62·2; H, 5·3; N, 21·1. $C_{14}H_{14}O_2N_4$ requires C, 62·2; H, 5·2; N, 20·7%). The xanthine (0·6 g.) was suspended in ethereal diazomethane (0·6 g. in 25 c.c.) and when no more nitrogen was evolved (*ca.* 2 hours) the crystalline solid (0·4 g.) was filtered off. More solid (0·15 g.) was obtained on evaporation of the filtrate (to 5 c.c.) and cooling to 0°. *8-Benzylcaffeine* was soluble in acid, but insoluble in alkali, and crystallised from ethanol as rods, m. p. 161—163° (Found: C, 64·2; H, 5·9; N, 19·5. $C_{15}H_{16}O_2N_4$ requires C, 63·7; H, 5·6; N, 19·7%).

8-Phenylxanthine.—Ethyl 4-amino-2-phenylglyoxaline-5-carboxylate (1·5 g.) and urea (0·7 g.) were heated in pyridine under reflux for 1½ hours; ammonia was evolved, and the solution became discoloured. The solution was diluted with ice-water (50 c.c.) whereby an oil was precipitated, which solidified slowly. The fawn-coloured solid (1·4 g.) was crystallised from aqueous ethanol, dissolved in 5% sodium hydroxide solution (20 c.c.), and heated to 80°; the solution became red and on acidification with excess of acetic acid a dark gummy solid separated which redissolved on rapid stirring and separated again on cooling as an amorphous red solid (0·3 g.). *8-Phenylxanthine* was dissolved in 2% sodium hydroxide (10 c.c.) (charcoal), and precipitated with acid. This was repeated until the purine was obtained as a pale red gelatinous solid melting indefinitely at *ca.* 360° (decomp.) (Found: C, 57·5; H, 3·9; N, 24·7. $C_{11}H_8O_2N_4$ requires C, 57·9; H, 3·5; N, 24·5%).

8-Benzylxanthine.—Ethyl 4-amino-2-benzyglyoxaline-5-carboxylate (2 g.) and urea (0·7 g.) were heated in pyridine (4 c.c.) under reflux for 4 hours. The solution was cooled and diluted with ice-water (100 c.c.); the precipitated oil solidified on stirring at 0—5°. A solution of the solid in 5% sodium hydroxide (20 c.c.) was heated to 80°. On acidification of the hot somewhat discoloured solution with glacial acetic acid a dark solid was precipitated which redissolved on rapid stirring; *8-benzylxanthine* (0·4 g.) separated as a red solid on cooling. After repeated acidification of its solution in alkali, the xanthine was obtained as a reddish gelatinous solid which darkened and softened above 300° (Found: N, 23·5. $C_{12}H_{10}O_2N_4$ requires N, 23·1%).

8-Phenyl-7-methylxanthine.—Ethyl 4-amino-2-phenyl-1-methylglyoxaline-5-carboxylate (1 g.) and urea (0·5 g.) were heated in pyridine (2 c.c.) under reflux for 3 hours; ammonia was evolved and, when the solution was kept at 0°, solid (0·2 g.), m. p. 193—194°, separated. More of the 4-ureido-derivative (0·3 g.) was obtained on dilution of the mother-liquor with water (20 c.c.). The ureide was dissolved in hot 5% sodium hydroxide (15 c.c.) and acidified; *8-phenyl-7-methylxanthine* separated as colourless prisms, m. p. 340° (Found: N, 23·2. $C_{12}H_{10}O_2N_4$ requires N, 23·1%).

2-Thio-8-phenylxanthine.—Ethyl 4-amino-2-phenylglyoxaline-5-carboxylate (2·2 g.) and acetyl *iso*thiocyanate (1·5 g.) were heated in chloroform (80 c.c.) under reflux for 45 minutes. The glyoxaline rapidly dissolved and yellow crystals (1·4 g.) separated. More solid (1·3 g.) separated on evaporation of the solvent *in vacuo*. *Ethyl 4-N'-acetylthioureido-2-phenylglyoxaline-5-carboxylate* crystallised from methanol as octahedra, m. p. 225° (Found: C, 54·1; H, 4·8. $C_{15}H_{16}O_3N_4S$ requires C, 54·2; H, 4·8%). The acetylthioureido-compound (0·7 g.) was suspended in 2N-hydrochloric acid (20 c.c.) containing ethanol (10 c.c.), and the solution heated under reflux for one hour. *Ethyl 4-thioureido-2-phenylglyoxaline-5-carboxylate* (0·5 g.) separated on cooling of the solution; a sample crystallised from ethanol as rods, m. p. 256° (Found: C, 53·4; H, 4·9; N, 19·3. $C_{13}H_{14}O_2N_4S$ requires C, 53·8; H, 4·8; N, 19·3%). Dissolution of this ester in alkali, and subsequent acidification of the hot solution, yielded *2-thio-8-phenylxanthine* as a colourless gelatinous solid (Found: C, 54·3; H, 3·6. $C_{11}H_8ON_4S$ requires C, 54·1; H, 3·3%).

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