228. *Studies in the Azole Series. Part XIV. A New Synthesis of Purines.*

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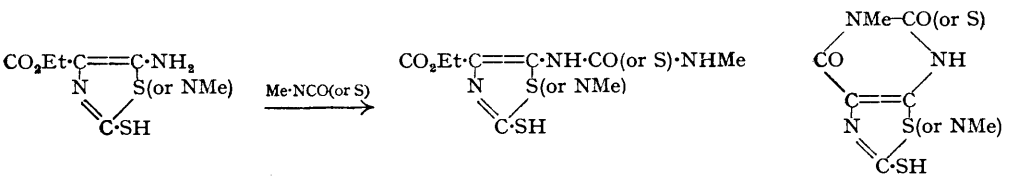
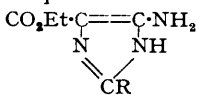
4-Aminoglyoxalines are generally accessible by condensing α-amino-nitriles with imino-ethers, thioimino-ether hydrochlorides, or formamidine hydrochloride. 4-Amino-5-carbethoxyglyoxalines (I) react with methyl *iso*thiocyanate or *iso*cyanate to yield 4-*N'*-methyl-thioureido- or -ureido-5-carbethoxyglyoxalines (IV; X = S or O, respectively) which are readily cyclised to 1-methyl-thioxanthines or -xanthines (III; X = S or O, respectively). These constitutions follow not only from analytical and other evidence, but also from the oxidation of typical compounds whereby the 5-membered dihydroglyoxaline ring is removed and a dimethylalloxantin and thence 3-methylalloxazine, identical with the materials prepared from theobromine, are obtained.

Parts XII and XIII of the present series (preceding papers) demonstrated the facile fusion of a pyrimidine ring to an existing thiazole or, in one instance, to a glyoxaline structure in the following general manner :



As one step in making this a generally useful procedure, it was first necessary to devise a general synthesis of 4-amino-5-carbethoxyglyoxalines (I). It had been recorded (Abraham, Baker, Barltrop, Chain, Waley, and Robinson, C.P.S. 549) that the reaction between ethyl aminocyanoacetate and phenacetiminoethyl ether could proceed in two ways : in the presence of one molecular proportion of hydrochloric acid the product was *N*-(α-cyano-α-carbethoxymethyl)phenacetiminoethyl ether (II), whereas interaction of the free bases afforded another base regarded as 4-amino-5-carbethoxy-2-benzylglyoxaline (I; R = CH_2Ph). With other iminoethers and ethyl aminocyanoacetate, always as free bases, this ring synthesis appears to be almost generally applicable, and 4-*amino*-5-*carbethoxy*-2-*methyl*- and -2-*phenyl*-*glyoxaline* (I; R = Me and Ph, respectively) were formed at room temperature. With formimino-ethyl or -*iso*propyl ether reaction was unsatisfactory, but the required 4-*amino*-5-*carbethoxyglyoxaline* (I; R = H) was obtained by replacing these iminoethers by formamidine hydrochloride. The reaction between α-aminonitriles and thioiminoethers proved, however, more satisfactory as a preparative method. The latter reactants could be used as their hydrochlorides in hot solvents, the glyoxaline hydrochlorides then being obtained directly in yields superior to those arising from *O*-iminoethers. In addition to the glyoxalines mentioned above, 4-*amino*-5-*phenyl*-2-*benzyl*-, -2-*phenyl*-, and -2-*methyl*-*glyoxaline* were prepared in this manner from α-aminobenzyl cyanide.

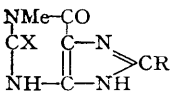
The new glyoxalines were generally stable bases which could all be diazotised. Representative compounds were characterised as their *picrates*, *acetyl* derivatives, and *benzylideneamino*-compounds.



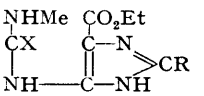
(I.)

$CH_2Ph{\cdot}C(OEt){:}N{\cdot}CH(CN){\cdot}CO_2Et$

(II.)



(III.)



(IV.)

Previous syntheses of purines from glyoxalines were briefly reviewed in Part XII and the present work is concerned with the conversion of the 4-amino-5-carbethoxyglyoxalines described above into 1-methyl- and 1-methyl-2-thio-xanthines (III; X = O or S, respectively). 4-Amino-5-carbethoxy-2-benzylglyoxaline (I; R = CH_2Ph) reacted with methyl *iso*thiocyanate in boiling pyridine to give 4-N′-*methylthioureido*-5-*carbethoxy*-2-*benzylglyoxaline* (IV; R = CH_2Ph, X = S). The latter behaved like the analogous compounds described in the preceding papers when dissolved in dilute sodium hydroxide, the *sodium* salt of 2-*thio*-8-*benzyl*-1-*methylxanthine* (III; R = CH_2Ph, X = S) being formed, and the free purine being obtained on subsequent acidification. 4-N′-*Methylthioureido*-5-*carbethoxyglyoxaline* and its 2-*methyl* and 2-*phenyl* derivatives (IV; R = H, Me, and Ph, respectively; X = S) were similarly prepared and cyclised to 2-*thio*-1-*methyl*-, -1 : 8-*dimethyl*-, and -8-*phenyl*-1-*methyl*-*xanthine* (III; R = H, Me, and Ph, respectively; X = S).

In a similar fashion reaction of the appropriate 4-amino-5-carbethoxyglyoxaline with methyl *iso*cyanate afforded 4-N′-*methylureido*-5-*carbethoxy*-2-*methyl*- and -2-*phenyl*-*glyoxaline* (IV; R = Me and Ph, respectively, X = O). These compounds cyclised in the same manner as the analogous thioureido-derivatives. By warming with dilute sodium hydroxide, 1 : 8-*dimethyl*-*xanthine* and 8-*phenyl*-1-*methyl*-*xanthine* (III; R = Me and Ph, respectively; X = O) were so prepared; the latter was also obtained by the desulphurisation of 2-thio-8-phenyl-1-methyl-xanthine with alkaline hydrogen peroxide.

The purine nature of these products could hardly be questioned, as all responded to the murexide test when oxidised with potassium chlorate in hydrochloric acid. It was, however, finally placed beyond doubt when 8-phenyl-1-methyl- and 1 : 8-dimethyl-xanthine were oxidised with potassium chlorate and the product reduced with stannous chloride to yield dimethylalloxantin identical with that prepared from theobromine (Biltz, *Ber.*, 1912, **45**, 3675). The identity was confirmed by its condensation with *o*-phenylenediamine to give the same 3-methylalloxazine as was obtained from authentic dimethylalloxantin prepared from theobromine (Kühling, *Ber.*, 1891, **24**, 3030).

Experimental.

4-*Amino*-5-*carbethoxy*-2-*benzylglyoxaline* (I; R = CH_2Ph).—Ethyl aminocyanoacetate (15 g.) and thiophenylacetiminobenzyl ether hydrochloride (30 g.) were dissolved in dry chloroform (200 c.c.) and heated under reflux for 1 hour. The solution was evaporated to 90 c.c., benzene (100 c.c.) added, and the whole kept at 0° for 3 days; the glyoxaline hydrochloride (20 g.) then separated. The hydrochloride was dissolved in the minimum quantity of hot water and just neutralised with 10% sodium hydroxide,

the free base (15 g.) being precipitated. The *picrate* crystallised from ethanol as rhombic prisms, m. p. 221° (decomp.) (Found : C, 48·4; H, 3·9; N, 17·8. $C_{19}H_{18}O_9N_6$ requires C, 48·1; H, 3·8; N, 17·7%).

4-*Amino*-5-*carbethoxy*-2-*phenylglyoxaline* (I; R = Ph).—(*a*) Benziminoethyl ether (15 g.) was added to ethyl aminocyanoacetate (17 g.; 1·3 moles) in ether (50 c.c.), and the solution kept at room temp. for 24 hours; the *glyoxaline* (1·75 g.) separated out. A further quantity (0·4 g.) was obtained on evaporating the solvent in a vacuum and keeping the residue at 0°. The glyoxaline was insoluble in water or ether and sparingly soluble in acetone or chloroform; it crystallised from ethanol as colourless prisms, m. p. 218° (decomp.) (Found : C, 61·9; H, 5·8; N, 18·0. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%).

(*b*) Thiobenziminobenzyl ether hydrochloride (3 g.) and ethyl aminocyanoacetate (1·5 g.) were heated under reflux for 30 minutes in chloroform (25 c.c.); the *glyoxaline hydrochloride* (2·3 g.) which separated crystallised from methanol; m. p. 216° (decomp.) (Found : C, 53·5; H, 5·3. $C_{12}H_{14}O_2N_3Cl$ requires C, 53·8; H, 5·3%). The free base (1·1 g.) was precipitated from a hot aqueous solution of the hydrochloride (1·3 g.) by neutralisation with the minimum quantity of alkali. The *picrate*, prepared in ethanol, crystallised from this solvent as yellow needles, m. p. 224° (decomp.) (Found : C, 47·4; H, 3·6; N, 18·2. $C_{18}H_{16}O_9N_6$ requires C, 47·0; H, 3·5; N, 18·3%). Acetylation with acetic anhydride and concentrated sulphuric acid yielded a *monoacetyl* compound, which crystallised from water as colourless needles, m. p. 174° (Found : N, 15·8. $C_{14}H_{15}O_3N_3$ requires N, 15·4%). The *benzylidene-amino*-compound was prepared by dissolving the glyoxaline in hot benzaldehyde; it crystallised from ethanol as pale yellow microcrystalline needles, m. p. 214° (decomp.) (Found : N, 12·9. $C_{19}H_{17}O_2N_3$ requires N, 13·2%).

4-*Amino*-5-*carbethoxy*-2-*methylglyoxaline* (I; R = Me).—(*a*) Ethyl aminocyanoacetate (2·5 g.) and acetiminoethyl ether (2·9 g.) in ether (36 c.c.) deposited an oil on standing at room temperature for 24 hours; by treatment with ethanol and ether this yielded a small quantity of solid (0·1 g.), m. p. 167° (decomp.).

(*b*) Thioacetiminobenzyl ether hydrochloride (5 g.) was heated under reflux for 4 hours with excess of ethyl aminocyanoacetate (5 g.) in chloroform (30 c.c.); the *glyoxaline hydrochloride* (3·3 g.; 65%) which separated crystallised from a very small volume of ethanol as microscopic needles, m. p. 213—214° (decomp.) (Found : N, 20·6. $C_7H_{12}O_2N_3Cl$ requires N, 20·4%). The hydrochloride (2·8 g.) was converted into the free base (1·8 g.) in the usual manner, and the basified solution kept at 0° for 30 minutes to complete the precipitation. 4-*Amino*-5-*carbethoxy*-2-*methylglyoxaline* was sparingly soluble in hot ether or benzene, more soluble in water, chloroform, or ethyl acetate, and readily soluble in ethanol; it crystallised from chloroform as colourless, granular, irregular prisms, m. p. 167° (decomp.) (Found : C, 49·4; H, 6·3; N, 25·1. $C_7H_{11}O_2N_3$ requires C, 49·7; H, 6·5; N, 24·9%). The m. p. of a mixture with the substance prepared from acetiminoethyl ether was undepressed.

4-*Amino*-5-*carbethoxyglyoxaline* (I; R = H).—To a solution of ethyl aminocyanoacetate (9 g.) in chloroform (200 c.c.) was added formamidine hydrochloride (5·6 g.) with just sufficient ethanol to dissolve it in the chloroform solution. On being heated under reflux for 2 hours, the solution darkened and was left for a further 12 hours at room temperature; the greater part of the ammonium chloride (2·8 g.; 80%) calculated for the reaction had then separated. Ether was added to the filtrate until a faint turbidity was obtained. On standing at 0° for 6 hours a very small quantity of black oil separated from which the solution was decanted, and on concentration by evaporation in a vacuum 4-*amino*-5-*carbethoxyglyoxaline* (2·4 g.; 40%) crystallised out; this was readily soluble in alcohol and warm acetone, chloroform, or water, and crystallised from ethyl acetate–ethanol as colourless needles, m. p. 180—181° (Found : C, 46·4; H, 5·6; N, 26·6. $C_6H_9O_2N_3$ requires C, 46·4; H, 5·8; N, 27·1%).

4-*Amino*-5-*phenyl*-2-*benzylglyoxaline*.—Thiophenacetiminobenzyl ether hydrochloride (3 g.) was heated under reflux with α-aminobenzyl cyanide (1·7 g.) in chloroform for 12 hours, the glyoxaline hydrochloride gradually separating as a solid, m. p. 200° (decomp.). Precipitation of the solid (3 g.) was completed on standing at 0° for 12 hours. On dissolving this in the minimum quantity of water and just neutralising it with 10% sodium hydroxide, the *base* was precipitated (1·5 g.; 44%). It crystallised from pyridine or, better, methanol as leaflets, m. p. 199° (Found : C, 76·8; H, 6·0; N, 17·2. $C_{16}H_{15}N_3$ requires C, 77·1; H, 6·1; N, 16·9%). The *picrate* crystallised from ethanol as tufts of orange needles, m. p. 215° (Found : C, 55·3; H, 3·5; N, 17·3. $C_{22}H_{18}O_7N_6$ requires C, 55·2; H, 3·8; N, 17·6%). Acetylation with acetic anhydride and concentrated sulphuric acid at 100° yielded a *diacetyl* compound, which crystallised from methanol as colourless needles, m. p. 215° (Found : C, 71·8; H, 5·9; N, 12·3. $C_{20}H_{19}O_2N_3$ requires C, 72·0; H, 5·7; N, 12·6%).

4-*Amino*-2 : 5-*diphenylglyoxaline*.—Thiobenziminobenzyl ether hydrochloride (2 g.) and α-aminobenzyl cyanide (1 g.) were heated under reflux in chloroform for 2 hours, the glyoxaline hydrochloride (1·7 g.) being precipitated. The base was precipitated from a hot aqueous solution of the hydrochloride on neutralisation with sodium hydroxide as a white solid (1 g.) which rapidly turned green. The *picrate* formed silky needles, m. p. 220°, on crystallisation from ethanol (Found : C, 54·1; H, 3·5; N, 18·2. $C_{21}H_{18}O_7N_6$ requires C, 54·3; H, 3·5; N, 18·2%).

4-*Amino*-5-*phenyl*-2-*methylglyoxaline*.—Thioacetiminobenzyl ether hydrochloride (5 g.) and α-aminobenzyl cyanide (3·5 g.) were heated under reflux in chloroform (25 c.c.); an oil separated which, on cooling, solidified as colourless crystals (5 g.). The solid was very soluble in water or methanol and insoluble in acetone, and was not diazotisable in dilute hydrochloric acid. On rapid heating it melted at 125°; on continued heating gradual solidification occurred, followed by a second fusion at 225°. On 15 minutes' heating at 200°, the *glyoxaline hydrochloride* was obtained, which crystallised from methanol as colourless crystals, m. p. 238° (Found : N, 20·3. $C_{10}H_{12}N_3Cl$ requires N, 20·0%). It diazotised in dilute hydrochloric acid solution.

4-Amino-5-carbethoxy-2-benzylglyoxaline (1·2 g.) was added to a solution of methyl *iso*thiocyanate (0·4 g.) in pyridine (5 c.c.) and heated under reflux for 1 hour. On pouring into water (20 c.c.), a white solid (1·3 g.) was obtained which was sparingly soluble in ether or dilute hydrochloric acid, and soluble in ethanol, chloroform, or ethyl acetate. Long thin needles of 4-N′-*methylthioureido*-5-*carbethoxy*-2-*benzylglyoxaline*, m. p. 174°, crystallised from ethanol (Found : C, 56·6; H, 5·9; N, 17·7; S, 10·1. $C_{15}H_{18}O_2N_4S$ requires C, 56·6; H, 5·7; N, 17·8; S, 10·1%). On dissolving this in 10% sodium

hydroxide, warming it for 1 minute, and acidifying the hot solution with acetic acid, 2-*thio*-8-*benzyl*-1-*methylxanthine* was precipitated as a gelatinous solid (Found : C, 57·0; H, 4·4; N, 21·0; S. 12·2. $C_{13}H_{12}ON_4S$ requires C, 57·4; H, 4·4; N, 20·6; S, 11·8%).

4-Amino-5-carbethoxy-2-phenylglyoxaline (1·6 g.) and methyl *iso*thiocyanate (1 g.) were heated under reflux for 1 hour in pyridine (5 c.c.). On cooling at 0°, crystals of 4-N′-*methylthioureido*-5-*carbethoxy*-2-*phenylglyoxaline* (1·3 g.) separated. A further quantity (0·7 g.) was obtained by pouring the mother-liquor into water (20 c.c.). The glyoxaline crystallised from ethanol in microprisms, m. p. 245° (Found : C, 55·1; H, 5·0. $C_{14}H_{16}O_2N_4S$ requires C, 55·3; H, 5·3%). On alkali treatment, followed by acidification, 2-*thio*-8-*phenyl*-1-*methylxanthine* was obtained (Found : C, 55·8; H, 4·2; N, 21·5; S, 11·9. $C_{12}H_{10}ON_4S$ requires C, 55·8; H, 3·9; N, 21·7; S, 12·4%).

4-Amino-5-carbethoxy-2-phenylglyoxaline (5 g.) and a very large excess of methyl *iso*cyanate (15 g.) in pyridine (25 c.c.) were heated under reflux for 2 hours and then poured into water; 4-N′-*methylureido*-5-*carbethoxy*-2-*phenylglyoxaline* (5·5 g.) was precipitated, and crystallised from ethanol as colourless prisms, m. p. 181—182° (Found : C, 58·2; H, 5·7; N, 19·1. $C_{14}H_{16}O_3N_4$ requires C, 58·3; H, 5·6; N, 19·4%). 8-*Phenyl*-1-*methylxanthine* was obtained by alkali treatment followed by acid (Found : C, 59·9; H, 4·4; N, 23·1. $C_{12}H_{10}O_2N_4$ requires C, 59·5; H, 4·1; N, 23·1%). 2-Thio-8-phenyl-1-methylxanthine (1·5 g.) was dissolved in 5% sodium hydroxide (50 c.c.) to which was added at 0° hydrogen peroxide (20-vol., 13·5 c.c.). The solution was kept at 0° for one week. On boiling and acidifying with acetic acid, 8-phenyl-1-methylxanthine was precipitated (Found : C, 59·6; H, 4·2; N, 22·9%).

4-N′-*Methylthioureido*-5-*carbethoxy*-2-*methylglyoxaline* (1·8 g.) was obtained in the usual manner from 4-amino-5-carbethoxy-2-methylglyoxaline (2 g.) and methyl *iso*thiocyanate (1 g.). The compound was soluble in acetone, ethanol, or benzene and could be crystallised from ethyl acetate as colourless prisms, m. p. 194° (Found : C, 44·9; H, 5·8; N, 22·9. $C_9H_{14}O_2N_4S$ requires C, 44·6; H, 5·8; N, 23·1%). 2-*Thio*-1 : 8-*dimethylxanthine* was precipitated on acidification of an alkaline solution of the ureido-compound (Found : C, 42·4; H, 4·1. $C_7H_8ON_4S$ requires C, 42·8; H, 4·1%).

4-Amino-5-carbethoxy-2-methylglyoxaline (3·1 g.) and a large excess of methyl *iso*cyanate (10 g.) in pyridine (10 c.c.) were heated under reflux for 2 hours. The pyridine was removed in a vacuum, and the residue boiled with 10% sodium hydroxide; acidification with acetic acid gave 1 : 8-*dimethylxanthine* (2·2 g.; 67%), which separated as microcrystalline needles (Found : C, 47·1; H, 4·3; N, 31·3. $C_7H_8O_2N_4$ requires C, 46·7; H, 4·4; N, 31·1%).

4-Amino-5-carbethoxyglyoxaline (1·6 g.) and methyl *iso*thiocyanate (0·8 g.) in pyridine (5 c.c.) were heated under reflux for 1 hour and then poured into water; the thioureido-compound, m. p. 163° (2·0 g.), was precipitated. On dissolving this in alkali and acidification with acetic acid, 2-*thio*-1-*methylxanthine* was obtained as small lustrous needles (Found : C, 39·7; H, 3·6; N, 30·4; S, 17·2. $C_6H_6ON_4S$ requires C, 39·6; H, 3·3; N, 30·8; S, 17·6%).

8-Phenyl-1-methylxanthine (2 g.) was suspended in a solution of concentrated hydrochloric acid (2·7 c.c.) and water (5 c.c.) at 60° and potassium chlorate (0·5 g.) was added during 30 minutes, care being taken to see that the temperature did not exceed 60°. The purine slowly dissolved, but towards the end of the experiment a solid started to crystallise and the deposition was completed by standing at 0° for 1 hour. The crystalline solid (0·6 g.) was filtered off, and air bubbled through the filtrate for 3 hours to remove excess of chlorine. Stannous chloride (1·3 g.) in concentrated hydrochloric acid (1 c.c.) was dripped into the solution, cooled to 0° to −5° in a carbon dioxide–ethanol bath, during 30 minutes. On standing at 0° for 12 hours, dimethylalloxantin (0·4 g.) separated, contaminated, probably, with some methyldialuric acid; it had m. p. 200° (to a red liquid) (Biltz, *Ber.*, 1912, **45**, 3675, gives m. p. 210—215°). A mixed m. p. with some dimethylalloxantin prepared from theobromine was undepressed. On boiling this with *o*-phenylenediamine hydrochloride in aqueous solution, 3-methylalloxazine was precipitated as a yellow-green solid which could be crystallised from acetic acid–ethanol (Found : C, 57·9; H, 3·3; N, 24·9. Calc. for $C_{11}H_8O_2N_4$: C, 57·9; H, 3·5; N, 24·6%). Both the 3-methyl-alloxazine prepared above and a specimen prepared from the theobromine decomposed at *ca.* 280° (Kühling, *Ber.*, 1891, **24**, 3030, gives decomp. 250°).

1 : 8-Dimethylxanthine (2 g.) was oxidised under identical conditions. Reduction of the oxidation product with stannous chloride yielded dimethylalloxantin (0·8 g.), which crystallised from water as colourless prisms, m. p. 207° (Found : C, 38·0; H, 3·3; N, 17·8. Calc. for $C_{10}H_{10}O_8N_4$: C, 38·2; H, 3·2; N, 17·6%).

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