326. *Purines, Pyrimidines, and Glyoxalines. Part XIII.* Some New Unambiguous Syntheses of 5-Aminoglyoxalines and 5-Aminoglyoxaline-4-carboxyamides, and a Synthesis of 5-Amino-1-β-D-ribofuranosylglyoxaline-4-carboxyamide.*

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Ethyl *N*-cyanomethyl-acetimidate (or -formimidate) prepared from ethyl acetimidate (or formimidate) hydrochloride and aminoacetonitrile, with primary amines including D-galactosylamine, gave corresponding 1-substituted 5-aminoglyoxalines. The related ethyl *N*-(carbamoylcyanomethyl)-acetimidate (or -formimidate) and ethyl *N*-(cyano-*N*-methylcarbamoylmethyl)-acetimidate (or -formimidate) were prepared from α-amino-α-cyanoacetamide or α-amino-α-cyano-*N*-methylacetamide and ethyl acetimidate (or formimidate) hydrochloride in aqueous solution. Reaction of these compounds with primary amines readily gave 1-substituted 5-aminoglyoxaline-4-carboxyamides (or -*N*-methylcarboxyamides). The reactions have been adapted to include a synthesis of 5-amino-1-β-D-ribofuranosylglyoxaline-4-carboxyamide.

Intermediates in the biosynthesis of purine nucleotides include the 5′-*O*-phosphates of 5-amino-1-β-D-ribofuranosylglyoxaline (Ia; R = H, R′ = β-D-ribofuranosyl) and the corresponding 4-carboxyamide (Ib; R = R″ = H, R′ = β-D-ribofuranosyl).[1]

* Part XII, *J.*, 1959, 1169.

[1] Buchanan, " Chemistry and Biology of the Purines," Ciba Foundation Symposium, Little, Brown & Co., Boston, 1957; Baddiley and Buchanan, *Quart. Rev.*, 1957, 329.

The unstable parent aminoglyoxaline (Ia; R = R′ = H) has been prepared as a hydrochloride by reduction of 5-nitroglyoxaline [2] (IIa; R = H), and a 1-methyl derivative (Ia; R = H, R′ = Me) was obtained by desulphurisation of the mercaptoglyoxaline (Ia; R = SH, R′ = Me) with Raney nickel.[3] The last compound was prepared by reaction of methyl *iso*thiocyanate with aminoacetonitrile and base-catalysed rearrangement of the resulting thiazole (IIIa).

The parent carboxyamide (Ib; R = R′ = R″ = H) has been prepared by (1) the cyclisation of α-*N*-formamidomalonamidamidine,[4] (2) reaction of formamidine hydrochloride [5] or ethyl formimidate [6] with α-amino-α-cyanoacetamide (other imidates give 2-substituted derivatives [7]), and (3) reduction of 5-nitroglyoxaline-4-carboxyamide [8] (IIc; R = H). In addition, the amidine (Id; R = R′ = H) has been obtained by cyclisation of α-*N*-formamidomalondiamidine [9] or by acid hydrolysis of adenine,[10] the ester (Ic; R = R′ = H) from formamidine hydrochloride and ethyl α-amino-α-cyanoacetate,[11] and a 1-methyl derivative (Ib; R = R″ = H, R′ = Me) by desulphurisation of the mercaptoglyoxaline (Ib; R = SH, R′ = Me, R″ = H) with Raney nickel.[3] The last compound was prepared from methyl *iso*thiocyanate and ethyl α-amino-α-cyanoacetate which gave the thiazole (IIIb) from which the amide (IIIc) was obtained, and this rearranged to the thiol (Ib; R = SH, R′ = Me, R″ = H) with alkali.

Method (3) has been adapted to a synthesis of the riboside (Ib; R = R″ = H, R′ = β-D-ribofuranosyl) by reaction of 2 : 3 : 5-tri-*O*-benzoylribofuranosyl chloride with the nitroglyoxaline (IIb; R = H) to give a mixture of the isomeric 1- and 3-substituted derivatives which were separated; the 1-isomer (IIb; R = β-D-2 : 3 : 5-tri-*O*-benzoylribofuranosyl) with ammonia gave the amide (IIc; R = β-D-ribofuranosyl) which was reduced to the amino-carboxyamide (Ib; R = R″ = H, R′ = β-D-ribofuranosyl).[12] In a second synthesis benzylation of inosine gave the 1-benzyl derivative (IV; R = β-D-ribofuranosyl, R′ = CH_2Ph), converted by alkali into the *N*-benzyl-carboxyamide (Ib; R = H, R′ = β-D-ribofuranosyl, R″ = CH_2Ph) which with sodium in liquid ammonia gave the required product (Ib; R = R″ = H, R′ = β-D-ribofuranosyl).[13]

Apart from their biochemical interest, the amino-carboxyamides (Ib) and related esters, amidines, etc., are of potential value as intermediates for the synthesis of purines and purine nucleosides and nucleotides. The parent amide (Ib; R = R′ = H) and the corresponding ethyl ester and amidine have been converted into several purines by closure of the pyrimidine ring with formic acid and its derivatives, urea, and *iso*cyanates, and 2-azapurines are obtained with nitrous acid.[14] In addition, the riboside (Ib; R = R″ = H, R′ = β-D-ribofuranosyl) has similarly been converted into inosine with formic acid and acetic anhydride.[15,9]

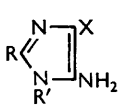
We now report some preliminary experiments which lead to simple, convenient, and unambiguous syntheses of compounds of type (Ib) by methods which closely parallel previous syntheses of pyrimidines and pyrimidine nucleosides, in that a 1-substituent is introduced *via* a primary amine. The preparation of glyoxalines (Ia) and (Ib) through the thiazoles (IIIa) and (IIIc) is also unambiguous but has not been extended to include

[2] Hunter and Nelson, *Canad. J. Res.*, 1941, **19**, *B*, 296.
[3] Cook, Downer, and Heilbron, *J.*, 1948, 2028.
[4] Shaw and Woolley, *J. Biol. Chem.*, 1949, **181**, 89.
[5] Cook, Heilbron, and Smith, *J.*, 1949, 1440.
[6] Miller, Gurin, and Wilson, *Science*, 1950, **112**, 654.
[7] *Idem*, *J. Amer. Chem. Soc.*, 1952, **74**, 2892.
[8] Windaus and Langenbeck, *Ber.*, 1923, **56**, 683.
[9] Shaw, *J. Biol. Chem.*, 1950, **185**, 439.
[10] Cavalieri, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 3973.
[11] Cook and Heilbron, B.P. 683,523/1952.
[12] Baddiley, Buchanan, and Stewart, *Proc. Chem. Soc.*, 1957, 149.
[13] Shaw, *J. Amer. Chem. Soc.*, 1958, **80**, 3899.
[14] Hofmann, "Imidazoles and Derivatives," Interscience Publ. Inc., New York, 1953; Chargaff and Davidson, "The Nucleic Acids," Academic Press, Inc., New York, 1955.
[15] Greenberg and Spilman, *J. Biol. Chem.*, 1956, **219**, 411.

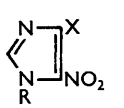
the preparation of glycosides although the use of glycosyl *iso*thiocyanates in these reactions was foreshadowed.[16]

Initially we examined the compound (V) which has been prepared from ethyl acetimidate hydrochloride and glycine ethyl ester.[17] This reacted smoothly with methylamine and ethylamine, to give the corresponding hydroxyglyoxalines (VIa; R = Me and Et respectively). The analogous nitrile (VII; R = Me), prepared in a similar manner from ethyl acetimidate hydrochloride and aminoacetonitrile,[18] with methylamine and D-galactosylamine readily gave the aminoglyoxalines (Ia; R = Me, R′ = Me or D-galactopyranosyl respectively). The structures assigned to these compounds followed from their ability to diazotise and couple with β-naphthol or α-naphthylethylenediamine, and the absence of the CN bands in their infrared spectra.

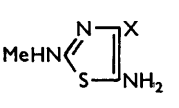
In a similar manner, reaction of aminoacetonitrile and ethyl formimidate hydrochloride in water readily gave the linear compound (VII; R = H) which with methylamine and ethylamine afforded the aminoglyoxalines (Ia; R = H, R′ = Me or Et respectively). An attempt was also made to prepare the riboside (Ia; R = H, R′ = β-D-ribofuranosyl) by reaction of the compound (VII; R = H) with 2 : 3 : 5-tri-*O*-benzoylribofuranosylamine. Debenzoylation of the product gave unstable material, and the riboside could not be isolated although there is little doubt that it was formed during these reactions, since ultraviolet absorption spectra of the solutions were similar to those recorded for the 5′-phosphate.[19]



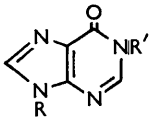
(Ia) X = H
(Ib) X = CO·NHR″
(Ic) X = CO_2Et
(Id) X = C(:NH)·NH_2



(IIa) X = H
(IIb) X = CO_2Me
(IIc) X = CO·NH_2

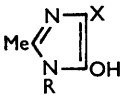


(IIIa) X = H
(IIIb) X = CO_2Et
(IIIc) X = CO·NH_2



(IV)

(V) Me·C(OEt):N·CH_2·CO_2Et
(VII) R·C(OEt):N·CH_2·CN
(VIII) R·C(OEt):N·CH(CN)·CO·NHR′



(VIa) X = H
(VIb) X = CO_2Et

These reactions were extended to include the preparation of aminoglyoxalinecarboxyamides. When ethyl acetimidate hydrochloride and α-amino-α-cyanoacetamide were mixed in aqueous solution at room temperature, the linear derivative (VIII; R = Me, R′ = H) quickly separated. It reacted rapidly and smoothly with ammonia, methylamine, *cyclo*hexylamine, and D-xylosylamine to give the corresponding amino-amides (Ib; R = Me, R′ = H, Me, *cyclo*hexyl, and D-xylopyranosyl, R″ = H). The structures assigned to these compounds followed from their ability to diazotise and couple, and in addition the 1-methyl derivative (Ib; R = R′ = Me, R″ = H) is apparently identical with the material prepared from the ester (IIIc).

Similarly, the imino-ether (VIII; R = R′ = H) was readily obtained crystalline by extraction of an aqueous solution of α-amino-α-cyanoacetamide and ethyl formimidate hydrochloride with ether. This compound with ammonia, methylamine, ethylamine, and *cyclo*hexylamine gave the glyoxalines (Ib; R = R″ = H, R′ = H, Me, Et, or *cyclo*hexyl). When exposed to the atmosphere the imidate slowly decomposed to a higher-melting more stable compound, presumably the glyoxaline [Ib; R = R″ = H, R′ = ·CH(CN)·CO·NH_2], which is probably formed by partial hydrolysis of the linear derivative

[16] Heilbron, *J.*, 1949, 2099.
[17] Schmidt, *Ber.*, 1914, **47**, 2548; Cornforth and Cornforth, *J.*, 1947, 96.
[18] Cornforth, *J.*, 1948, 1969.
[19] Levenberg and Buchanan, *J. Biol. Chem.*, 1957, **224**, 1005.

(VIII; R = R′ = H) and subsequent condensation of the α-amino-α-cyanoacetamide so formed with the imidate (VIII; R = R′ = H). A similar reaction has been observed by Cornforth and Cornforth [17] in which ethyl *N*-(diethoxycarbonylmethyl)acetimidate is converted into the glyoxaline [VIb; R = $CH(CO_2Et)_2$].

Also, reaction of the imino-ether (VIII; R = R′ = H) with 2 : 3 : 5-tri-*O*-benzoyl-ribofuranosylamine and debenzoylation of the product gave the riboside (Ib; R = R″ = H, R′ = β-D-ribofuranosyl) as an analytically pure glass; it readily gave a pure crystalline picrate, however, and its paper-chromatographic behaviour in several solvent systems, and its ultraviolet absorption spectra at differing pH values, were identical with those reported for the naturally occurring material.[15] In addition, the structure of the riboside was confirmed by conversion into inosine (IV; R = β-D-ribofuranosyl, R′ = H). The average yield of glyoxaline riboside obtained was about 40%.

These reactions clearly allow many variations. One of these in which we have been interested includes the preparation of *N*-substituted carboxyamides (Ib; R″ = alkyl, aryl, etc.) in which the substituent R″ would eventually appear, after cyclisation, at position 1 in the corresponding purine. Accordingly, in order to establish the generality of the reactions, we have examined the preparation of the group of compounds (Ib; R″ = Me). α-Cyano-*N*-methylacetamide with nitrous acid gave the *C*-hydroxyimino-derivative which was readily reduced by aluminium amalgam in aqueous methanol to α-amino-α-cyano-*N*-methylacetamide. This with ethyl acetimidate (or formimidate) hydrochloride in water gave the linear imidates (VIII; R = R′ = Me; and R = H, R′ = Me) from which the glyoxalines (Ib; R = R″ = Me, R′ = H, Me, or *cyclo*hexyl) and (Ib; R = H, R′ = H or Me, R″ = Me) were obtained by reaction with ammonia or the appropriate primary amines.

Experimental

5-Hydroxy-1 : 2-dimethylglyoxaline.—To a solution of ethyl *N*-(ethoxycarbonylmethyl)-acetimidate [17] (3·18 g.) in ethanol (2 ml.) was added 33% ethanolic methylamine (6 ml.). The mixture was set aside for 24 hr., then a crystalline precipitate was collected. The *glyoxaline* (0·95 g.) separated from ethyl acetate as needles, m. p. 165° (decomp.) (Found: C, 53·1; H, 6·95; N, 24·55. $C_5H_8ON_2$ requires C, 53·55; H, 7·2; N, 25·0%). The compound gave a blue colour with ferric chloride.

1-Ethyl-5-hydroxy-2-methylglyoxaline.—Ethyl *N*-(ethoxycarbonylmethyl)acetimidate (10 g.) and ethylamine (5 ml.) similarly gave the *glyoxaline* (9·7 g.) which separated from ethyl acetate as needles, m. p. 190° (decomp.) (Found: C, 57·1; H, 8·1; N, 21·9. $C_6H_{10}ON_2$ requires C, 57·1; H, 7·95; N, 22·2%).

5-Amino-1 : 2-dimethylglyoxaline.—33% Ethanolic methylamine (3 ml.) was added to ethyl *N*-cyanomethylacetimidate [18] (4·5 g.) in ethanol (10 ml.). After 20 min. the solution was treated with picric acid (7 g.) in ethanol. The *glyoxaline picrate* was filtered off after 12 hr. It separated from water as brownish-yellow needles, m. p. 193° (decomp.) (Found: C, 39·05; H, 3·8; N, 24·55. $C_5H_9N_3,C_6H_3O_7N_3$ requires C, 38·85; H, 3·55; N, 24·7%).

5-Amino-1-D-galactosyl-2-methylglyoxaline.—A suspension of D-galactosylamine (10·4 g.) in ethanol (30 ml.) was shaken with ethyl *N*-cyanomethylacetimidate (7·3 g.) for 20 min. with gentle warming. The mixture was filtered from undissolved galactosylamine (8 g.), and picric acid (2 g.) in ethanol added to the filtrate. The *glyoxaline picrate* (0·6 g.) separated after 24 hr. and recrystallised from water as brownish-yellow plates, m. p. 172° (decomp.) (Found: C, 39·7; H, 4·35; N, 26·3. $C_{10}H_{17}O_5N_3,C_6H_3O_7N_3$ requires C, 39·35; H, 4·1; N, 26·3%).

Ethyl N-Cyanomethylformimidate.—A solution of potassium carbonate (6·9 g.) and amino-acetonitrile sulphate (7·7 g.) in water (20 ml.) was covered with ether (200 ml.), then treated with ethyl formimidate hydrochloride (5·5 g.). The mixture was shaken for 3 min., the ether decanted, and the mixture shaken with a further portion of ether (100 ml.). The combined and dried extracts were evaporated to an oil which was distilled *in vacuo* to give *ethyl N-cyano-methylformimidate* (1·96 g.), b. p. 51°/0·8 mm., n_D^{29} 1·4305 (Found: C, 53·4; H, 7·3; N, 24·8. $C_5H_8ON_2$ requires C, 53·55; H, 7·2; N, 25·0%). The compound slowly darkened at room temperature but was stable for long periods when kept in the refrigerator.

5-Amino-1-methylglyoxaline.—The foregoing imidate (0·17 g.) in methanol (1 ml.) was heated on a water-bath for 5 min. with 33% ethanolic methylamine (0·17 ml.). Saturated methanolic picric acid was added to the cooled solution to precipitate the glyoxaline picrate (0·2 g.), greenish-yellow prisms, m. p. 189° (decomp.) (from ethanol) (Found: C, 36·65; H, 2·9; N, 25·6. Calc. for $C_4H_7N_3,C_6H_3O_7N_3$: C, 36·8; H, 3·1; N, 25·8%). Cook, Downer, and Heilbron [3] describe the free base as very unstable and give m. p. 177° (decomp.) for the picrate.

5-Amino-1-ethylglyoxaline.—Similarly the imidate (0·34 g.) and 33% ethanolic ethylamine (0·5 ml.) gave the *glyoxaline picrate* (0·31 g.), pale yellow laths, m. p. 185° (decomp.) (from ethanol) (Found: C, 38·9; H, 3·4; N, 24·4. $C_5H_9N_3,C_6H_3O_7N_3$ requires C, 38·8; H, 3·6; N, 24·7%).

Ethyl N-(Carbamoylcyanomethyl)acetimidate.—Water (10 ml.) was added to a mixture of α-amino-α-cyanoacetamide [20] (5 g.) and ethyl acetimidate hydrochloride (12 g.). The mixture was shaken for a few min., a clear solution being obtained which then rapidly gave a crystalline precipitate. The *acetimidate* (5·7 g.) separated from ethyl acetate–light petroleum (b. p. 40—60°) as plates, m. p. 105° (Found: C, 49·95; H, 6·5; N, 24·8. $C_7H_{11}O_2N_3$ requires C, 49·7; H, 6·55; N, 24·85%).

5-Amino-1 : 2-dimethylglyoxaline-4-carboxyamide.—The foregoing acetimidate (0·4 g.) in methanol (1 ml.) with 33% ethanolic methylamine (0·3 ml.) gave after a short time a crystalline precipitate. The *glyoxaline* (0·13 g.) separated from methanol as plates, m. p. 286° (decomp.) (Found: C, 46·95; H, 6·7; N, 36·3. $C_6H_{10}ON_4$ requires C, 46·75; H, 6·55; N, 36·4%). A further quantity (0·07 g.) of the glyoxaline separated from the mother-liquors after 1 hr. The glyoxaline gave red colours with diazotised sulphanilic acid or when diazotised and coupled with alkaline β-naphthol.

5-Amino-1-cyclohexyl-2-methylglyoxaline-4-carboxyamide.—The foregoing acetimidate (1 g.) and *cyclo*hexylamine (0·7 ml.) were heated in methanol (1·5 ml.) for 15 min. on a water-bath. The cooled solution gave a crystalline precipitate of the *glyoxaline monohydrate* (0·35 g.), needles (from ethanol), m. p. 240° (decomp.) (Found: C, 54·8; H, 8·15; N, 23·2. $C_{11}H_{18}ON_4,H_2O$ requires C, 55·0; H, 8·35; N, 23·35%). A further quantity (0·25 g.) of the glyoxaline separated from the mother-liquors after evaporation.

5-Amino-2-methylglyoxaline-4-carboxyamide.—The acetimidate (0·5 g.) was heated on a water-bath for 20 min. with 10% ethanolic ammonia (5 ml.). Excess of ammonia was removed by evaporation and the solution treated with picric acid (0·7 g.) in ethanol (10 ml.) to give the *glyoxaline picrate* (0·8 g.), prisms (from ethanol), m. p. 240° (decomp. with darkening from 200°) (Found: C, 36·05; H, 2·95; N, 24·25. $C_5H_8ON_4,C_6H_3O_7N_3$ requires C, 35·8; H, 3·0; N, 24·65%). A suspension of the picrate (0·5 g.) in acetone with dry hydrogen chloride gave a colourless insoluble precipitate. The glyoxaline hydrochloride (0·1 g.) separated from methanol–ether as prisms, m. p. 246—247° (with preliminary darkening) (Found: C, 34·15; H, 4·9; N, 31·55. Calc. for $C_5H_8ON_4,HCl$: C, 34·0; H, 5·15; N, 31·75%). Cook *et al.*[3] give m. p. 239—240°.

5-Amino-2-methyl-1-D-xylopyranosylglyoxaline-4-carboxyamide.—A suspension of D-xylosylamine (0·8 g.) in ethanol (15 ml.) containing the above acetimidate (0·7 g.) was gently warmed and stirred until the xylosylamine had dissolved (20 min.). The solution was heated for a further 15 min., cooled, and set aside overnight, a crystalline precipitate separating. The *glyoxaline monohydrate* (0·26 g.) crystallised from water as needles, m. p. 186—187° (decomp.) (Found: C, 41·45; H, 6·05; N, 19·45. $C_{10}H_{16}O_5N_4,H_2O$ requires C, 41·4; H, 6·25; N, 19·45%). The compound gave a red colour with diazotised sulphanilic acid, and diazotised and coupled with alkaline β-naphthol to give a red colour.

9-cyclohexyl-8-methylhypoxanthine.—A solution of 5-amino-1-*cyclo*hexyl-2-methylglyoxaline-4-carboxyamide (0·33 g.) in acetic anhydride (5 ml.) and formic acid (5 ml.) was heated on a water-bath for 2 hr. The solution was evaporated to dryness *in vacuo* and the residue evaporated with ethanol to give a solid. The *hypoxanthine* (0·3 g.) separated from ethanol as short rods, m. p. 285° (Found: C, 61·6; H, 7·15; N, 24·05. $C_{12}H_{16}ON_4$ requires C, 62·05; H, 6·95; N, 24·15%).

Ethyl N-(Carbamoylcyanomethyl)formimidate.—A solution of α-amino-α-cyanoacetamide (2 g.) in water (40 ml.), covered by ether (200 ml.), was treated with ethyl formimidate hydrochloride (2·5 g.), and the mixture was shaken. The ethereal solution was separated, and the aqueous phase treated with a further portion of the imidate (1 g.) and again extracted with ether (100 ml.). The combined, dried extracts were evaporated *in vacuo* to about 10 ml.,

[20] Smith and Yates, *J. Amer. Chem. Soc.*, 1954, **76**, 6080.

crystals separating. The *formimidate* (0·625 g.) was pure at this stage but crystallised from ether as needles, m. p. 86—87° (Found: C, 46·5; H, 5·7; N, 27·3. $C_6H_9O_2N_3$ requires C, 46·4; H, 5·8; N, 27·1%). A further quantity (0·315 g.) was obtained from the mother-liquors. In this preparation the ethereal solution should not be evaporated to dryness, and the compound should be kept in a desiccator. When exposed to the atmosphere the compound slowly decomposed into a more stable substance. This, presumably 5-*amino*-2-(*carbamoylcyanomethyl*)*glyoxaline*-4-*carboxyamide*, separated from water as needles, m. p. 212—216° (decomp.) (Found: C, 40·3; H, 3·4; N, 40·0. $C_7H_8O_2N_6$ requires C, 40·4; H, 3·9; N, 40·4%).

5-*Aminoglyoxaline*-4-*carboxyamide*.—The foregoing formimidate (0·1 g.) in methanol (1 ml.) was warmed with methanolic ammonia for 5 min. Evaporation then gave the glyoxaline (0·05 g.) which separated from ethanol as needles, m. p. 170° (Found: C, 37·95; H, 4·7; N, 44·35. Calc. for $C_4H_6ON_4$: C, 38·1; H, 4·8; N, 44·45%). The mother-liquors with picric acid gave the glyoxaline picrate which separated from acetic acid, as an *adduct* with acetic acid, as greenish-yellow prisms, m. p. 230° (decomp.) (Found: C, 34·9; H, 2·9; N, 23·45. $C_4H_6ON_4,C_2H_4O_2,C_6H_3O_7N_3$ requires C, 34·7; H, 3·2; N, 23·6%), or from ethanol as yellow prisms, m. p. 240° (decomp.) (Found: C, 33·65; H, 2·4; N, 27·55. Calc. for $C_4H_6ON_4,C_6H_3O_7N_3$: C, 33·8; H, 2·55; N, 27·6%).

5-*Amino*-1-*methylglyoxaline*-4-*carboxyamide*.—The foregoing formimidate (0·2 g.) in methanol (1 ml.) was heated on a water-bath for 5 min. with 33% methanolic methylamine (0·2 ml.). The cooled solution gave a crystalline precipitate. The glyoxaline (0·11 g.) separated from ethanol as needles, m. p. 260° (Found: C, 42·85; H, 5·5; N, 40·0. Calc. for $C_5H_8ON_4$: C, 42·85; H, 5·75; N, 40·0%). Cook, Downer, and Heilbron [3] give m. p. 254°. The compound gave a red colour with diazotised sulphanilic acid, and after treatment with nitrous acid followed by alkaline β-naphthol. The mother-liquor from this experiment with methanolic picric acid gave the *glyoxaline picrate* (0·1 g.), greenish-brown prisms (from acetic acid), m. p. 249° (decomp.) (Found: C, 35·9; H, 3·0; N, 26·5. $C_5H_8ON_4,C_6H_3O_7N_3$ requires C, 35·8; H, 3·0; N, 26·6%).

5-*Amino*-1-*ethylglyoxaline*-4-*carboxyamide*.—The foregoing formimidate (0·25 g.) in methanol (1 ml.) with 33% ethanolic ethylamine (0·3 ml.) precipitated the *glyoxaline* (0·15 g.), needles (from ethanol), m. p. 230—232° (Found: C, 46·7; H, 6·3; N, 36·6. $C_6H_{10}ON_4$ requires C, 46·7; H, 6·5; N, 36·3%). The mother-liquors gave the *glyoxaline picrate* (0·09 g.), greenish-yellow needles (from acetic acid), m. p. 240° (decomp. with preliminary decomp.) (Found: C, 37·6; H, 3·4; N, 25·6. $C_6H_{10}ON_4,C_6H_3O_7N_3$ requires C, 37·6; H, 3·4; N, 25·6%).

5-*Amino*-1-cyclo*hexylglyoxaline*-4-*carboxyamide*.—The above formimidate (0·2 g.) in methanol (2 ml.) and *cyclo*hexylamine (0·13 g.) gave the *glyoxaline* (0·11 g.), needles (from ethanol), m. p. 209° (Found: C, 57·6; H, 7·5; N, 27·0. $C_{10}H_{16}ON_4$ requires C, 57·6; H, 7·7; N, 26·9%).

5-*Amino*-1-β-D-*ribofuranosylglyoxaline*-4-*carboxyamide*.—2 : 3 : 5-Tri-*O*-benzoylribofuranosyl azide [21] (2·44 g.) in ethyl acetate (300 ml.) was hydrogenated over platinic oxide (0·2 g.) for 2 hr. The solution was treated with the foregoing formimidate (0·76 g.) then heated on a water-bath for 30 min. and finally evaporated *in vacuo* to a gum. This was dissolved in chloroform, filtered from a little amorphous material, and again evaporated and the residue in methanol (20 ml.) was treated with a solution from sodium (0·012 g.) in methanol (5 ml.). After 24 hr. the solution was treated with a slight excess of " Zeocarb 225 " to remove sodium, then evaporated *in vacuo*, and the residue extracted with ether and evaporated with water (2 × 25 ml.) *in vacuo* to remove methyl benzoate. A pale amber-coloured gum remained, and did not crystallise. A portion of the gum (0·1 g.) with aqueous picric acid immediately gave the glyoxaline picrate (0·07 g.), m. p. 164° (decomp.), which was pure but crystallised from water (Found: C, 35·45; H, 3·65; N, 19·4. Calc. for $C_9H_{14}O_5N_4,C_6H_3O_7N_3,H_2O$: C, 35·65; H, 3·7; N, 19·4%). A further portion (0·4 g.) of the gum was purified by ion-exchange chromatography using Greenberg and Spilman's method; [15] a sharp fraction with $\lambda_{max.}$ 267 mμ was readily eluted from the column. Evaporation of this fraction gave the glyoxaline as an almost colourless glass (Found: C, 39·35; H, 5·6; N, 20·55. Calc. for $C_9H_{14}O_5N_4,H_2O$: C, 39·15; H, 5·8; N, 20·3%). The substance gave a single absorbing spot on paper chromatograms with R_F values very similar to those reported for the natural material. In addition the ultraviolet absorption spectra of the compound in aqueous solution at different pH values were identical with those recorded.[15] An average yield of the riboside from several experiments was about 40%. The compound was readily converted into inosine by E. Shaw's method [9]

[21] Baddiley, Buchanan, Hodges, and Prescott, *J.*, 1957, 4769.

and was identified by paper chromatography in several solvents, and spectroscopically. Inosine was the sole absorbing material formed in this reaction.

α-*Cyano*-α-*hydroxyimino*-N-*methylacetamide*.—α-Cyano-*N*-methylacetamide (127 g.) and sodium nitrite (92 g.) in water (300 ml.) with acetic acid (120 ml.) gave overnight a crystalline precipitate. This was dissolved in water and acidified with hydrochloric acid to precipitate the *hydroxyimino-derivative* (45 g.) which crystallised from water as needles, m. p. 212° (Found: C, 37·85; H, 3·9; N, 32·95. $C_4H_5O_2N_3$ requires C, 37·8; H, 3·95; N, 33·05%).

α-*Amino*-α-*cyano*-N-*methylacetamide*.—A solution of the foregoing hydroxyimino-compound (45 g.) in methanol (200 ml.) was added slowly to a mixture of aluminium amalgam (from 20 g. of aluminium) and methanol (200 ml.) with stirring during 30 min. Water (24 ml.) was added gradually to the stirred mixture which was kept at 30—40°. When the reaction was complete (2—3 hr.) the mixture was filtered and the solid washed with hot methanol (3 × 50 ml.). Evaporation of the combined methanol solutions gave α-*amino*-α-*cyano*-N-*methylacetamide* (7 g.) which crystallised from ethyl acetate as prisms, m. p. 115—116° (Found: C, 42·7; H, 6·15; N, 36·7. $C_4H_7ON_3$ requires C, 42·45; H, 6·25; N, 37·15%). A further quantity (5 g.) of the amine was obtained from the mother liquors.

Ethyl N-(*Cyano*-N-*methylcarbamoylmethyl*)*acetimidate*.—A mixture of ethyl acetimidate hydrochloride (10 g.) and α-amino-α-cyano-*N*-methylacetamide (5 g.) was shaken with water (10 ml.). A clear solution was soon obtained. This was extracted with ether. Evaporation of the dried extract gave an oil which soon solidified. The *acetimidate* (3·7 g.) crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 72° (Found: C, 52·05; H, 7·05; N, 23·25. $C_8H_{13}O_2N_3$ requires C, 52·45; H, 7·15; N, 22·95%).

5-*Amino*-2-*methylglyoxaline*-4-N-*methylcarboxyamide*.—The foregoing acetimidate (0·25 g.) in ethanol (1·5 ml.) was heated on a water-bath for 20 min. with 15N-ammonia (0·5 ml.). The cooled solution with methanolic picric acid gave a precipitate of the *glyoxaline picrate* (0·44 g.), yellow needles, from much ethanol, m. p. 250° (decomp.) (Found: C, 37·9; H, 3·45; N, 25·3. $C_6H_{10}ON_4,C_6H_3O_7N_3$ requires C, 37·55; H, 3·4; N, 25·6%).

5-*Amino*-1 : 2-*dimethylglyoxaline*-4-N-*methylcarboxyamide*.—The above acetimidate (0·5 g.) in ethanol (3 ml.) was heated on a water-bath with 33% ethanolic methylamine (0·5 ml.) for 30 min. Evaporation of the solution then gave the *glyoxaline* (0·3 g.) which separated from methanol-ether as needles, m. p. 176° (Found: C, 49·9; H, 6·95; N, 33·05. $C_7H_{12}ON_4$ requires C, 50·0; H, 7·2; N, 33·3%). The glyoxaline and methanolic picric acid gave a *picrate*, yellow needles (from ethanol), m. p. 221° (decomp.) (Found: C, 39·45; H, 3·75; N, 24·0. $C_7H_{12}ON_4,C_6H_3O_7N_3$ requires C, 39·3; H, 3·8; N, 24·35%).

5-*Amino*-1-cyclo*hexyl*-2-*methylglyoxaline*-4-N-*methylcarboxyamide*.—The above acetimidate (1 g.) in ethanol (2 ml.) and *cyclo*hexylamine (0·66 ml.) was heated on a water-bath for 30 min. Evaporation then gave an oil which solidified when evaporated with ether. The *glyoxaline monohydrate* (1·04 g.) crystallised from aqueous ethanol as needles, m. p. 161° (with apparent loss of solvent from 100°) (Found: C, 57·15; H, 8·35; N, 21·9. $C_{12}H_{20}ON_4,H_2O$ requires C, 56·7; H, 8·7; N, 22·05%). The *picrate* crystallised from ethanol as lemon-yellow needles, m. p. 220—228° (decomp.) (Found: C, 46·55; H, 4·8; N, 20·95. $C_{12}H_{20}ON_4,C_6H_3O_7N_3$ requires C, 46·45; H, 5·0; N, 21·05%).

Ethyl N-(*Cyano*-N-*methylcarbamoylmethyl*)*formimidate*.—α-Amino-α-cyano-*N*-methylacetamide (2·26 g.) in water (5 ml.) was covered with ether (30 ml.), and the mixture treated with ethyl formimidate hydrochloride (4 g.) with shaking. The ether was separated and the aqueous phase re-extracted. The combined and dried extract was evaporated *in vacuo* to a colourless oil which did not crystallise but was undoubtedly the *formimidate* (Found: N, 24·35. $C_7H_{11}O_2N_3$ requires N, 24·85%).

5-*Aminoglyoxaline*-4-N-*methylcarboxyamide*.—The foregoing formimidate (0·5 g.) was warmed on a water-bath for 20 min. with methanolic ammonia. Excess of ammonia was removed and then methanolic picric acid gave the *glyoxaline picrate* (0·88 g.), yellow prisms (from ethanol), m. p. 217° (decomp.) (Found: C, 35·7; H, 3·6; N, 25·15. $C_5H_8ON_4,C_6H_3O_7N_3$ requires C, 35·6; H, 3·0; N, 26·6%).

5-*Amino*-1-*methylglyoxaline*-4-N-*methylcarboxyamide*.—The last formimidate (0·5 g.) was warmed on a water-bath for 20 min. with 33% ethanolic methylamine (1·5 ml.). Excess of amine was removed and the solution treated with methanolic picric acid to give the *glyoxaline picrate* (0·92 g.), yellow needles (from much ethanol), m. p. 222° (decomp. with darkening from 212°) (Found: C, 37·75; H, 3·35; N, 25·6. $C_6H_{10}ON_4,C_6H_3O_7N_3$ requires C, 37·6; H, 3·4;

N, 25·6%). The picrate (0·69 g.) in warm dry acetone (30 ml.) with dry hydrogen chloride gave a precipitate of the *glyoxaline hydrochloride* (0·24 g.), needles (from ethanol–ether), m. p. 238° (decomp.), which retained a little water (Found: C, 33·05; H, 5·2; N, 30·1. $C_5H_8ON_4,HCl,\frac{1}{4}H_2O$ requires C, 33·15; H, 5·25; N, 30·95%).

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