Purines, Pyrimidines, and Glyoxalines. Part I. New Syntheses of Glyoxalines and Pyrimidines.

By G. SHAW.

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Diacylamines R·CH_2·CO·NH·COR′ have been prepared; on nitrosation and hydrogenation they gave amines NH_2·CHR·CO·NH·COR′ which cyclised spontaneously or in dilute alkali to dihydroglyoxalines (IV). Reaction of *N*-acyl-*N*-cyanoacetylamines with ethyl orthoformate and acetic anhydride gave ethoxymethylene derivatives which with dilute aqueous ammonia yielded pyrimidines (VI), and with aniline and phenylhydrazine aminomethylene derivatives (VII); two of these cyclised to pyrimidines (VI) when heated. Reaction of cyanoacetic acid, acetic anhydride, ethyl orthoformate, and amides gave the acylamidomethylene derivatives (IX), whose structures were confirmed by independent syntheses, and a reaction mechanism for their formation is discussed.

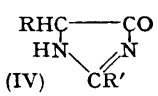
THE formation of pyrimidines by cyclisation, under mild and possibly physiological conditions, of certain β-aminoacylamines, has been recorded by Shaw and Sugowdz (*J.*, 1954, 665). The present investigation had as its objects (*a*) the preparation of α-aminoacylamines (III) and an examination of their cyclisation to dihydroglyoxalines (IV) and (*b*) an investigation of simpler and more general methods for the preparation of β-aminoacylamines and thence of pyrimidines. A note (Shaw, *Chem. and Ind.*, 1954, 546) on some of the present work has been published.

The reputed preparation of diglycylamine $(NH_2·CH_2·CO)_2NH$ by reaction of bischloroacetylamine with ammonia (Bergell, *Z. physiol. Chem.*, 1907, **51**, 209; Abderhalden and Riesz, *Fermentforsch.*, 1930, **12**, 180) has been shown to be incorrect and the product is now formulated as iminobisacetamide $(NH_2·CO·CH_2)_2NH$ (Backés, *Bull. Soc. chim.*, 1948, 1184). A similar reaction of *N*-chloroacetylbenzamide with ammonia (Aberhalden and Riesz, *loc. cit.*) failed to give the required amine; this reaction in our hands was also unsuccessful. It was considered, however, that the most useful intermediates for the preparation of the required α-aminoacylamines would be compounds of type (I) where R

R·CH_2·CO·NH·COR′ (I)

R·C(:N·OH)·CO·NH·COR′ (II)

R·CH(NH_2)·CO·NH·COR′ (III)



(IV)

is an electrophilic group, in particular CN, CO_2R, or COR; introduction of an amino-group on to the active methylene group should then follow by standard methods. Compounds containing one such group (I; R = Ph·CO) have already been prepared (Shaw and Sugowdz, *loc. cit.*) by hydrogenation of a 5-acylamido-3-phenyl*iso*oxazole and hydrolysis of the amine so formed. Two of these amides (I; R = Ph·CO, R′ = Ph or Me) readily gave nitroso-compounds (II; R = Ph·CO, R′ = Ph and Me); the compound (II; R = Ph·CO, R′ = Ph) was easily hydrogenated to the amine (III; R = Ph·CO, R′ = Ph) which cyclised to the glyoxaline (IV; R = Ph·CO, R′ = Ph) in warm dilute aqueous sodium hydroxide.

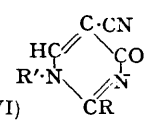
Preparation of the amides (I; R = Ph·CO) was somewhat laborious, even after improvement, and attention was turned to the cyanoacetyl- and malonyl-amides (I; R = CN and CO·NH·COR′ respectively). Cyanoacetamide or malonamide with acid anhydrides alone (Hentschel, *Ber.*, 1890, **23**, 2395) or in the presence of hydrogen chloride (Polya and Tardrew, *J.*, 1948, 1081) or with acid halides (Titherley and Holden, *J.*, 1912, **101**, 1880) were unchanged or decomposed, possibly owing to dehydration to the unstable malononitrile. Reaction of cyanoacetyl or malonyl chloride with simple amides or of chloroacetylamides with metal cyanides also failed to give the desired compounds. Now cyanoacetylurethane (I; R = CN, R′ = OEt) and the malonylbisurethane $CH_2(CO·NH·CO_2Et)_2$ have been prepared by heating on a water-bath for a few hours a

mixture of cyanoacetic or malonic acid respectively with urethane and acetic anhydride (Conrad and Schulze, *Ber.*, **1909**, **42**, 734). Urethane is, of course, more readily acylated than simple aliphatic or aromatic amides; however, when it was replaced in the above reactions by acetamide or benzamide, the required diacylamides (I; R = CN, R′ = Me and Ph) and (I; R = CO·NH·COMe, R′ = Me; R = CO·NH·COPh, R′ = Ph) were readily obtained. Nitrosation of these compounds in water or acetic acid gave, almost quantitatively, the hydroxyimino-compounds (II). Hydrogenation of the malonyl derivative (II; R = CO·NH·COMe, R′ = Me) as a suspension in ethanol, with platinum or nickel catalysts, gave an alcohol-insoluble residue which was largely soluble in hydrochloric acid; attempts to separate this compound, presumably the base (III; R = CO·NH·COMe, R′ = Me), from the catalyst by crystallisation from water gave the dihydroglyoxaline (IV; R = CO·NH·COMe, R′ = Me) and alkaline hydrolysis of this gave the carbamylglyoxaline (IV; R = CO·NH_2, R′ = Me). Similar hydrogenation of the nitrosocyanoacetyl compound (II; R = CN, R′ = Me) in ethanol gave a soluble product from which the glyoxaline derivative (IV; R = CN, R′ = Me) alone could be isolated; the amino-nitrile (III; R = CN, R′ = Me) is, however, present in solution (unpublished work). Hydrogenation of the benzoyl-hydroxyimino-compounds (II; R = CN and CO·NH·COPh, R′ = Ph), however, gave the more stable amines (III) which readily gave the corresponding glyoxalines (IV; R = CN and CO·NH·COPh, R′ = Ph) in dilute aqueous sodium hydroxide.

The cyanoacetylamines (I; R = CN, R′ = Me, Ph, and OEt) with molar quantities of ethyl orthoformate and acetic anhydride under reflux rapidly gave the crystalline ethoxymethylene derivatives (V; R′ = Me, Ph, and OEt), but the malonylamines failed to react. The ethoxymethylene compound (V; R = OEt) rapidly dissolved in 1% aqueous ammonia at room temperature and acidification then gave an excellent yield of 5-cyanouracil (VI; R = OH, R′ = H or the keto-isomer) which was readily converted into uracil by hydrolysis and decarboxylation. Similar treatment with methylamine in place of ammonia gave 5-cyano-1-methyluracil (VI; R = OH, R′ = Me). The pyrimidines (VI; R = Me and Ph, R′ = H) were obtained similarly from the corresponding ethoxymethylene derivatives and ammonia. These are perhaps the simplest pyrimidine syntheses yet recorded and can be regarded as taking place under "physiological" conditions. The pyrimidine (VI; R = Me, R′ = H) is of particular interest since it was an intermediate in a synthesis of thiamine (Todd and Bergel, *J.*, **1937**, 364).

The compounds (V; R = Me, Ph, and OEt) with ethanolic solutions of aniline and phenylhydrazine at room temperature gave the linear aminomethylene derivatives (VII; R = Me, Ph and OEt, R′ = Ph and NHPh) smoothly and rapidly. Two of these, (VII; R = OEt, R′ = Ph and Ph·NH), when heated for a short time near the melting point, gave quantitively the pyrimidines (VI; R = OH, R′ = Ph and Ph·NH). A single attempt to cyclise the compound (VII; R = Me, R′ = Ph) with aqueous sodium hydroxide resulted in hydrolysis to the amide (VIII).

CN·C(:CH·OEt)·CO·NH·COR
(V)


(VI)

CN·C(:CH·NHR′)·CO·NH·COR
(VII)

CN·C(:CH·NHPh)·CO·NH_2
(VIII)

It was considered possible that the ethoxymethylene compounds (V) might be obtained even more simply from cyanoacetic acid, ethyl orthoformate, an amide, and acetic anhydride. However, use of acetamide, benzamide, or urethane, gave different (isomeric) products, hydrolysed by alkali to ammonia, carbon dioxide, cyanoacetaldehyde, and, from the benzamide product, benzoic acid; the same products were formed by hydrolysis of the compounds (V; R = Me, Ph, and OEt). These isomers were singularly resistant to ammonia or aniline: *e.g.*, the isomer derived from benzamide failed to react with aniline in boiling ethanol but with ammonia it slowly gave benzamide. However, with aqueous methylamine each of the isomers gave the same substance $C_7H_{10}O_2N_2$ which

could only arise by replacement of R·CO·NH by Me·NH. These reactions established the presence of the grouping CN·C(:CH·)·CO·, so the isomers were geometrical isomers of the diacylamine (V) or the esters (IX), and the substance formed by reaction with methylamine was the amide (X) or the ester (XI).

$CN{\cdot}C(:CH{\cdot}NH{\cdot}COR){\cdot}CO_2Et$ (IX) $CN{\cdot}C(:CH{\cdot}OEt){\cdot}CO{\cdot}NHMe$ (X) $CN{\cdot}C(:CH{\cdot}NHMe){\cdot}CO_2Et$ (XI)

Models of the two forms of (V) showed that, in one, close approach of the NH group and the ethereal oxygen occurred, leading possibly to considerable internal hydrogen bonding; however, the formation of the monoacylamine (X) from such compounds seemed unlikely. The formation of the esters (IX) appears to be more complex but would be possible by the reaction sequence: $CN{\cdot}CH_2{\cdot}CO_2H \longrightarrow CN{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}COMe \longrightarrow CN{\cdot}C(:CH{\cdot}OEt){\cdot}CO{\cdot}O{\cdot}COMe \longrightarrow CN{\cdot}C(:CH{\cdot}O{\cdot}COMe){\cdot}CO_2Et \longrightarrow$ (IX). Several analogues of (IX), notably acetamidomethylenemalononitrile (Passalacqua, *Gazzetta*, 1913, **43**, II, 566) and ethyl acetamido(and benzamido)-methyleneacetoacetate (Claisen, *Annalen*, 1897, **297**, 31), have been prepared by heating the appropriate ethoxymethylene derivative with an amide.

The compounds (IX; R = Me, Ph, and OEt) were accordingly synthesised by heating at 140—150° equimolar quantities of ethyl α-cyano-α-ethoxyacrylate and the appropriate amide; they were identical with the above-mentioned "isomers"; similarly, the amino-ester (XI) was prepared from methylamine and the cyano-ester and was identical with the compound $C_7H_{10}O_2N_2$ mentioned previously.

Experimental

Hydrogenations were carried out at room temperature and atmospheric pressure; the recorded volumes of hydrogen refer to N.T.P.

N-*Acetyl-α-benzoylacetamide* (Shaw and Sugowdz, *loc. cit.*).—5-Acetamido-3-phenyl*iso*oxazole (*idem, loc. cit.*) (5 g.) in ethanol (250 ml.) was hydrogenated over Adams platinum catalyst until 1 mol. of hydrogen had been absorbed (1 hr.); the solution was filtered and warmed for a few minutes with 5N-hydrochloric acid (10 ml.). The solution was neutralised with aqueous ammonia, then evaporated to a small volume, cooled, filtered, and acidified with hydrochloric acid; *N*-acetyl-α-benzoylacetamide (2 g.) separated and, recrystallised from aqueous ethanol, had m. p. and mixed m. p. 104°. *N*-Benzoyl-α-benzoylamide was similarly prepared from 5-benzamido-3-phenyl*iso*oxazole.

Nitrosation of Benzoylacetamides.—To a cold solution of *N*-acetyl-α-benzoylacetamide (1 g.) in acetic acid (5 ml.) was added, dropwise and with shaking, a solution of sodium nitrite (0·5 g.) in water (5 ml.); a crystalline precipitate rapidly appeared; N-*acetyl-α-benzoyl-α-hydroxyimino-acetamide monohydrate* (0·8 g.) separated from ethanol as needles, m. p. 150° (decomp.) (Found: C, 52·6; H, 4·8; N, 11·4. $C_{11}H_{10}O_4N_2,H_2O$ requires C, 52·4; H, 4·8; N, 11·1%). The N-*benzoyl* derivative was similarly obtained as needles (from ethanol), m. p. 164° (decomp.) (Found: C, 64·65; H, 4·0; N, 9·25. $C_{16}H_{12}O_4N_2$ requires C, 64·85; H, 4·1; N, 9·5%).

Hydrogenation of N: *α-Dibenzoyl-α-hydroxyiminoacetamide.*—A suspension of the hydroxyimino-compound (0·5 g.) in ethanol (25 ml.) was hydrogenated over Adams platinum catalyst; hydrogen (85 ml. Calc. for 2 mol., 76 ml.) was absorbed during 1 hr. The filtered solution was evaporated *in vacuo*. The residue crystallised when stirred with a little water. *α-Amino*-N: *α-dibenzoylacetamide* (0·35 g.) separated from ethanol as prisms, m. p. 240—242° (Found: C, 67·15; H, 4·6; N, 9·85. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0; N, 9·9%). The amine (0·25 g.) was warmed with N-sodium hydroxide (5 ml.) for 10 min. Acidification of the clear solution precipitated *5-benzoyl-4: 5-dihydro-4-oxo-2-phenylglyoxaline* (0·2 g.) which separated from ethanol as prisms, m. p. >300° (Found: C, 72·4; H, 4·8; N, 10·9. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·5; N, 10·6%).

NN′-*Diacetylmalonamide.*—Malonic acid (50 g.), acetamide (60 g.), and acetic anhydride (200 g.) were heated on a water-bath for 4 hr., giving a dark-brown fluorescent solution which was cooled and filtered from a small amount of dark material, and the filtrate added to carbon tetrachloride (1 l.). A dark oil was precipitated which soon crystallised. It was filtered off and recrystallised three times from ethanol (charcoal) to give NN′-*diacetylmalonamide* (22 g.) as colourless needles, m. p. 138° (Found: C, 45·45; H, 5·5; N, 14·8. $C_7H_{10}O_4N_2$ requires C, 45·15; H, 5·4; N, 15·05%).

NN'-*Diacetyl-α-hydroxyiminomalonamide.*—*NN'*-Diacetylmalonamide (5 g.) was dissolved in warm water (40 ml.) containing sodium nitrite (1·85 g.); the solution was cooled to 5—10° (the amide occasionally crystallises out but generally there is little difficulty in obtaining a supersaturated solution) and 2N-hydrochloric acid (15 ml.) added dropwise with shaking; the *hydroxyimino-derivative* (5·5 g.) separated rapidly and recrystallised from methanol–water as needles, m. p. 190° (decomp.) (Found: C, 36·4; H, 4·75; N, 18·2. $C_7H_9O_5N_3,H_2O$ requires C, 36·05; H, 4·75; N, 18·05%). The compound gave a yellow solution with aqueous ammonia and a solution in aqueous sodium hydroxide gave a deep blue colour with ferrous sulphate.

Hydrogenation of NN'-*Diacetyl-α-hydroxyiminomalonamide.*—A suspension of the finely ground imino-compound (1 g.) in ethanol (30 ml.) was hydrogenated over Adams platinum catalyst; hydrogen (205 ml. Calc. for 2 mols., 192 ml.) was absorbed during 1 hr.; a crystalline precipitate remained, soluble in aqueous sodium hydroxide and in hydrochloric acid. The base crystallised from an excess of water to give 5-N-*acetylcarbamoyl*-4 : 5-*dihydro*-2-*methyl*-4-*oxoglyoxaline* (0·75 g.) as colourless diamond-shaped plates, m. p. >300° (decomp. from 250°, and some sublimation) (Found: C, 45·6; H, 4·75; N, 23·15. $C_7H_9O_3N_3$ requires C, 45·9; H, 4·95; N, 22·95%), soluble in dilute sodium hydroxide solution and insoluble in hydrochloric acid. Light absorption in 0·02% aqueous sodium carbonate: $\lambda_{max.}$ 2300 (infl.) (ε 4600) and 3140 Å (ε 16,700). The compound gave an orange-yellow dye with diazotised sulphanilic acid. A solution of the glyoxaline (0·5 g.) in N-sodium hydroxide (5 ml.) was boiled for 2 min.; the cooled solution was acidified to precipitate 5-*carbamoyl*-4 : 5-*dihydro*-2-*methyl*-4-*oxoglyoxaline* (0·35 g.) which crystallised from water as diamond-shaped plates, m. p. >300° (decomp. from 280°) (Found: C, 42·85; H, 5·0; N, 29·85. $C_5H_7O_2N_3$ requires C, 42·55; H, 4·95; N, 29·8%).

N-*Acetyl-α-cyanoacetamide.*—Cyanoacetic acid (17 g.), acetamide (11·8 g.), and acetic anhydride (37 ml.) were heated on a water-bath for 3 hr. Cooling gave a crystalline precipitate; N-*acetyl-α-cyanoacetamide* (8 g.) separated from ethanol (charcoal) as colourless plates, m. p. 156° (Found: C, 47·5; H, 5·0; N, 22·35. $C_5H_6O_2N_2$ requires C, 47·6; H, 4·8; N, 22·2%); evaporation of the acetic acid solution and crystallisation of the residue gave a further quantity (5 g.) of the amide. A solution of the amide (1·26 g.) in ethanol (10 ml.) containing aniline (0·93 g.) was boiled for ½ hr.; water was added to the cooled solution to precipitate cyanoacetanilide (0·45 g.), m. p. and mixed m. p. 198°.

N-*Acetyl-α-cyano-α-hydroxyiminoacetamide.*—A solution of *N*-acetyl-α-cyanoacetamide (2·52 g.) in warm water (50 ml.) containing sodium nitrite (1·4 g.) was cooled to 5—10° and to the supersaturated solution was added 2·5N-hydrochloric acid (8 ml.) dropwise with shaking and cooling. The *hydroxyimino-compound* (2·3 g.) separated rapidly, and recrystallised from ethanol–water (1 : 1) as nacreous plates, m. p. 207° (decomp.) (Found: C, 34·45; H, 4·05; N, 24·25. $C_5H_5O_3N_3,H_2O$ requires C, 34·7; H, 4·1; N, 24·25%); the compound gave colour reactions similar to those of the analogous malonyl compound.

Hydrogenation. A solution of the amide (1 g.) in ethanol (40 ml.) was reduced over platinum, hydrogen (265 ml. Calc. for 2 mols., 259 ml.) being absorbed during 5 hr. The filtered solution was evaporated to dryness *in vacuo* to give a pale yellow solid which was washed with ether; 5-*cyano*-1 : 5-*dihydro*-2-*methyl*-4-*oxoglyoxaline* (0·7 g.) crystallised from methanol as colourless laths, m. p. >300° (decomp. from 180° and sublimation) (Found: C, 48·5; H, 4·1; N, 33·9. $C_5H_5ON_3$ requires C, 48·75; H, 4·1; N, 34·15%), and formed a yellow dye with diazotised sulphanilic acid. The glyoxaline darkened when kept at room temperature for several days.

α-*Cyano*-β-*ethoxy*-N-*ethoxycarbonylacrylamide.*—*N*-Cyanoacetylurethane (Conrad and Schulze, *loc. cit.*) (3·12 g.), ethyl orthoformate (2·96 g.), and acetic anhydride (5 ml.) were boiled under reflux for 1 hr.; the crystalline *product* separated on cooling, was washed with light petroleum, and crystallised from benzene as needles (3·2 g.), m. p. 120° (Found: C, 50·8; H, 5·55; N, 13·45. $C_9H_{12}O_4N_2$ requires C, 50·95; H, 5·7; N, 13·2%).

β-*Anilino*-α-*cyano*-N-*ethoxycarbonylacrylamide.*—To a solution of the foregoing amide (0·2 g.) in ethanol (5 ml.) were added 2 or 3 drops of aniline; the *anilino-compound* crystallised almost immediately and separated from ethanol as prisms (0·2 g.), m. p. 167—170° (decomp.; resolidified and then had m. p. 290°) (Found: C, 60·35; H, 5·05; N, 16·45. $C_{13}H_{13}O_3N_3$ requires C, 60·2; H, 5·05; N, 16·2%).

5-*Cyano*-1 : 2 : 3 : 4-*tetrahydro*-2 : 4-*dioxo*-1-*phenylpyrimidine.*—The anilino-amide (0·1 g.) was kept at 200° (bath) for 2—3 min. It melted, effervesced, and resolidified. The solid residual *dione* separated from ethanol as plates, m. p. 290° (Found: C, 61·8; H, 3·3; N, 19·7. $C_{11}H_7O_2N_3$ requires C, 61·95; H, 3·3; N, 19·7%). Light absorption in 0·04% aqueous sodium carbonate: $\lambda_{max.}$ 2320 (ε 9650) and 2815 Å (ε 9750).

α-Cyano-N-ethoxycarbonyl-β-phenylhydrazinoacrylamide.—A solution of the ethoxyacrylamide (1 g.) in ethanol (5 ml.) was treated with phenylhydrazine (0·5 g.), giving gradually a crystalline precipitate; the yellow solid was collected and washed with ether which removed the colour; the *phenylhydrazino-urethane* (0·65 g.) separated from ethanol or benzene as colourless plates, m. p. 128—129° (Found : C, 57·15; H, 5·1; N, 20·55. $C_{13}H_{14}O_3N_4$ requires C, 56·95; H, 5·15; N, 20·45%). The ethanolic solution with ether gave a further quantity of material (0·2 g.); addition of acid or alkali to the ethanolic solution gave a cherry-red colour.

1-Anilino-5-cyano-1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxopyrimidine.—The phenylhydrazinourethane (0·5 g.), when heated at 140—150° (bath) for 5 min., melted and then crystallised; the *pyrimidine* (0·4 g.) separated from water (*ca.* 150 ml.) as colourless needles, m. p. 334° (decomp.) (Found : C, 57·9; H, 3·55; N, 24·6. $C_{11}H_8O_2N_4$ requires C, 57·9; H, 3·55; N, 24·55%). Light absorption in 0·04% aqueous sodium carbonate : $\lambda_{max.}$ 2380 (ε 7600) and 2600 Å (infl.) (ε 900).

5-Cyanouracil.—The ethoxyacrylamide (1 g.) was treated with 1% aqueous ammonia (10 ml.). It dissolved in a few minutes to form a pale yellow solution, whence acetic acid, after a short time, precipitated 5-cyanouracil (0·6 g.), diamond-shaped plates (from ethanol), m. p. 280° (decomp.) (Found : C, 43·8; H, 2·3; N, 30·75. Calc. for $C_5H_3O_2N_3$: C, 43·8; H, 2·2; N, 30·65%); light absorption in 0·02% aqueous sodium carbonate : $\lambda_{max.}$ 2330 (ε 10,400) and 2900 Å (ε 11,400); the compound gave a purple precipitate when boiled with bromine water, then treated with barium hydroxide solution; Johnson (*Amer. Chem. J.*, 1909, **42**, 513) gives m. p. 295° (decomp.). The compound was formed in similar yield when more concentrated ammonia was used.

The compound (0·5 g.) was boiled with 50% sulphuric acid (5 ml.) for 1 hr., then was cooled, diluted with water (10 ml.), and set aside. Uracil-5-carboxylic acid monohydrate (0·35 g.) crystallised and separated from water as prisms, m. p. 285° (decomp.) (Found : C, 34·9; H, 3·6; N, 16·2. Calc. for $C_5H_4O_4N_2,H_2O$: C, 34·5; H, 3·45; N, 16·1%); Ballard and Johnson (*J. Amer. Chem. Soc.*, 1942, **64**, 794) give, for the monhydrate, m. p. 268—270° (effervescence). The acid (0·5 g.) was kept at 280° (bath) for a few minutes; carbon dioxide was evolved (barium hydroxide solution) and the residue, uracil, separated from water as prisms (0·3 g.), m. p. and mixed m. p. 320° (decomp.) (Found : C, 42·7; H, 3·55; N, 24·85. Calc. for $C_4H_4O_2N_2$: C, 42·85; H, 3·6; N, 25·0%).

5-Cyano-1-methyluracil.—The ethoxyacrylamide (1 g.) dissolved readily in warm aqueous methylamine (5 ml.; 28%) to give a pale yellow solution; this was boiled to remove excess of methylamine, cooled, and acidified with acetic acid. The colourless precipitate of *5-cyano-1-methyluracil* (0·7 g.) crystallised from ethanol (*ca.* 50 ml.) as needles, m. p. 256° (Found : C, 47·85; H, 3·25; N, 27·95. $C_6H_5O_2N_3$ requires C, 47·7; H, 3·35; N, 27·8%). The same compound was formed in slightly better yield when dilute aqueous methylamine was used.

N-Acetyl-α-cyano-β-ethoxyacrylamide.—A solution of *N*-acetyl-α-cyanoacetamide (3·1 g.), ethyl orthoformate (3·6 g.), and acetic anhydride (5 g.) was boiled under reflux for 1 hr. The pale brown solution was evaporated to a small volume *in vacuo* and cooled. The crystalline precipitate of the *acrylamide* (2·8 g.) separated from benzene or benzene–light petroleum as needles, m. p. 109° (Found : C, 52·65; H, 5·7; N, 15·5. $C_8H_{10}O_3N_2$ requires C, 52·75; H, 5·55; N, 15·4%).

The amide (0·5 g.) was boiled with N-sodium hydroxide (10 ml.) for 10 min.; a clear solution was soon obtained and ammonia was liberated. The solution was acidified with hydrochloric acid, carbon dioxide being evolved (barium hydroxide solution), then treated with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid to give a yellow precipitate of cyanoacetaldehyde 2 : 4-dinitrophenylhydrazone, needles (from ethanol), m. p. 170—171° (Found : C, 43·1; H, 2·75; N, 28·45. Calc. for $C_9H_7O_4N_5$: C, 43·4; H, 2·85; N, 28·1%).

N-Acetyl-β-anilino-α-cyanoacrylamide.—To a solution of the foregoing amide (1 g.) in ethanol (10 ml.) was added aniline (1 ml.); after a few seconds crystals of the *anilino-compound* separated; this crystallised from methanol as needles (1 g.), m. p. 202—204° (decomp.) (Found : C, 62·65; H, 4·75; N, 18·4. $C_{12}H_{11}O_2N_3$ requires C, 62·85; H, 4·85; N, 18·3%). A mixture of the amide (0·6 g.), ethanol (5 ml.), and 2N-sodium hydroxide (2 ml.) was boiled for 5 min.; the clear solution so obtained was diluted with water (5 ml.), and acidified with acetic acid to give a crystalline precipitate of *β-anilino-α-cyanoacrylamide* (0·3 g.), needles (from ethanol–water), m. p. 209—210° (Found : C, 63·65; H, 4·85; N, 22·35. $C_{10}H_9ON_3$ requires C, 64·15; H, 4·85; N, 22·45%).

N-Acetyl-α-cyano-β-phenylhydrazinoacrylamide.—A solution of *N*-acetyl-α-cyano-5-ethoxyacrylamide (0·18 g.) in methanol (2 ml.), when treated with phenylhydrazine (0·11 g.), deposited crystals after a few minutes; the filtrate gave cherry-red colours with acid or alkali. The

β-*phenylhydrazino-compound* (0·1 g.) separated from methanol as needles, m. p. 212° (decomp.) (Found: C, 58·9; H, 4·9; N, 23·0. $C_{12}H_{12}O_2N_4$ requires C, 59·0; H, 4·95; N, 22·95%).

Reaction of N-*Acetyl-α-cyano-β-ethoxyacrylamide with Ammonia.*—The ethoxy-amide (0·2 g.) was treated with 1% ammonia solution (5 ml.); the amide soon dissolved and the clear yellow solution was acidified with acetic acid and set aside. *5-Cyano-1:4-dihydro-2-methyl-4-oxopyrimidine* (0·1 g.) separated from ethanol–water as needles, m. p. 235° (decomp.) (Found: C, 53·3; H, 3·4; N, 31·1. Calc. for $C_6H_5ON_3$: C, 53·35; H, 3·7; N, 31·1%). Light absorption in 0·02% aqueous sodium carbonate: $\lambda_{max.}$ 2340 (ε 7700) and 2920 Å (ε 5900). Todd and Bergel (*loc. cit.*) give m. p. 233—235°.

N-(*Cyanoacetyl*)*benzamide.*—Cyanoacetic acid (14·8 g.), benzamide (21 g.), and acetic anhydride (23 ml.) were heated on a water-bath for 1½ hr. A brown solution was obtained which when cooled gave a crystalline precipitate which was filtered off and washed with ether; N-(*cyanoacetyl*)*benzamide* (7 g.) separated from ethanol (charcoal) as needles, m. p. 184° (Found: C, 63·6; H, 4·15; N, 14·75. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%).

N-*Benzoyl-α-cyano-α-hydroxyiminoacetamide.*—*N*-(Cyanoacetyl)benzamide (5 g.) was dissolved in warm acetic acid (100 ml.); the solution was cooled (the amide may crystallise but generally remains in solution) and to it was added, rapidly with shaking and cooling, a solution of sodium nitrite (1·8 g.) in water (5 ml.); a crystalline solid rapidly precipitated and was filtered off and washed with ether. The *hydroxyimino-compound* (3·9 g.) separated from ethanol as prisms, m. p. 205° (decomp.) (Found: C, 55·5; H, 3·2; N, 19·55. $C_{10}H_7O_3N_3$ requires C, 55·3; H, 3·25; N, 19·35%); a further quantity (0·9 g.) separated from the mother-liquors overnight.

Hydrogenation. A suspension of the foregoing amide (1 g.) in ethanol was hydrogenated over Adams platinum catalyst; hydrogen (201 ml. Calc. for 2 mols., 207 ml.) was absorbed during 4 hr. The solution was evaporated to dryness *in vacuo* and the solid *α-amino*-N-*benzoyl-α-cyanoacetamide* (0·6 g.) crystallised from ethanol as hexagonal prisms, m. p. >300° (decomp. from *ca.* 220°) (Found: C, 58·95; H, 4·3; N, 20·9. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·45; N, 20·7%). The amine (0·25 g.) was dissolved in N-sodium hydroxide (5 ml.) and kept at room temperature for 30 min.; the solution was acidified and the precipitate collected; *5-cyano-4:5-dihydro-4-oxo-2-phenylglyoxaline* (0·1 g.) separated from water as needles, m. p. >300° (Found: C, 64·65; H, 3·8; N, 22·9. $C_{10}H_7ON_3$ requires C, 64·85; H, 3·8; N, 22·7%).

NN′-*Dibenzoylmalonamide.*—Malonic acid (10 g.), benzamide (24 g.), and acetic anhydride (40 ml.) were heated on a water-bath for 3 hr. On cooling, a crystalline precipitate was obtained; this was filtered off and washed with ethanol and ether; NN′-*dibenzoylmalonamide* (14 g.) finally crystallised from ethanol as needles, m. p. 179—181° (Found: C, 65·65; H, 4·5; N, 9·05. $C_{17}H_{14}O_4N_2$ requires C, 65·8; H, 4·55; N, 9·05%).

NN′-*Dibenzoyl-α-hydroxyiminomalonamide.*—Treating a solution of *NN′*-dibenzoylmalonamide (3·1 g.) in acetic acid (100 ml.) with sodium nitrite (0·7 g.) in water (5 ml.) gave an almost immediate precipitate; an equal volume of water was added and the solid filtered off; NN′-*dibenzoyl-α-hydroxyiminomalonamide* (2·7 g.) separated from ethanol (*ca.* 200 ml.) as laths, m. p. 180° (effervescence) (Found: C, 60·2; H, 3·8; N, 12·3. $C_{17}H_{13}O_5N_3$ requires C, 60·15; H, 3·85; N, 12·4%).

Hydrogenation. The compound (1 g.) in ethanol (50 ml.) with Adams platinum catalyst absorbed hydrogen (130 ml. Calc. for 2 mols., 132 ml.) during 1 hr.; a solid precipitate remained and was crystallised from an excess of water; *α-amino*-NN′-*dibenzoylmalonamide* (0·65 g.) was obtained as laths, m. p. 205° (decomp.) (Found: C, 62·95; H, 4·55; N, 13·15. $C_{17}H_{15}O_4N_3$ requires C, 62·75; H, 4·65; N, 12·9%). The amino-compound (0·5 g.) was boiled with N-sodium hydroxide (10 ml.) for 2 min.; the cooled solution was acidified with acetic acid to precipitate 5-N-*benzoylcarbamoyl-4:5-dihydro-4-oxo-2-phenylglyoxaline* which separated from acetic acid as needles, m. p. >300° (0·35 g.) (Found: C, 65·3; H, 4·1; N, 14·05. $C_{17}H_{13}O_3N_3$ requires C, 66·1; H, 4·25; N, 13·7%).

Bromination of N-(*Cyanoacetyl*)*benzamide.*—To a solution of *N*-(cyanoacetyl)benzamide (1·88 g.) in warm acetic acid (50 ml.) was added bromine (1·6 g.); the halogen was rapidly absorbed and hydrogen bromide was freely evolved. The solution was cooled, and water (200 ml.) added until the solution was opalescent; when this was kept overnight a colourless solid separated; the *dibromo-compound* (1·3 g.) crystallised from ethanol as prisms, m. p. 140° (Found: C, 34·0; H, 2·25; N, 8·0. $C_{10}H_6O_2N_2Br_2$ requires C, 34·6; H, 1·7; N, 8·1%).

N-*Benzoyl-α-cyano-β-ethoxyacrylamide.*—*N*-(Cyanoacetyl)benzamide (6·9 g.), ethyl orthoformate (5·7 g.), and acetic anhydride (8 g.) were boiled under reflux for 1 hr.; the crystals which separated on cooling were filtered off and washed with a little ethanol; the *ethoxy-compound*

(5 g.) crystallised from ethanol as needles, m. p. 143° (Found: C, 63·25; H, 4·7; N, 11·55. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 4·95; N, 11·45%). Hydrolysis of the amide with N-sodium hydroxide gave ammonia, carbon dioxide, benzoic acid, and cyanoacetaldehyde (2 : 4-dinitrophenylhydrazone).

β-Anilino-N-benzoyl-α-cyanoacetamide.—To a solution of the ethoxy-amide (0·2 g.) in warm ethanol (5 ml.) was added aniline (1 or 2 drops). Cooling gave the crystalline *anilino-amide* (0·15 g.) which separated from ethanol as needles, m. p. 180° (Found: C, 69·9; H, 4·35; N, 14·45. $C_{17}H_{13}O_2N_3$ requires C, 70·1; H, 4·5; N, 14·45%).

N-Benzoyl-α-cyano-β-phenylhydrazinoacrylamide.—The ethoxy-amide (0·5 g.) and phenylhydrazine (0·3 g.) in warm ethanol (5 ml.) gave an orange-yellow solution which when cooled soon gave the crystalline *phenylhydrazino-amide* (0·25 g.) which separated from ethanol as needles, m. p. 155° (Found: C, 66·3; H, 4·6; N, 18·25. $C_{17}H_{14}O_2N_4$ requires C, 66·65; H, 4·6; N, 18·3%).

5-Cyano-1 : 2 : 3 : 4-tetrahydro-4-oxo-2-phenylpyrimidine.—*N*-Benzoyl-α-cyano-β-ethoxyacrylamide (0·5 g.) was treated with 1% aqueous ammonia (20 ml.); the amide soon dissolved when the suspension was shaken and set aside for a short time; acidification with acetic acid then precipitated the *phenylpyrimidine* (0·35 g.) which crystallised from ethanol as needles, m. p. 295—297° (Found: C, 66·4; H, 3·4; N, 21·1. Calc. for $C_{11}H_7ON_3$: C, 67·0; H, 3·6; N, 21·3%); Mitter and Palit (*J. Indian Chem. Soc.*, 1925, **2**, 61) give m. p. 295°.

Reaction of Cyanoacetic acid, Ethyl Orthoformate, Acetic Anhydride, and Amides.—(*a*) Cyanoacetic acid (8·5 g.), acetamide (6·1 g.), ethyl orthoformate (16·5 ml.), and acetic anhydride (40 g.) were boiled under reflux for 1 hr. The clear pale brown solution was evaporated to a small volume *in vacuo* to give a syrup which soon crystallised; *ethyl acetamidomethylenecyanoacetate* (5·6 g.) separated from light petroleum as needles, m. p. 95—96° (Found: C, 52·8; H, 5·3; N, 15·5%); hydrolysis with N-sodium hydroxide gave ammonia, carbon dioxide, and cyanoacetaldehyde. The ester (1 g.) was boiled with aqueous methylamine (10 ml.; 25%) for 10 min.; the solution was cooled and the solid collected; *ethyl α-cyano-N-methylaminomethyleneacetate* (0·6 g.) separated from water as plates or needles, m. p. 75° (Found: C, 54·6; H, 6·45; N, 18·3. $C_7H_{10}O_2N_2$ requires C, 54·55; H, 6·5; N, 18·1%).

(*b*) Cyanoacetic acid (8·5 g.), urethane (8·9 g.), ethyl orthoformate (16·5 ml.), and acetic anhydride (40 g.) were boiled together under reflux and the solution evaporated to a syrup *in vacuo*; this was stirred with cold water (100 ml.) to give a crystalline residue admixed with oil; the solid was readily separated by filtration; *ethyl α-cyano-N-ethoxycarbonylaminomethyleneacetate* (4·5 g.) crystallised from water as needles, m. p. 114—115° (Found: C, 51·3; H, 5·75; N, 13·4%); treatment of this compound with N-sodium hydroxide and with methylamine gave the same results as in the preceding experiment.

(*c*) Cyanoacetic acid (8·5 g.), benzamide (12·1 g.), ethyl orthoformate (16·5 ml.), and acetic anhydride (40 g.) similarly gave *ethyl benzamidomethylenecyanoacetate* (8 g.) which crystallised from ethanol as laths, m. p. 113—114° (Found: C, 64·1; H, 4·75; N, 11·6%); hydrolysis with N-sodium hydroxide gave ammonia, carbon dioxide, cyanoacetaldehyde, and benzoic acid, and treatment of the ester with methylamine gave the same result as recorded in (*a*) and (*b*). The ester (0·5 g.) slowly dissolved in concentrated aqueous ammonia; the solution eventually deposited benzamide, m. p. and mixed m. p. 120°.

Reaction of Ethyl α-Cyano-α-ethoxymethyleneacetate with Amides.—This ester (0·24 g.) and acetamide (0·1 g.) were heated at 140—150° (bath) for 30 min. to give a clear pale brown melt which crystallised when cooled; ethyl acetamidomethylenecyanoacetate (0·15 g.) separated from ethanol–water as needles, m. p. 95° not depressed with the compound prepared as above. Analogous compounds were obtained when acetamide was substituted for benzamide or urethane and the compounds so obtained did not depress the m. p.s of the corresponding substances prepared as above.

Reaction of Ethyl α-Cyano-α-ethoxymethyleneacetate with Methylamine.—The ester (1 g.) was treated with aqueous methylamine (5 ml.; 28%); a clear solution was rapidly obtained which deposited ethyl α-cyano-*N*-methylaminomethyleneacetate (0·8 g.) which separated from water as plates or needles, m. p. 75°, and the m. p. was not depressed when admixed with the compound prepared as above.

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UNIVERSITY OF TECHNOLOGY, SYDNEY, N.S.W., AUSTRALIA. [*Received, January 19th*, 1955.]