572. *Pyrazine Derivatives. Part XI. Synthesis of Cyclic Hydroxamic Acids Related to Aspergillic Acid.*

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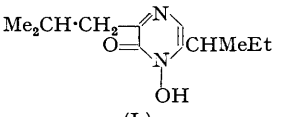
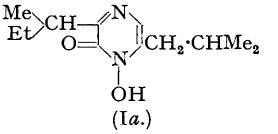
It is shown that condensation of α-amino-hydroxamic acids with 1 : 2-dicarbonyl compounds yields pyrazine cyclic hydroxamic acids. Using methylglyoxal and phenylglyoxal as the 1 : 2-dicarbonyl component, the reaction leads to unsymmetrically (3 : 5-)substituted pyrazine cyclic hydroxamic acids (VI).

Treatment of α-amino-hydroxamic acids with 2-bromocinnamaldehyde gives the corresponding Schiff's bases (X) in good yield. Treatment of the compounds (X) with alkali-metal alkoxides yields the symmetrically (3 : 6-)substituted pyrazine cyclic hydroxamic acids (XI). The last series of reactions offers a feasible route to the synthesis of aspergillic acid (I) or (I*a*).

Aspergillic acid is a pyrazine cyclic hydroxamic acid of structure (I) or (I*a*) (Dunn, Gallagher, Newbold, and Spring, this vol., p. S 126; Dunn, Newbold and Spring, *ibid.*, p. S 131). Although

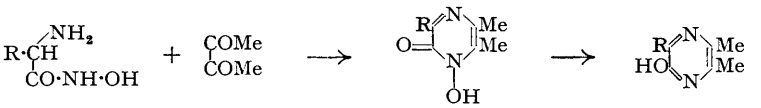


(I.)



(I*a*.)

various methods for the synthesis of hydroxy- and ethoxy-pyrazines have been described in previous Parts of this series, repeated attempts to synthesise a pyrazine cyclic hydroxamic acid have been unsuccessful. A general method for the synthesis of pyridine cyclic hydroxamic acids was described by Newbold and Spring (J., 1948, 1864; Cunningham, Newbold, Spring, and Stark, this vol., p. 2091) in which a 2-ethoxypyridine is peroxidised to yield a 2-ethoxypyridine 1-oxide, hydrolysis of which with dilute mineral acid gives the pyridine cyclic hydroxamic acid. This method was successfully extended to the synthesis of quinoline cyclic hydroxamic acids, but failed when applied to 3-ethoxy-2 : 5-dimethylpyrazine or 2-ethoxyquinoxaline (Newbold and Spring, *J.*, 1948, 519; Baxter, Newbold, and Spring, *J.*, 1948, 1859). For the last two compounds peroxidation occurs at the nitrogen remote from the ethoxy-group; the opinion was expressed that the synthesis of a pyrazine cyclic hydroxamic acid by the direct oxidation of a pyrazine derivative is impracticable. Methods for the synthesis of pyrazine cyclic hydroxamic acids have



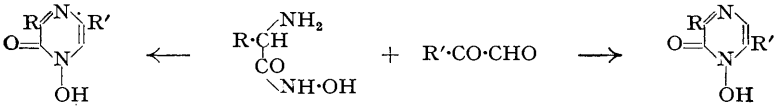
(II.) (III.) (IV.)

now been developed in which use is made of the readily available α-amino-hydroxamic acids prepared by the action of hydroxylamine on α-amino-esters (Cunningham, Newbold, Spring and Stark, *loc. cit.*).

In the first synthesis the α-amino-hydroxamic acids are condensed with 1 : 2-dicarbonyl compounds using the conditions employed by Jones (*J. Amer. Chem. Soc.*, 1949, **71**, 78) for the synthesis of hydroxypyrazines from α-amino-acid amides and 1 : 2-dicarbonyl compounds. Treatment of DL-alanine hydroxamic acid (II; R = Me) with diacetyl gives the cyclic hydroxamic acid 1-*hydroxy*-2-*keto*-3 : 5 : 6-*trimethyl*-1 : 2-*dihydropyrazine* (III; R = Me), which gives a positive ferric chloride reaction and shows the typical properties of a cyclic hydroxamic acid. In particular, it was characterised by reduction with hydrazine which gave 2-hydroxy-3 : 5 : 6-trimethylpyrazine (IV; R = Me) identical with a specimen prepared by an independent method (Newbold and Spring, *J.*, 1947, 373). In a similar manner DL-*phenylglycine hydroxamic acid* (II; R = Ph) was condensed with diacetyl to yield 1-*hydroxy*-2-*keto*-3-*phenyl*-5 : 6-*dimethyl*-1 : 2-*dihydropyrazine* (III; R = Ph) which is soluble with effervescence in sodium hydrogen carbonate solution. When reduced with hydrazine this cyclic hydroxamic acid yields 2-hydroxy-3-phenyl-5 : 6-dimethylpyrazine (IV; R = Ph) identical with a specimen prepared by the condensation of DL-phenylglycine amide with diacetyl (Jones, *loc. cit.*).

The application of the method described above to the synthesis of aspergillic acid will involve the condensation of an α-amino-hydroxamic acid with a keto-aldehyde. In such a case con-

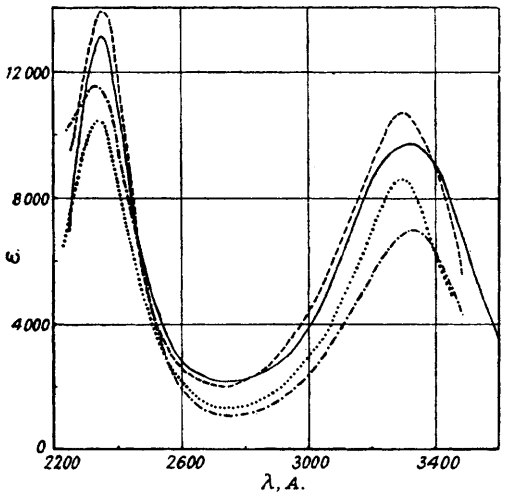
densation may occur in one or both of two directions. Thus, condensation of DL-alanine hydroxamic acid (II; R = Me) with methylglyoxal (V; R′ = Me) might give 1-hydroxy-2-keto-3 : 5- (VI; R = R′ = Me) or -3 : 6-dimethyl-1 : 2-dihydropyrazine (VII; R = R′ = Me), or a mixture of both. Condensation in the latter sense would be required in a synthesis of



(VI.) (II.) (V.) (VII.)

aspergillic acid. In the synthesis of hydroxypyrazines by the interaction of α-amino-acid amides and 1 : 2-keto-aldehydes (Jones, *loc. cit.*) condensation occurs exclusively in the unsymmetrical sense to yield 3 : 5-disubstituted 2-hydroxypyrazines. Our experience with

Absorption spectra, in ethanol.



———— 1-*Hydroxy*-2-*keto*-6-*benzyl*-1 : 2-*dihydropyrazine*.
· · · · · · · · *Aspergillic acid*.
— . — . — 1-*Hydroxy*-2-*keto*-3 : 5 : 6-*trimethyl*-1 : 2-*dihydropyrazine*.
— — — — 1-*Hydroxy*-2-*keto*-6-*benzyl*-3-*ethyl*-1 : 2-*dihydropyrazine*.

α-amino-hydroxamic acids and 1 : 2-keto-aldehydes was similar. Condensation of DL-alanine hydroxamic acid and methylglyoxal gives exclusively 1-*hydroxy*-2-*keto*-3 : 5-*dimethyl*-1 : 2-*dihydropyrazine* (VI; R = R′ = Me), a rigorous examination of the reaction mixture failing to disclose the presence of any of the isomeric acid (VII; R = R′ = Me). The structure of the reaction product was established by its reduction to 2-hydroxy-3 : 5-dimethylpyrazine which differs considerably from 3-hydroxy-2 : 5-dimethylpyrazine and is identical with the product obtained by the condensation of DL-alanine amide and methylglyoxal.

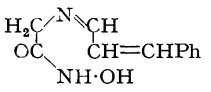
In a similar manner, condensation of DL-phenylglycine hydroxamic acid (II; R = Ph) with phenylglyoxal (V; R = Ph) yields 1-*hydroxy*-2-*keto*-3 : 5-*diphenyl*-1 : 2-*dihydropyrazine* (VI; R = R′ = Ph), the structure of which was established by its reduction to a hydroxy-diphenylpyrazine which is not identical with 3-hydroxy-2 : 5-diphenylpyrazine (Gallagher, Newbold, Spring, and Woods, this vol., p. 910) but is identical with 2-*hydroxy*-3 : 5-*diphenylpyrazine* obtained by the condensation of DL-phenylglycine amide with phenylglyoxal.

Two other cases of the reaction were examined and, although the structures of the resulting pyrazine cyclic hydroxamic acids were not rigidly demonstrated, they are inferred by analogy with the cases described above. Condensation of DL-alanine hydroxamic acid (II; R = Me) with phenylglyoxal (V; R′ = Ph) gave a cyclic hydroxamic acid to which we ascribe the structure of 1-*hydroxy*-2-*keto*-5-*phenyl*-3-*methyl*-1 : 2-*dihydropyrazine* (VI; R = Me, R′ = Ph). When reduced with hydrazine it gives a hydroxy-methylphenylpyrazine identical with that obtained by the condensation of DL-alanine amide with phenylglyoxal and assumed to be 2-hydroxy-5-phenyl-3-methylpyrazine. The condensation of DL-alanine hydroxamic acid with

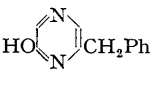
phenylglyoxal was examined using a variety of reaction conditions. Under alkaline, acid, or neutral reaction conditions, the product was 1-hydroxy-2-keto-5-phenyl-3-methyl-1 : 2-dihydropyrazine and in no case was the simultaneous formation of the isomeric acid (VII; R = Me, R′ = Ph) observed. Finally, although reaction of glycine hydroxamic acid with 1 : 2-dicarbonyl compounds did not proceed as smoothly as the condensations described above, when phenylglyoxal was used as the 1 : 2-dicarbonyl component, a small yield of a pyrazine cyclic hydroxamic acid was isolated to which we ascribe the structure 1-*hydroxy*-2-*keto*-5-*phenyl*-1 : 2-*dihydropyrazine* (VI; R = H, R′ = Ph).

The general method for the synthesis of pyrazine cyclic hydroxamic acids described above will not serve for a synthesis of aspergillic acid since it leads to the formation of unsymmetrically (3 : 5-)disubstituted acids exclusively. With the object of forcing condensation between an α-amino-hydroxamic acid (II) and a potential 1 : 2-keto-aldehyde (V) to give a 3 : 6-disubstituted 1-hydroxy-2-keto-1 : 2-dihydropyrazine (VII), a study has been made of the condensation of α-aminohydroxamic acids and αβ-unsaturated α-bromo-aldehydes. This has led to the elaboration of a method for the synthesis of 3 : 6-disubstituted pyrazine cyclic hydroxamic acids of the aspergillic acid type which has the advantage that it allows the introduction of dissimilar substituents at the 3 and 6 positions. In the first place, it was observed that glycine hydroxamic acid and cinnamaldehyde readily condense to give the Schiff's base *cinnamylideneglycine hydroxamic acid* (VIII). This is readily hydrolysed by dilute mineral acid with regeneration of cinnamaldehyde. When it is treated with Brady's reagent, the 2 : 4-dinitrophenylhydrazone of cinnamaldehyde is quickly precipitated. Under a variety of reaction conditions the Schiff's base was not cyclised to 2-hydroxy-6-benzylpyrazine (IX).

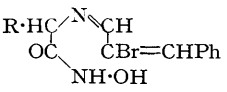
Glycine hydroxamic acid readily condenses with 2-bromocinnamaldehyde yielding 2-*bromocinnamylideneglycine hydroxamic acid* (X; R = H) in high yield. This is not soluble in aqueous sodium hydrogen carbonate but is soluble in caustic alkali solutions. It has been characterised by the formation of *di*- and *mono-benzoyl* derivatives, of which only the latter is soluble in alkali. Treatment of (X) with sodium ethoxide in alcohol gives the pyrazine cyclic hydroxamic acid, 1-*hydroxy*-2-*keto*-6-*benzyl*-1 : 2-*dihydropyrazine* (XI; R = H). Like aspergillic acid, this cyclic hydroxamic acid is soluble in sodium hydrogen carbonate solution with effervescence, sublimes readily, and yields a copper salt. Its ultra-violet absorption spectrum is similar to that of aspergillic acid.



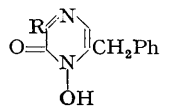
(VIII.)



(IX.)



(X.)



(XI.)

In a similar manner, condensation of α-*amino*-n-*butyrohydroxamic acid* with 2-bromocinnamaldehyde yields α-(2-*bromocinnamylideneamino*)-n-*butyrohydroxamic acid* (X; R = Et). The cyclisation of this Schiff's base proved to be more difficult than in the homologous case and the compound was recovered unchanged after treatment with sodium ethoxide in alcohol. Treatment with potassium *tert.*-butoxide in boiling *tert.*-butyl alcohol gave, in small yield, 1-*hydroxy*-2-*keto*-6-*benzyl*-3-*ethyl*-1 : 2-*dihydropyrazine* (XI; R = Et), which like the homologous acid (XI; R = H) shows the typical properties of a cyclic hydroxamic acid.

Experimental.

1-*Hydroxy*-2-*keto*-3 : 5 : 6-*trimethyl*-1 : 2-*dihydropyrazine* (III; R = Me).—A suspension of DL-alanine hydroxamic acid (3·0 g.; Cunningham, Newbold, Spring, and Stark, *loc. cit.*) in water (100 c.c.) and methanol (75 c.c.) was cooled to −60° and treated with a solution of diacetyl (2·9 g.) in methanol (15 c.c.) cooled to −30°, and then with aqueous sodium hydroxide (8 c.c.; 5N.) added dropwise with stirring during 5 minutes while the temperature was maintained below −30°. The reaction mixture was gradually heated to −10° during 1 hour, dissolution then being complete. After being kept overnight at 0° the solution was acidified to pH 3·0 with hydrochloric acid (*d* 1·19) and evaporated under reduced pressure. The residue was extracted with boiling chloroform (3 × 25 c.c.) and the dried (Na_2SO_4) extract evaporated. Sublimation of the residue at 130—140°/2 mm. gave a colourless, crystalline sublimate (1·2 g.), m. p. 159°. Crystallisation from acetone–methanol gave 1-*hydroxy*-2-*keto*-3 : 5 : 6-*trimethyl*-1 : 2-*dihydropyrazine* as prisms, m. p. 176—177° (Found: C, 54·3; H, 6·5; N, 18·5. $C_7H_{10}O_2N_2$ requires C, 54·5; H, 6·5; N, 18·2%). Light absorption in ethanol: Maxima at 2330 A., ε = 11,600, and 3340 A., ε = 7000. The hydroxamic acid gives a claret colour with ferric chloride and liberates carbon dioxide from aqueous sodium hydrogen carbonate. It is very soluble in water, ethanol, or pyridine, slightly so in benzene, acetone, chloroform, or dioxan, and insoluble in light petroleum.

2-*Hydroxy*-3 : 5 : 6-*trimethylpyrazine* (IV; R = Me).—A solution of 1-hydroxy-2-keto-3 : 5 : 6-trimethyl-1 : 2-dihydropyrazine (400 mg.) in methanol (2·5 c.c.) was treated with hydrazine hydrate

(1·0 g.; 90%) and heated at 180° for 4 hours. Removal of the methanol under reduced pressure, followed by sublimation of the solid (350 mg.) at 100°/10^{-1} mm., gave 2-hydroxy-3 : 5 : 6-trimethylpyrazine as needles, m. p. 197° alone or mixed with the specimen described by Newbold and Spring (*J.*, 1947, 373).

1-*Hydroxy*-2-*keto*-3 : 5-*dimethyl*-1 : 2-*dihydropyrazine* (VI; R = R′ = Me).—By the method described above, a solution of methylglyoxal (1·5 g.) in methanol (25 c.c.) was treated with DL-alanine hydroxamic acid (1·8 g.) in water (75 c.c.) and methanol (75 c.c.) in the presence of sodium hydroxide solution (6 c.c.; 5N.). After acidification to pH 3·0 the light-yellow solution was evaporated to dryness under reduced pressure, and the residue extracted with boiling chloroform (5 × 20 c.c.) and then with boiling methanol (2 × 25 c.c.). Evaporation of the extracts gave yellow prisms, m. p. 118—120° (1·2 g.), sublimation of which at 90°/10^{-5} mm. followed by crystallisation of the sublimate from acetone gave 1-*hydroxy*-2-*keto*-3 : 5-*dimethyl*-1 : 2-*dihydropyrazine* as colourless needles, m. p. 135° (Found: C, 51·4; H, 5·9; N, 20·3. $C_6H_8O_2N_2$ requires C, 51·4; H, 5·7; N, 20·0%). Light absorption in ethanol: Maxima at 2340 A., ε = 8000, and 3300 A., ε = 5400. The hydroxamic acid gives a claret colour with ferric chloride solution and liberates carbon dioxide from sodium hydrogen carbonate solution.

2-*Hydroxy*-3 : 5-*dimethylpyrazine*.—Treatment of 1-hydroxy-2-keto-3 : 5-dimethyl-1 : 2-dihydropyrazine (0·3 g.) with hydrazine as described above gave a product (0·13 g.) which was purified by sublimation at 140°/2 mm., followed by crystallisation from light petroleum (b. p. 60—80°) from which 2-hydroxy-3 : 5-dimethylpyrazine separated as prisms, m. p. 146—147° (Found: C, 58·2; H, 6·6; N, 22·4. Calc. for $C_6H_8ON_2$: C, 58·1; H, 6·45; N, 22·6%). Light absorption in ethanol: Maxima at 2280 A., ε = 5000, and 3270 A., ε = 4200. Jones (*J. Amer. Chem. Soc.*, 1949, **71**, 78) gives m. p. 145—146° for 2-hydroxy-3 : 5-dimethylpyrazine obtained by condensation of methylglyoxal and DL-alanine amide.

1-*Hydroxy*-2-*keto*-5-*phenyl*-3-*methyl*-1 : 2-*dihydropyrazine* (VI; R = Me, R′ = Ph).—A solution of DL-alanine hydroxamic acid (3·0 g.) in water (75 c.c.) and methanol (50 c.c.) was condensed with phenylglyoxal hydrate (5·1 g.) in methanol (35 c.c.) in the presence of sodium hydroxide solution (8 c.c.; 5 N.) as described above. Acidification of the reaction mixture to pH 3·0 with hydrochloric acid (*d* 1·19) gave a solid (3·6 g.; m. p. 183°) which was collected after cooling at 0° for 1 hour. After sublimation at 140°/10^{-4} mm., followed by crystallisation from aqueous methanol, 1-*hydroxy*-2-*keto*-5-*phenyl*-3-*methyl*-1 : 2-*dihydropyrazine* separated as needles, m. p. 185° (Found: C, 65·5; H, 5·2; N, 14·2. $C_{11}H_{10}O_2N_2$ requires C, 65·35; H, 4·95; N, 13·9%). Light absorption in ethanol: Maxima at 2810 A., ε = 17,500, and 3450 A., ε = 8800. The hydroxamic acid is soluble in sodium hydrogen carbonate solution with effervescence and gives a claret colour with aqueous ferric chloride.

2-*Hydroxy*-5-*phenyl*-3-*methylpyrazine*.—Treatment of 1-hydroxy-2-keto-5-phenyl-3-methyl-1 : 2-dihydropyrazine (0·5 g.) with methanolic hydrazine gave 2-hydroxy-5-phenyl-3-methylpyrazine (0·42 g.) which after sublimation at 140°/10^{-4} mm. and crystallisation from methanol formed needles, m. p. 222—223° (Found: C, 71·25; H, 5·7; N, 15·05. Calc. for $C_{11}H_{10}ON_2$: C, 71·0; H, 5·4; N, 15·05%). Light absorption in ethanol: Maxima at 2760 A., ε = 17,100, and 3400 A., ε = 6500. A specimen of 2-hydroxy-5-phenyl-3-methylpyrazine prepared as described by Jones (*loc. cit.*) was obtained as needles (from methanol), m. p. 222—223° alone or when mixed with that described above. Jones gives m. p. 212—213° for this compound.

1-*Hydroxy*-2-*keto*-5-*phenyl*-1 : 2-*dihydropyrazine* (VI; R = H, R′ = Ph).—Glycine hydroxamic acid (Ley and Mannchen, *Ber.*, 1913, **46**, 754; Jones and Sneed, *J. Amer. Chem. Soc.*, 1917, **39**, 673) (3·0 g.), suspended in methanol (20 c.c.), was cooled below −30° and treated with a similarly cooled solution of phenylglyoxal hydrate (4·5 g.) in methanol (20 c.c.). Aqueous sodium hydroxide (8·3 c.c.; 5 N.) was added with stirring. The temperature was allowed to rise to −3° during 2 hours and maintained at this temperature overnight. Water (20 c.c.) was added and the mixture heated to 40° for 14 minutes; dissolution was then complete. The cooled solution was adjusted to pH 4·5 with dilute hydrochloric acid, and the solid collected and sublimed at 130°/10^{-3} mm. to give a yellow sublimate (250 mg.). Crystallisation from methanol yielded 1-*hydroxy*-2-*keto*-5-*phenyl*-1 : 2-*dihydropyrazine* as plates, m. p. 194—196° (decomp.) (Found: C, 63·9; H, 4·3; N, 15·1. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·25; N, 14·9%). Light absorption in ethanol: Maxima at 2700 A., ε = 13,600, and 3620 A., ε = 5800. The hydroxamic acid is soluble in hot methanol and ethanol; it gives a claret colour with aqueous ferric chloride and liberates carbon dioxide from aqueous sodium hydrogen carbonate.

DL-*Phenylglycine Hydroxamic Acid* (II; R = Ph).—A solution of DL-phenylglycine methyl ester hydrochloride (20·15 g.) in methanol (50 c.c.) was treated with sodium methoxide (5·4 g.) in methanol (50 c.c.). The mixture was filtered from salt, and the filtrate treated at 0° with a methanolic solution of hydroxylamine, prepared from hydroxylamine hydrochloride (13·9 g.) in methanol (200 c.c.) and sodium methoxide (10·8 g.) in methanol (100 c.c.). After 4 days at 0° the solution was evaporated under reduced pressure. The residue was triturated with cold water (25 c.c.) and filtered, and the solid washed with a little cold water and dried (yield, 7·5 g.); m. p. 168—169° (decomp.). DL-*Phenylglycine hydroxamic acid* separates from water as sheaves of plates, m. p. 169° (decomp.) (Found: C, 58·3; H, 6·1; N, 17·2. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0; N, 16·9%).

1-*Hydroxy*-2-*keto*-3-*phenyl*-5 : 6-*dimethyl*-1 : 2-*dihydropyrazine* (III; R = Ph).—DL-Phenylglycine hydroxamic acid (1·66 g.), suspended in methanol (20 c.c.) and water (5 c.c.) and cooled at −30°, was treated with a solution of diacetyl (0·9 g.) in methanol (5 c.c.) at the same temperature. The mixture was treated with sodium hydroxide solution (6·25 c.c.; 2N.) during 5 minutes with vigorous stirring below −30°. The temperature of the reaction mixture was allowed to rise to −15° and was maintained at this temperature for 45 minutes, dissolution then being complete. After 2 hours at 0° the solution was adjusted to pH 6·0 with dilute hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with hot chloroform, and the extract evaporated to yield a yellow solid (0·71 g.), m. p. 150—152°. Sublimation at 130/10^{-3} mm., followed by crystallisation from methanol, gave 1-*hydroxy*-2-*keto*-3-*phenyl*-5 : 6-*dimethyl*-1 : 2-*dihydropyrazine* as pale yellow prisms, m. p. 154—156° (Found: C, 66·8; H, 5·7; N, 13·05. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%). Light absorption in ethanol: Maxima at 2570 A., ε = 9500, and 3700 A., ε = 14,200. A methanolic solution of the acid gives a deep red colour with ferric chloride and dissolves in sodium hydrogen carbonate solution with effervescence.

2-Hydroxy-3-phenyl-5 : 6-dimethylpyrazine (IV; R = Ph).—The hydroxamic acid (III; R = Ph) (200 mg.) was heated with hydrazine hydrate (2 c.c.; 90%) in ethanol (3 c.c.) at 160° for 1½ hours. After filtration from a trace of insoluble material, the solution was evaporated under reduced pressure. The solid residue crystallised from ethanol as small pale yellow needles, m. p. 235—238°, and sublimed readily at 150—160°/10^{-4} mm. (Found: C, 72·2; H, 5·9; N, 14·2. Calc. for $C_{12}H_{12}ON_2$: C, 72·0; H, 6·0; N, 14·0%). Light absorption in ethanol: Maxima at 2560 A., ε = 9800, and 3650 A., ε = 12,200. A sample of the hydroxypyrazine prepared from DL-phenylglycine amide and diacetyl after Jones (*loc. cit.*) was purified by many recrystallisations from ethanol, followed by sublimation. It had m. p. 234—237° and was undepressed on admixture with the specimen described above; Jones gives m. p. 222—226°.

1-Hydroxy-2-keto-3 : 5-diphenyl-1 : 2-dihydropyrazine (VI; R = R′ = Ph).—A solution of phenylglyoxal hydrate (3·04 g.) in methanol (30 c.c.) at −30° was added to a suspension of DL-phenylglycine hydroxamic acid (3·33 g.) in methanol (30 c.c.) and water (20 c.c.) at −30°. Sodium hydroxide solution (12·5 c.c.; 2N.) was added dropwise during 5 minutes, and the mixture stirred at −30° for 15 minutes. The temperature was raised to 0° during the next 30 minutes, dissolution being then complete. Stirring was continued at 0° for 1 hour and then for a further 2 hours at 10°. The solid (*A*) (2·4 g.) was collected and the filtrate acidified to pH 4·0, a yellow solid (*B*) separating. The solid (*B*) was collected, washed with water, and dried (2·65 g.; m. p. 160—163°). Recrystallisation of *B* from ethyl acetate–light petroleum (b. p. 40—60°) gave *1-hydroxy-2-keto-3 : 5-diphenyl-1 : 2-dihydropyrazine* (1·85 g.) as scintillating lemon-yellow plates, m. p. 165—166° after sintering at 160° (Found: C, 73·1; H, 4·5; N, 11·0. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·5; N, 10·6%). Light absorption in ethanol: Maxima at 2770 A., ε = 17,300, and 3890 A., ε = 7700. The acid is insoluble in water, sparingly soluble in ether or methanol, and soluble in ethyl acetate or chloroform. An ethyl acetate–methanol solution gives a deep red colour with the ferric reagent. The compound does not liberate carbon dioxide from aqueous sodium hydrogen carbonate but dissolves in warm 2N-sodium hydroxide. The solid (*A*) is a sodium salt (residue on ignition). A solution of (*A*) in hot aqueous methanol was acidified to pH 4·0 with dilute hydrochloric acid, whereupon 1-hydroxy-2-keto-3 : 5-diphenyl-1 : 2-dihydropyrazine (1·7 g.) separated, having m. p. 162—165° alone or when mixed with the specimen described above.

2-Hydroxy-3 : 5-diphenylpyrazine.—(*a*) 1-Hydroxy-2-keto-3 : 5-diphenyl-1 : 2-dihydropyrazine (200 mg.) was heated with hydrazine hydrate (2 c.c.; 90%) and ethanol (3 c.c.) at 160—170° for 2 hours. The reaction mixture was evaporated to dryness under reduced pressure and the residue crystallised from glacial acetic acid, from which *2-hydroxy-3 : 5-diphenylpyrazine* (125 mg.), m. p. 270—272°, separated as pale yellow needles (Found: C, 77·0; H, 5·2; N, 11·0. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%). Light absorption in ethanol: Maxima at 2780 A., ε = 19,300, and 3720 A., ε = 9200. A mixture with 3-hydroxy-2 : 5-diphenylpyrazine (Gallagher, Newbold, Spring, and Woods, this vol., p. 910; m. p. 283°) had m. p. 239—252°.

(*b*) DL-Phenylglycine amide (1·5 g.) in methanol (15 c.c.) was cooled to −30° and treated with a solution of phenylglyoxal hydrate (1·52 g.) in methanol (20 c.c.) at −30°. Sodium hydroxide (6·25 c.c.; 2N.) was added dropwise, with stirring, during 15 minutes at −20°. The mixture was kept at 0° for 2 hours and then acidified to pH 5·0 with dilute hydrochloric acid. The solid (1·2 g.) was collected and crystallised from glacial acetic acid from which 2-hydroxy-3 : 5-diphenylpyrazine was obtained as pale yellow needles, m. p. 270—272° alone or mixed with the specimen described under (*a*) (Found: C, 77·7; H, 5·0; N, 11·0%).

Cinnamylideneglycine Hydroxamic Acid.—Glycine hydroxamic acid (2·0 g.) was treated with a solution of cinnamaldehyde (3·0 g.) in ethanol (25 c.c.), and the mixture heated under reflux for 30 minutes, dissolution being then complete. On cooling a solid separated which was crystallised from aqueous ethanol, to give *cinnamylideneglycine hydroxamic acid* (1·3 g.) as small pale orange prisms, m. p. 204° (decomp.). This acid is insoluble in water but soluble in 3N-sodium hydroxide (Found: C, 65·4; H, 6·0. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9%).

2-Bromocinnamylideneglycine Hydroxamic Acid.—Glycine hydroxamic acid (5·0 g.) was treated with 2-bromocinnamaldehyde (11·7 g.) in ethanol (900 c.c.), and the mixture heated under reflux until dissolution was complete (25 minutes). The crystalline product (11 g.) separating on cooling was collected and crystallised from ethanol; *2-bromocinnamylideneglycine hydroxamic acid* separated as needles, m. p. 157—158° (decomp.) (Found: C, 46·6; H, 3·9; N, 9·4. $C_{11}H_{11}O_2N_2Br$ requires C, 46·65; H, 3·9; N, 9·9%). Light absorption in ethanol: Maximum at 2525 A., ε = 6800. The acid is insoluble in water but soluble in 3N-sodium hydroxide, and dissolves slowly in a saturated sodium hydrogen carbonate solution without effervescence.

A solution of 2-bromocinnamylideneglycine hydroxamic acid (0·5 g.) in 3N-sodium hydroxide solution (0·6 c.c.) was treated dropwise with benzoyl chloride (0·25 g.). The solid was collected, washed with hot light petroleum (b. p. 60—80°), and crystallised from ethanol, to give the *dibenzoyl* derivative (0·2 g.) as colourless needles, m. p. 185° (Found: C, 61·0; H, 3·6; N, 5·5. $C_{25}H_{19}O_4N_2Br$ requires C, 61·1; H, 3·9; N, 5·7%). Reduced-pressure evaporation of the ethanolic mother-liquors from the dibenzoyl derivative gave a residue which was crystallised from ethanol to give the *monobenzoyl* derivative (50 mg.) as colourless needles, m. p. 225° (decomp.) (Found: C, 56·1; H, 4·0. $C_{18}H_{15}O_3N_2Br$ requires C, 55·8; H, 3·9%). The monobenzoyl derivative is soluble in 3N-sodium hydroxide.

1-Hydroxy-2-keto-6-benzyl-1 : 2-dihydropyrazine.—A refluxing solution of 2-bromocinnamylideneglycine hydroxamic acid (4 g.) in dry ethanol (500 c.c.) was treated with a solution of sodium (0·33 g.) in dry ethanol (20 c.c.). After 30 minutes the mixture was filtered and the filtrate concentrated under reduced pressure to 50 c.c. The solid (2 g.) separating on dilution of the solution with water was collected (solution *A*), dried, and crystallised from ethanol. It proved to be 2-bromocinnamylideneglycine hydroxamic acid, m. p. 158° (decomp.).

Acidification of the solution *A* precipitated a crystalline solid (1·2 g.) which after crystallisation from benzene, sublimation at 100°/10^{-3} mm., and crystallisation from benzene, gave *1-hydroxy-2-keto-6-benzyl-1 : 2-dihydropyrazine* as small needles, m. p. 171° (Found: C, 65·7; H, 5·4; N, 13·9%; equiv., 200. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0; N, 13·9%; equiv., 202). The acid is soluble with

effervescence in sodium hydrogen carbonate solution, and gives an intense red colour with aqueous ferric chloride solution. Light absorption in ethanol : Maxima at 2350 A., ε = 13,200, and 3330 A., ε = 9800.

α-*Amino*-n-*butyrohydroxamic Acid.*—To a solution of hydroxylamine (15 g.) in methanol (200 c.c.) was added methyl α-amino-*n*-butyrate (11·5 g.), and after 3 days at 0° the crystalline solid (5·0 g.) was collected. Crystallisation from water gave α-*amino*-n-*butyrohydroxamic acid* as small prisms, m. p. 166—167° (Found : C, 41·0; H, 8·6. $C_4H_{10}O_2N_2$ requires C, 40·7; H, 8·5%).

α-(2-*Bromocinnamylideneamino*)-n-*butyrohydroxamic Acid.*—α-Amino-*n*-butyrohydroxamic acid (3 g.) was heated under reflux with 2-bromocinnamaldehyde (5·4 g.) in ethanol (250 c.c.) until dissolution was complete (30 minutes). On cooling, a crystalline solid (4·2 g.) separated, which after crystallisation from ethanol gave α-(2-*bromocinnamylideneamino*)-n-*butyrohydroxamic acid* as transparent plates, m. p. 166° (decomp.) (Found : C, 50·3; H, 5·1; N, 9·1. $C_{13}H_{15}O_2N_2Br$ requires C, 50·2; H, 4·8; N, 9·0%).

1-*Hydroxy*-2-*keto*-3-*ethyl*-6-*benzyl*-1 : 2-*dihydropyrazine.*—A refluxing solution of the foregoing hydroxamic acid (3·0 g.) in dry *tert.*-butyl alcohol (220 c.c.) was treated with a solution of potassium (0·38 g.) in dry *tert.*-butyl alcohol (20 c.c.), and the mixture heated under reflux for 5 hours. Potassium bromide (0·4 g.) was removed and the filtered solution evaporated to near-dryness under reduced pressure. After acidification with dilute hydrochloric acid the mixture was evaporated to dryness, and the residue extracted with hot benzene (500 c.c.). The extract (charcoal) was evaporated to dryness, the residue washed with a little ethanol, and the solid (80 mg.) collected. Sublimation at 100°/10^{-3} mm. and crystallisation from benzene gave 1-*hydroxy*-2-*keto*-6-*benzyl*-3-*ethyl*-1 : 2-*dihydropyrazine* in clusters of small pale yellow prisms, m. p. 137—138° (Found : C, 68·1; H, 6·3; N, 11·9. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2%). This is soluble with effervescence in sodium hydrogen carbonate solution and gives a deep red colour with aqueous ferric chloride solution. Light absorption in ethanol : Maxima at 2350 A., ε = 13,900, and 3290 A., ε = 10,600.

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