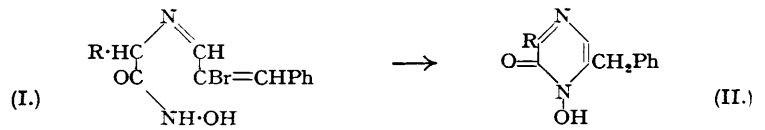
668. *Pyrazine Derivatives. Part XII. Synthesis of Homologues of Aspergillic Acid.*

By D. W. C. Ramsay and F. S. Spring.

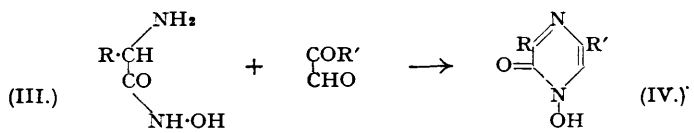
Condensation of the bisulphite derivative of pyruvohydroxamic acid (VI) with aminoacetone gives 1 : 2-dihydro-1-hydroxy-2-keto-3 : 6-dimethylpyrazine (VII) in good yield. The Schiff's base method for the synthesis of pyrazine cyclic hydroxamic acids (see Part XI, *J.*, 1949, 2707) has been extended to the preparation of 3 : 6-diethyl-1 : 2-dihydro-1-hydroxy-2-ketopyrazine (IX).

The only method available for the synthesis of a 3 : 6-disubstituted pyrazine hydroxamic acid involves the condensation of an α-amino-hydroxamic acid with 2-bromocinnamaldehyde to yield the Schiff's base (I) which is then treated with an alkali-metal alkoxide to yield the required hydroxamic acid (II) (Dunn, Elvidge, Newbold, Ramsay, Spring, and Sweeny, *J.*, 1949, 2707). The method has limitations, the most serious of which is the difficulty encountered in the ring closure (I ⟶ II). For the Schiff's base (I; R = H) derived from glycine



(I.) (II.)

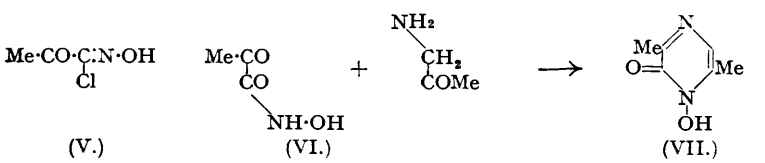
hydroxamic acid, refluxing with ethanolic sodium ethoxide sufficed to effect ring closure, 6-benzyl-1 : 2-dihydro-1-hydroxy-2-ketopyrazine (II; R = H) being isolated in 40% yield. The corresponding Schiff's base from α-amino-*n*-butyrohydroxamic acid (I; R = Et) could not be cyclised by sodium ethoxide, whilst with potassium *tert.*-butoxide in boiling *tert.*-butyl alcohol the cyclic hydroxamic acid (II; R = Et) was obtained in only 5% yield; many variations in reaction conditions did not improve this yield.



(III.) (IV.)

A new synthesis of a 3 : 6-disubstituted pyrazine cyclic hydroxamic acid was therefore sought. The condensation of an α-amino-hydroxamic acid (III) with an α-keto-aldehyde has been shown to proceed smoothly to give a 3 : 5-disubstituted pyrazine cyclic hydroxamic acid (IV) exclusively, and not the 3 : 6-isomeride (Part XI, *loc. cit.*). A preliminary study of the condensation of an α-keto-hydroxamic acid (VI) and an α-amino-ketone is now described.

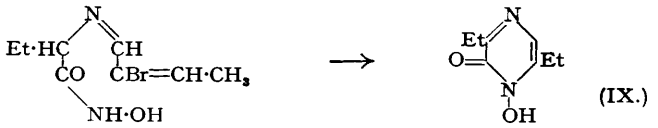
Treatment of pyruvohydroxamyl chloride (V) (Ponzio and Charrier, *Gazzetta*, 1907, **37**, II,



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

65) with sodium hydrogen sulphite gives the bisulphite derivative of pyruvohydroxamic acid (Gastaldi, *ibid.*, 1923, **53**, 635). Condensation of the crude bisulphite derivative of pyruvohydroxamic acid with aminoacetone gave, in early experiments, 2-hydroxy-3 : 6-dimethylpyrazine in small yield; the mother-liquors from this yielded an impure solid which unlike 2-hydroxy-3 : 6-dimethylpyrazine gave a strong ferric test, but a homogeneous product could not be isolated. The formation of a hydroxypyrazine rather than a cyclic hydroxamic acid is to be attributed to the reducing action of the excess of sodium hydrogen sulphite in the crude bisulphite derivative employed. Repetition of the experiment, using the bisulphite derivative of pyruvohydroxamic acid freed from sodium hydrogen sulphite by repeated precipitation of the latter from an aqueous solution of the crude bisulphite derivative by means of ethanol, gave in good yield the required cyclic hydroxamic acid, 1 : 2-dihydro-1-hydroxy-2-keto-3 : 6-dimethylpyrazine (VII). The hydroxamic acid, which gives a deep red colour

with aqueous ferric chloride solution and dissolves with effervescence in sodium hydrogen carbonate solution, was characterised by its ultra-violet absorption spectrum which is very similar to that of aspergillic acid, by its reduction with hydrazine to 2-hydroxy-3 : 6-dimethylpyrazine, and by the formation of a crystalline copper salt.



(VIII.) (IX.)

A further development of the Schiff's base method for the synthesis of 3 : 6-disubstituted pyrazine cyclic hydroxamic acids is now reported. The two acids previously synthesised by this method were derived from Schiff's bases from α-amino-hydroxamic acids and α-bromocinnamaldehyde and consequently contained a benzyl substituent. The method has now been successfully used for the synthesis of a hydroxamic acid in which both substituents are aliphatic. Condensation of α-amino-*n*-butyrohydroxamic acid with α-bromocrotonaldehyde yielded α-(2-bromocrotonylideneamino)-*n*-butyrohydroxamic acid (VIII) which when treated with potassium *tert.*-butoxide in *tert.*-butyl alcohol gave, in low yield, 3 : 6-diethyl-1 : 2-dihydro-1-hydroxy-2-ketopyrazine (IX).

Experimental.

Pyruvohydroxamyl Chloride.—This was prepared by the method of Ponzio and Charrier (*loc. cit.*). After repeated crystallisation from benzene, it separated as small plates, m. p. 112—113° (Ponzio and Charrier give m. p. 107°) (Found : N, 11·6. Calc. for $C_3H_4O_2NCl$: N, 11·5%). The 2 : 4-*dinitrophenylhydrazone* separates from benzene in orange prisms, m. p. 212° (Found : C, 35·9; H, 2·7; N, 23·5. $C_9H_8O_5N_5Cl$ requires C, 35·8; H, 2·7; N, 23·2%).

2-*Hydroxy*-3 : 6-*dimethylpyrazine.*—Pyruvohydroxamyl chloride (12 g.) was treated with a solution of sodium metabisulphite (28 g.) in water (48 c.c.) saturated with sulphur dioxide. After 12 hours, methanol (500 c.c.) was added and the mixture cooled to 0°. The crude bisulphite compound of pyruvohydroxamic acid (9 g.) was collected and washed with ethanol. A solution of the bisulphite compound (9 g.) in water (50 c.c.) was treated with aminoacetone hydrochloride (4 g.) and sodium acetate (3 g.) in acetic acid (30 c.c.; 25%). The solution was heated at 50° for 6 hours and then kept at room temperature overnight. The mixture was evaporated to dryness under reduced pressure, and the residue extracted with hot chloroform (5 × 50 c.c.). The dried (Na_2SO_4) extract was evaporated and the residue sublimed at 130°/10^{-3} mm. The sublimate (200 mg.) was crystallised from acetone and finally from benzene–light petroleum (b. p. 60—80°), to give 2-hydroxy-3 : 6-dimethylpyrazine as felted needles, m. p. 208—210°, undepressed when mixed with a specimen prepared from 2-amino-3 : 6-dimethylpyrazine (Baxter, Newbold, and Spring, *J.*, 1947, 370) (Found : C, 58·3; H, 6·0. Calc. for $C_6H_8ON_2$: C, 58·1; H, 6·45%). Evaporation of the acetone mother-liquors to dryness yielded a solid which with aqueous ferric chloride solution gave an intense red colour; crystallisation failed to give a homogeneous product.

1 : 2-*Dihydro*-1-*hydroxy*-2-*keto*-3 : 6-*dimethylpyrazine.*—Pyruvohydroxamyl chloride (15 g.) was treated with a solution of sodium metabisulphite (35 g.) in water (60 c.c.) saturated with sulphur dioxide. After 16 hours, methanol (500 c.c.) was added and the mixture kept at 0° overnight. The separated solid (19 g.) was collected, dissolved in water (100 c.c.), and treated with ethanol (80 c.c.). After 12 hours at 0°, the precipitated sodium hydrogen sulphite (5 g.) was removed and the filtrate diluted with an equal volume of ethanol. A further period of cooling precipitated more sodium hydrogen sulphite; the dilution process was repeated until the precipitate gave a positive ferric test. The mixture was then evaporated to dryness under reduced pressure and gave the bisulphite compound of pyruvohydroxamic acid (10 g.; m. p. >300°) as a pale yellow amorphous powder.

The purified bisulphite compound (10 g.) in water (30 c.c.) was treated with aminoacetone hydrochloride (4 g.) and sodium acetate (3 g.) in acetic acid (20 c.c.; 50%), and the mixture kept at 60—70° for 11 hours. The mixture was filtered and the filtrate kept overnight at room temperature. The separated solid (0·75 g.; m. p. 180—185°) was combined with a second crop (0·75 g.) which separated on concentration of the mother-liquor and sublimed at 100°/10^{-3} mm. The sublimate was crystallised from acetone, to give the *monohydrate* of 1 : 2-*dihydro*-1-*hydroxy*-2-*keto*-3 : 6-*dimethylpyrazine* as pale yellow prisms. m. p. 194—195° (sintering at 160°) (Found : C, 45·6; H, 6·3; N, 17·7. $C_6H_8O_2N_2,H_2O$ requires C, 45·6; H, 6·4; N, 17·7%). After drying over phosphoric oxide at 20°/10^{-2} mm., for 18 hours, the water of crystallisation was removed (Found : N, 20·1. $C_6H_8O_2N_2$ requires N, 20·0%). The acid is soluble in sodium hydrogen carbonate solution with effervescence, and gives a deep red colour with aqueous ferric chloride solution. Light absorption in ethanol : Maxima at 2340 A.,ε = 8100, and at 3265 A., ε = 7000.

A solution of the acid (100 mg.) in water (10 c.c.) was treated with a slight excess of a saturated copper acetate solution. The precipitate (70 mg.) was crystallised from dioxan to give the *copper* salt as light-green transparent plates, m. p. 280° (decomp.) [Found : C, 41·7; H, 4·1. $Cu(C_6H_7O_2N_2)_2$ requires C, 42·2; H, 4·1%].

2-*Hydroxy*-3 : 6-*dimethylpyrazine.*—A solution of 1 : 2-dihydro-1-hydroxy-2-keto-3 : 6-dimethylpyrazine (170 mg.) in methanol (15 c.c.) was heated with hydrazine hydrate (0·5 g.; 90%) at 180° for

4 hours. The residue obtained after removal of the methanol under reduced pressure gave a negative ferric test. Sublimation of the residue at 80°/10^{-3} mm., followed by crystallisation of the sublimate from benzene–light petroleum (b. p. 60—80°), gave 2-hydroxy-3 : 6-dimethylpyrazine (90 mg.) as felted needles, m. p. 208—210°, undepressed when mixed with a specimen prepared from 2-amino-3 : 6-dimethylpyrazine (Baxter, Newbold, and Spring, *loc. cit.*) (Found : C, 58·1; H, 6·2. Calc. for $C_6H_8ON_2$: C, 58·1; H, 6·45%). Light absorption in ethanol : Maxima at 2260 A., $\varepsilon = 8350$, and at 3210 A., $\varepsilon = 7800$.

α-(2-*Bromocrotonylideneamino*)-n-*butyrohydroxamic Acid.*—α-Amino-*n*-butyrohydroxamic acid (Dunn, Elvidge, Newbold, Ramsay, and Spring, *loc. cit.*) (6 g.) was heated under reflux with 2-bromocrotonaldehyde (9 g.) in ethanol (300 c.c.) until dissolution was complete (30 minutes). The product (7 g.) separating on cooling, was collected and recrystallised from ethanol, to yield α-(2-*bromocrotonylideneamino*)-n-*butyrohydroxamic acid* as transparent plates, m. p. 135—137° (decomp.) (Found : C, 38·5; H, 5·0; N, 11·4. $C_8H_{13}O_2N_2Br$ requires C, 38·6; H, 5·3; N, 11·2%).

3 : 6-*Diethyl*-1 : 2-*dihydro*-1-*hydroxy*-2-*ketopyrazine.*—A hot solution of α-(2-bromocrotonylideneamino)-*n*-butyrohydroxamic acid (12 g.) in dry *tert.*-butyl alcohol (300 c.c.) was treated with the solution from potassium (1·9 g.) and dry *tert.*-butyl alcohol (50 c.c.) and refluxed for 8 hours. Potassium bromide (1·8 g.) was removed and the filtered solution concentrated under reduced pressure to 100 c.c. The mixture was acidified (to pH 6·0) with dilute hydrochloric acid and kept at 0° overnight. The crystalline solid (6·0 g.) was filtered off; it proved to be α-(2-bromocrotonylideneamino)-*n*-butyrohydroxamic acid, m. p. and mixed m. p. 135—137° (decomp.). The filtrate was evaporated under reduced pressure and the residue extracted with boiling ether (3 × 200 c.c.). The dried (Na_2SO_4) extract was concentrated to 100 c.c., and a second crop of α-(2-bromocrotonylideneamino)-*n*-butyrohydroxamic acid (1·0 g.) removed. The filtrate was extracted with 2% sodium hydrogen carbonate solution, and the extract acidified to pH 4 with dilute hydrochloric acid. The solution was extracted with ether (5 × 50 c.c.), the dried (Na_2SO_4) extract evaporated, and the residue dissolved in a minimum volume of warm water. Treatment of the hot solution with an excess of saturated copper acetate solution gave a solid precipitate (210 mg.) which was collected and crystallised from dioxan, to yield the *copper* salt of 3 : 6-diethyl-1 : 2-dihydro-1-hydroxy-2-ketopyrazine as transparent light-green plates, m. p. 237—239° (decomp.) [Found : C, 48·5; H, 5·6; N, 14·4. $Cu(C_8H_{11}O_2N_2)_2$ requires C, 48·3; H, 5·6; N, 14·1%].

A solution of the copper salt (200 mg.) in dioxan (20 c.c.) and water (50 c.c.) was treated with hydrogen sulphide. The mixture was evaporated to dryness and the residue extracted with hot ethanol. The filtered (Hiflo) extract was evaporated to dryness and the residue sublimed at 70°/10^{-4} mm. Crystallisation of the sublimate from acetone gave 3 : 6-*diethyl*-1 : 2-*dihydro*-1-*hydroxy*-2-*ketopyrazine* as rosettes of pale yellow needles (25 mg.). After sublimation at 50°/10^{-3} mm., it had m. p. 95—97° (Found : C, 56·5; H, 7·3; N, 16·5. $C_8H_{12}O_2N_2$ requires C, 57·1; H, 7·2; N, 16·7%). 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 2335 A., $\varepsilon = 9250$, and 3265 A., $\varepsilon = 7860$.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, September 8th,* 1950.]