372. *Pyrazine Derivatives. Part VII. The Preparation of Hydroxypyrazine Derivatives by Gastaldi's Method.*

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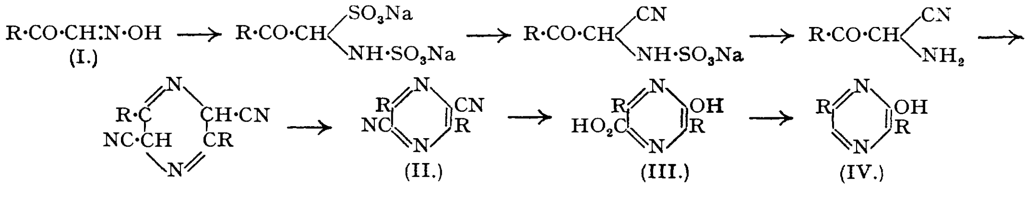
Oximinomethyl ethyl ketone has been converted into 2 : 5-*dicyano*-3 : 6-*diethylpyrazine*. Alkaline hydrolysis of the dicyano-compound gives 2-*hydroxy*-3 : 6-*diethylpyrazine*-5-*carboxylic acid*, decarboxylation of which yields 2-hydroxy-3 : 6-diethylpyrazine.

Two methods for the synthesis of alkylhydroxypyrazine derivatives had been reported when this series of investigations commenced. The first is due to Gastaldi (*Gazzetta*, 1921, **51**, I, 233) and the second to Tota and Elderfield (*J. Org. Chem.*, 1942, **7**, 317). Several methods for the synthesis of hydroxypyrazines have subsequently been described in this series (Baxter, Newbold, and Spring, *J.*, 1947, 370; Newbold and Spring, *J.*, 1947, 1183; Baxter and Spring, *J.*, 1947, 1179), and in addition Tota and Elderfield's method, which is limited to the preparation of 5 : 6-disubstituted and 3 : 5 : 6-trisubstituted 2-hydroxypyrazines, has been modified to yield a 2-hydroxy-3 : 6-dialkylpyrazine (Baxter, Newbold, and Spring, *loc. cit.*). Gastaldi's method was of particular interest to us since it gave a 3 : 6-disubstituted 2-hydroxypyrazine, and the primary object of our study was the synthesis of 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (cf. Newbold and Spring, *J.*, 1947, 373). The method consists in the treatment of the bisulphite compound of an oximinoketone with potassium cyanide, followed by heating the reaction product with hydrochloric acid, whereby a 2 : 5-dicyano-3 : 6-disubstituted pyrazine (II) is obtained. When heated with alkali, the dicyano-compound (II) undergoes a remarkable hydrolytic reaction to yield a 3 : 6-disubstituted 2-hydroxypyrazine-5-carboxylic acid (III), decarboxylation of which gives the required 3 : 6-disubstituted 2-hydroxypyrazine (IV). The reaction sequence is formulated by Gastaldi as follows :



Gastaldi applied the method to oximinoacetone and oximinoacetophenone. We have extended the method to *oximinomethyl ethyl ketone* (I; R = Et), obtained by the action of nitrous acid on sodium propionylacetate. The bisulphite compound of the oximino-ketone was treated with potassium cyanide, and the reaction mixture heated with hydrochloric acid, whereby 2 : 5-*dicyano*-3 : 6-*diethylpyrazine* (II; R = Et) was obtained. Hydrolysis of the dicyano-compound with alkali gave 2-*hydroxy*-3 : 6-*diethylpyrazine*-5-*carboxylic acid* (III; R = Et), which on heating yielded 2-hydroxy-3 : 6-diethylpyrazine (IV; R = Et) identical with the specimen obtained by Newbold, Spring, and Sweeny (Part V, this vol., p. 1855) from 2-amino-3 : 6-diethylpyrazine.

The formation of 2 : 5-dicyano-3 : 6-dimethylpyrazine (II; R = Me) from oximinoacetone has been reinvestigated and conditions are described in the experimental section whereby a 46% yield of the dicyano-derivative can be obtained. For comparison purposes, 2 : 5-dicyano-3 : 6-dimethylpyrazine was obtained from ethyl 3 : 6-dimethylpyrazine-2 : 5-dicarboxylate (Wleügel, *Ber.*, 1882, **15**, 1051; Gabriel and Posner, *Ber.*, 1894, **27**, 1141; Kalischer, *Ber.*, 1895, **28**, 1518; Cerchez and Colesiu, *Bull. Soc. chim.*, 1931, **49**, 1291; Adkins and Reeve, *J. Amer. Chem. Soc.*, 1938, **60**, 1328). The ester was converted into the corresponding diamide, which on dehydration yielded 2 : 5-dicyano-3 : 6-dimethylpyrazine identical with the specimen obtained by Gastaldi's method.

The remarkable behaviour of 2 : 5-dicyanopyrazine derivatives when treated with alkali proceeds under relatively mild reaction conditions; thus, when a solution of 2 : 5-dicyano-3 : 6-dimethylpyrazine is warmed for 2 minutes with 1% aqueous potassium hydroxide the presence of potassium cyanide is readily detected.

EXPERIMENTAL.

Oximinomethyl Ethyl Ketone.—Ethyl propionylacetate (40 g., b. p. 185—196°), obtained in 56% yield from ethyl cyanoacetate by Blaise's method (*Compt. rend.*, 1901, **132**, 978; Willstätter and Clarke, *Ber.*, 1914, **47**, 298), was added to a solution of sodium hydroxide (2·4%; 600 c.c.), and the mixture kept at room temperature for 24 hours. A solution of sodium nitrite (21 g.) in water (80 c.c.) was added, and the mixture treated at 5° with sulphuric acid (20%; 172 g.), added slowly with stirring. After the addition of ice and sodium hydroxide solution (40%; 40 c.c.), the mixture was extracted with ether. The aqueous solution was acidified with sulphuric acid (20%) at 5° and kept at this temperature for 1 hour. The mixture was extracted with ether (6 × 150 c.c.), the extract dried ($CaCl_2$), and the solvent removed. The residual oil crystallised (15·7 g.), and on recrystallisation (charcoal) from light petroleum (b. p. 60—80°) gave *oximinomethyl ethyl ketone* in hygroscopic needles, m. p. 55°; it has an odour similar to that of oximinoacetone (Found: C, 47·1; H, 6·9; N, 14·2. $C_4H_7O_2N$ requires C, 47·5; H, 6·9; N, 13·9%).

2 : 5-*Dicyano*-3 : 6-*diethylpyrazine.*—Oximinomethyl ethyl ketone (40 g.) was gradually added with shaking to a solution of sodium metabisulphite (183 g.) in water (317 c.c.) saturated with sulphur dioxide. The solution, which became warm during the addition, was kept overnight at room temperature. Alcohol (1500 c.c.) containing acetic acid (7·5 c.c.) was added gradually with shaking, and the precipitated solid collected next day when it had become granular. A solution of the solid in water (600 c.c.) was treated with alcohol (600 c.c.), and the mixture kept overnight. The precipitated sodium hydrogen sulphite was removed, and the filtrate diluted with alcohol (3000 c.c.) and kept overnight. The separated crude bisulphite compound of oximinomethyl ethyl ketone (126 g.; theoretical yield 115 g.) was collected and washed with alcohol; although contaminated with sodium hydrogen sulphite it was not further purified. A solution of the bisulphite compound (50 g.) in water (100 c.c.) was treated with potassium cyanide (22 g.) which was added slowly with shaking, and the solution kept at 45—50° for 5 hours, during which time the colour changed to yellow, through orange to red, and finally to brown. Hydrochloric acid (20%; 27 c.c.) was added, and the mixture heated at 55—60° for 1 hour. Concentrated hydrochloric acid (45 c.c.) was added slowly with stirring, and the solution kept at 55—60° for 24 hours during which time a crystalline solid separated. The mixture was cooled, and the solid collected, washed with water, dried, and extracted with boiling alcohol. On concentration and cooling the extract, a crystalline solid separated which when recrystallised (charcoal) from alcohol gave 2 : 5-*dicyano*-3 : 6-*diethylpyrazine* (2·82 g.) as plates, m. p. 115°. It is more soluble in alcohol than the 3 : 6-dimethyl homologue and volatilises from solutions heated on the water-bath (Found: C, 64·7; H, 5·4; N, 29·7. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1%).

2-*Hydroxy*-3 : 6-*diethylpyrazine*-5-*carboxylic Acid.*—A solution of 2 : 5-dicyano-3 : 6-diethylpyrazine (0·35 g.) in potassium hydroxide solution (15%; 10 c.c.) was refluxed for 24 hours. The cold solution was acidified with dilute hydrochloric acid, whereupon the odour of hydrogen cyanide was detected and a mixture of silica and reaction product was precipitated. The reaction mixture was evaporated to dryness, and the dried residue extracted with boiling alcohol (60 c.c.). Alcohol was removed from the filtered extract, and the orange-coloured solid crystallised from benzene (charcoal) to yield 2-*hydroxy*-3 : 6-*diethylpyrazine*-5-*carboxylic acid* (0·21 g.) as small prisms, m. p. 166°. There was no sign of decarboxylation at its m. p., but brisk evolution of carbon dioxide occurred at 200° (Found: C, 55·7; H, 6·1; N, 14·7. $C_9H_{12}O_3N_2$ requires C, 55·1; H, 6·2; N, 14·3%).

2-*Hydroxy*-3 : 6-*diethylpyrazine.*—A " Pyrex " tube containing a mixture of 2-hydroxy-3 : 6-diethylpyrazine-5-carboxylic acid (0·7 g.) and powdered glass (1·4 g.) was heated rapidly by immersion in a bath at 300° for 5 minutes. The acid melted, carbon dioxide was evolved, and a crystalline solid (0·35 g.) sublimed. Resublimation at 100°/0·005 mm. gave 2-hydroxy-3 : 6-diethylpyrazine as needles, m. p. 135°, undepressed when mixed with the specimen described in Part V (*loc. cit.*) (Found: C, 62·8; H, 7·8; N, 18·4. Calc. for $C_8H_{12}ON_2$: C, 63·2; H, 7·9; N, 18·4%).

2 : 5-*Dicyano*-3 : 6-*dimethylpyrazine*.—(*a*) Starting from oximinoacetone and using the procedure detailed above, 2 : 5-dicyano-3 : 6-dimethylpyrazine was obtained as lustrous plates, m. p. 210° (Gastaldi, *loc. cit.*, give m. p. 207°) (yield, 46%) (Found: C, 60·4; H, 3·8; N, 35·3. Calc. for $C_8H_6N_4$: C, 60·8; H, 3·8; N, 35·4%). Hydrolysis of this compound with 15% potassium hydroxide solution as described for the 3 : 6-diethyl homologue gave 2-hydroxy-3 : 6-dimethylpyrazine-5-carboxylic acid as prismatic needles from water, m. p. 268° (Gastaldi, *loc. cit.*, gives m. p. 270°) (yield, 50%). When heated with powdered glass, using the method described above, the acid was converted into 2-hydroxy-3 : 6-dimethylpyrazine, which was obtained as prismatic needles from light petroleum (b. p. 100—120°), m. p. 207—209° undepressed when mixed with an authentic specimen (yield, 77%) (Found: C, 57·8; H, 6·7. Calc. for $C_6H_8ON_2$: C, 58·1; H, 6·45%).

(*b*) * Ethyl 3 : 6-dimethylpyrazine-2 : 5-dicarboxylate (m. p. 80—83°, 3·5 g.) prepared by catalytic reduction of ethyl α-oximinoacetoacetate in ethanol solution using a Raney nickel catalyst, was dissolved in a solution of ethanol saturated at room temperature with dry ammonia and kept for 3 days. The crystalline solid was collected (2·5 g.) and recrystallised from water to yield 3 : 6-dimethylpyrazine-2 : 5-dicarboxyamide as fine needles, m. p. 297—298° (with previous darkening and some sublimation); Gastaldi and Princevalle (*Gazzetta*, 1928, **58**, 414) give m. p. 290° (Found: C, 49·6; H, 5·3. Calc. for $C_8H_{10}O_2N_4$: C, 49·5; H, 5·15%).

The diamide (5 g.) and phosphoric oxide (19 g.) were stirred in boiling toluene for 16 hours. The cold mixture was filtered and the black solid extracted with toluene (Soxhlet). Removal of the toluene under reduced pressure, followed by crystallisation of the residue from ethanol, gave 2 : 5-dicyano-3 : 6-dimethylpyrazine as glistening leaflets, m.p. 210·5—211·5°, undepressed when mixed with the specimen prepared by method (*a*) (Found: C, 60·7; H, 3·9; N, 35·4%).

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