289. *Pyrazine Derivatives. Part X. 2 : 5-Disubstituted 3 : 6-Dicyanopyrazines.*

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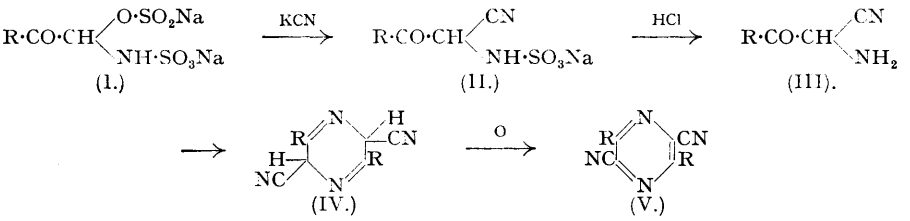
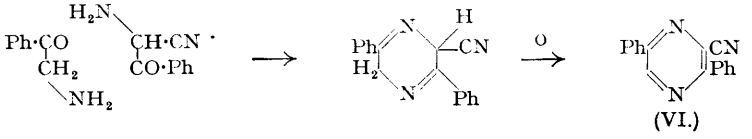
The Gastaldi method for the preparation of 2 : 5-disubstituted 3 : 6-dicyanopyrazines is discussed, and some reactions of 3 : 6-dicyano-2 : 5-dimethylpyrazine are described.

The method of Gastaldi (*Gazzetta*, 1921, **51**, I, 233) has been used by Sharp and Spring (*J.*, 1948, 1862) for the preparation of 3 : 6-dicyano-2 : 5-dialkylpyrazines. In this reaction the bisulphite derivative of an oximino-ketone is treated successively with potassium cyanide and hydrochloric acid; according to Gastaldi, the bisulphite derivative (I) reacts with potassium cyanide to give the compound (II), acid hydrolysis of which yields an α-amino-α-cyano-ketone (III). Self-



condensation of (III) gives a dicyanodihydropyrazine (IV) which is oxidised by air to the dicyanopyrazine (V). This reaction scheme is improbable, since it assumes the self-condensation of the amino-cyano-ketone (III) in a strongly acid medium. α-Amino-ketones are stable in acid solution, the typical pyrazine condensation occurring in either a neutral or alkaline medium. When the reaction is applied to the bisulphite derivative of oximinoacetophenone, a mixture of 3 : 6-dicyano-2 : 5-diphenylpyrazine (V; R = Ph) and 3-cyano-2 : 5-diphenylpyrazine (VI) is obtained. Gastaldi attributes formation of the latter compound to the formation of ω-aminoacetophenone by the decomposition of part of the intermediate amino-cyano-ketone. Condensation of ω-aminoacetophenone with the amino-cyano-ketone is assumed to give 3-cyano-2 : 5-diphenyldihydropyrazine, oxidation of which yields 3-cyano-2 : 5-diphenylpyrazine :

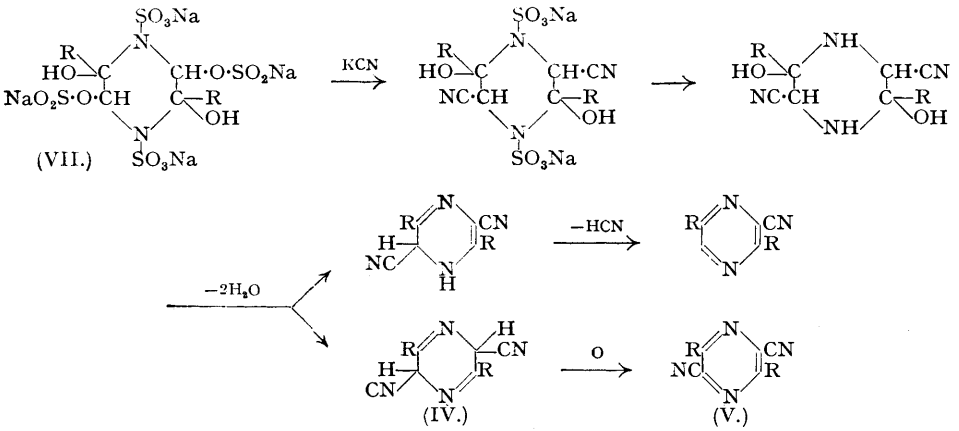


These assumptions are not only improbable, but also unnecessary. Thus we find that the addition of aminoacetone hydrochloride to the Gastaldi reaction mixture from oximinoacetone bisulphite derivative at the commencement of the acid hydrolysis stage does not lead to the formation of 3-cyano-2 : 5-dimethylpyrazine. The formation of 3-cyano-2 : 5-diphenylpyrazine from oximinoacetophenone is almost certainly to be attributed to an alternative method for the aromatisation of the dihydro-intermediate (IV) involving loss of hydrogen cyanide. This view accords with numerous similar observations of alternative means by which dihydropyrazine derivatives change into the aromatic form. Thus, treatment of alanine anhydride with phosphoryl chloride gives 3-chloro-2 : 5-dimethylpyrazine in addition to 3 : 6-dichloro-2 : 5-dimethylpyrazine (Baxter and Spring, *J.*, 1947, 1179). Again, treatment of DL-phenylglycine anhydride with phosphoryl chloride yields 3-hydroxy-2 : 5-diphenylpyrazine in addition to 3 : 6-dichloro-2 : 5-diphenylpyrazine (Gallagher, Newbold, Spring and Woods, this vol., p. 910).

Concerning the mechanisms of the principal Gastaldi reaction, it seems to us more plausible to ascribe the dimeric formula (VII) to the intermediate bisulphite derivatives, the subsequent stages in the reaction being as shown on p. 1365.

In support of this view we find that treatment of a mixture of the bisulphite derivatives of oximinoacetone and oximinomethyl ethyl ketone with potassium cyanide, and then with hydrochloric acid, gives a mixture of products from which only 3 : 6-dicyano-2 : 5-dimethylpyrazine and 3 : 6-dicyano-2 : 5-diethylpyrazine could be obtained; 3 : 6-dicyano-2-methyl-5-ethylpyrazine was not isolated. Similarly, when a mixture of the bisulphite derivatives of

oximinoacetophenone and oximinoacetone was subjected to the Gastaldi reaction, the formation of 3 : 6-dicyano-2-phenyl-5-methylpyrazine was not observed, 3 : 6-dicyano-2 : 5-dimethyl-



pyrazine, 3 : 6-dicyano-2 : 5-diphenylpyrazine, and 3-cyano-2 : 5-diphenylpyrazine being the only products isolated. Although these observations appear to favour the cyclic dimeric structure (VII) rather than the simpler structure (I) for the bisulphite derivatives of oximino-ketones, this argument must be used with caution, particularly in view of the fact that, when a mixture of oximinoacetone and oximinoacetophenone was treated with sodium bisulphite solution, and the mixed bisulphite derivative was subjected to the Gastaldi reaction, the formation of 3 : 6-dicyano-2-phenyl-5-methylpyrazine was not observed, only 3 : 6-dicyano-2 : 5-dimethylpyrazine, 3 : 6-dicyano-2 : 5-diphenylpyrazine, and 3-cyano-2 : 5-diphenylpyrazine being isolated. A molecular-weight determination for the bisulphite derivative of an oximino-ketone would help to differentiate between the structures (I) and (VII), but so far it has been impossible to free these compounds from sodium bisulphite.

Some further reactions of 3 : 6-dicyano-2 : 5-dimethylpyrazine have been studied. Treatment with dilute sodium hydroxide solution at room temperature gives 3-*hydroxy*-6-*cyano*-2 : 5-*dimethylpyrazine*,* and similar treatment of 3 : 6-dicyano-2 : 5-diethylpyrazine yields 3-*hydroxy*-6-*cyano*-2 : 5-*diethylpyrazine*. When heated under reflux with concentrated alkali, these hydroxy-cyano-compounds are hydrolysed to the previously described 3-hydroxy-2 : 5-dialkylpyrazine-6-carboxylic acids (Sharp and Spring, *J.*, 1948, 1862). With boiling phosphoryl chloride, 3-hydroxy-6-cyano-2 : 5-dimethylpyrazine yields 3-*chloro*-6-*cyano*-2 : 5-*dimethylpyrazine*.

Treatment of 3 : 6-dicyano-2 : 5-dimethylpyrazine with sodium ethoxide gives 3-*cyano*-6-*ethoxy*-2 : 5-*dimethylpyrazine* which, on hydrolysis with mineral acid, is converted into 3-hydroxy-6-cyano-2 : 5-dimethylpyrazine. Various peroxidations of 2-substituted pyrazine derivatives have been described by Baxter, Newbold and Spring (*J.*, 1948, 1859). Although these oxidations were undertaken with the object of preparing a cyclic hydroxamic acid of pyrazine, they led, in general, to the formation of 3-substituted pyrazine 1-oxides and not to the required 2-substituted pyrazine 1-oxide. The oxidation of 3-cyano-6-ethoxy-2 : 5-dimethylpyrazine was investigated since, if oxidation occurs at either the 1- or 4-positions, suitable treatment of the product may give rise to a cyclic hydroxamic acid. When treated with hydrogen peroxide in acetic acid, 3-cyano-6-ethoxy-2 : 5-dimethylpyrazine gave a *mono-oxide* which liberates iodine from acidified potassium iodide. If this is the 1-oxide, hydrolysis with hydrochloric acid would be expected to give a cyclic hydroxamic acid; however, it led to rupture of the ring system, hydrogen cyanide being evolved and ammonium chloride produced. A similar decomposition occurred when the oxide was treated with alkali.

Experimental.

3 : 6-*Dicyano*-2 : 5-*dimethylpyrazine*, 3 : 6-*Dicyano*-2 : 5-*diphenylpyrazine, and* 3-*Cyano*-2 : 5-*diphenylpyrazine*.—A mixture of the crude bisulphite compounds, individually prepared from oximinoacetone

* This compound was first prepared by Dr. R. A. Raphael by hydrolysis of the dinitrile with 15% methanolic potassium hydroxide (private communication).

(9 g.) and oximinoacetophenone (15 g.), was shaken with water (80 c.c.), and potassium cyanide (45 g.) was added in portions. When dissolution was complete, the mixture was kept at room temperature for 3 hours. Hydrochloric acid (20%; 40 c.c.) was added, and the mixture kept at 55° for 3 hours. Concentrated hydrochloric acid (80 c.c.) was added, and the mixture was kept at 55° for a further four hours. The dark-coloured mixture was filtered after standing overnight (filtrate A), and the solid (3·4 g.) extracted with hot ethanol. Crystallisation of the final residue from a large volume of ethanol yielded 3 : 6-dicyano-2 : 5-diphenylpyrazine (0·3 g.) as plates, m. p. 203°, undepressed when mixed with an authentic specimen prepared according to Gastaldi (*Gazzetta*, 1921, **51**, I, 233). Further crops of 3 : 6-dicyano-2 : 5-diphenylpyrazine were obtained from the alcoholic mother-liquors.

The filtrate A was concentrated and cooled. The solid separating was collected (filtrate B) and crystallised from aqueous ethanol, from which 3 : 6-dicyano-2 : 5-dimethylpyrazine (0·7 g.) separated as plates, m. p. and mixed m. p. 207—208°.

Filtrate B was diluted with water, and the precipitated solid repeatedly crystallised (charcoal) from dilute alcohol to give 3-cyano-2 : 5-diphenylpyrazine (0·8 g.) as long prisms, m. p. and mixed m. p. 120—121°.

A similar procedure to that detailed above was employed using a mixture of the bisulphite derivatives of oximinoacetone and oximinomethyl ethyl ketone, and using the bisulphite compound obtained by treatment of a mixture of equimolecular quantities of oximinoacetone and oximinoacetophenone with sodium bisulphite solution.

3-*Hydroxy*-6-*cyano*-2 : 5-*dimethylpyrazine*.—3 : 6-Dicyano-2 : 5-dimethylpyrazine (100 mg.) was shaken at room temperature with aqueous sodium hydroxide (10 c.c.; 5%). Dissolution was complete in 4 hours; after six hours the solution was acidified with dilute hydrochloric acid; the liberation of hydrogen cyanide was detected. The mixture was evaporated to dryness and the residue sublimed at 140°/5·8 × 10^{-4} mm. The sublimate was thrice crystallised from benzene, to yield 3-*hydroxy*-6-*cyano*-2 : 5-*dimethylpyrazine* as needles (50 mg.), m. p. 220—221° (Found : C, 56·2; H, 4·8; N, 27·7. $C_7H_7ON_3$ requires C, 56·4; H, 4·7; N, 28·2%).

A solution of 3-hydroxy-6-cyano-2 : 5-dimethylpyrazine (25 mg.) in 15% aqueous potassium hydroxide (5 c.c.) was heated under reflux for 10 hours; ammonia was evolved. The solution was acidified with concentrated hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with boiling ethanol, the extract evaporated to dryness, and the residue crystallised from water, to give 3-hydroxy-2 : 5-dimethylpyrazine-6-carboxylic acid as needles, m. p. 265° undepressed when mixed with the specimen described by Sharp and Spring (*J.*, 1948, 1862).

3-*Hydroxy*-6-*cyano*-2 : 5-*diethylpyrazine*.—Treatment of 3 : 6-dicyano-2 : 5-diethylpyrazine with 5% potassium hydroxide solution at room temperature, as described above, gave 3-*hydroxy*-6-*cyano*-2 : 5-*diethylpyrazine* which separated from benzene as needles, m. p. 129—130° (yield, 40%) (Found : C, 60·4; H, 6·3; N, 23·3. $C_9H_{11}ON_3$ requires C, 61·0; H, 6·2; N, 23·7%). Hydrolysis of 3-hydroxy-6-cyano-2 : 5-diethylpyrazine with boiling 15% aqueous potassium hydroxide gives 3-hydroxy-2 : 5-diethylpyrazine-6-carboxylic acid as prisms (from benzene), m. p. 164°, undepressed when mixed with the specimen described by Sharp and Spring (*loc. cit.*).

3-*Cyano*-6-*ethoxy*-2 : 5-*dimethylpyrazine*.—3 : 6-Dicyano-2 : 5-dimethylpyrazine (2·0 g.) was shaken for 10 hours at room temperature with a solution of sodium ethoxide in ethanol (from 1 g. of sodium and 25 c.c. of ethanol). The mixture was evaporated under reduced pressure, and the residue dissolved in a little water and acidified with hydrochloric acid. The precipitated solid was collected, washed with water, and dried. Sublimation of this solid at 80°/1·5 × 10^{-4} mm. gave 3-*cyano*-6-*ethoxy*-2 : 5-*dimethylpyrazine*, which separated from aqueous ethanol as needles (1·5 g.), m. p. 61° (Found : C, 60·7; H, 6·3; N, 23·9. $C_9H_{11}ON_3$ requires C, 61·0; H, 6·2; N, 23·7%). After removal of 3-cyano-6-ethoxy-2 : 5-dimethylpyrazine, the temperature was raised. At 180°/1·5 × 10^{-4} mm., a second sublimate was obtained, which separated from benzene as needles, m. p. 219°, undepressed when mixed with 3-hydroxy-6-cyano-2 : 5-dimethylpyrazine (m. p. 220—221°).

3-Cyano-6-ethoxy-2 : 5-dimethylpyrazine (40 mg.) was heated under reflux for 2 hours with 4N-hydrochloric acid (5 c.c.). The solution was evaporated to dryness, and the residue sublimed at 180°/1·5 × 10^{-4} mm. The sublimate was crystallised from benzene to yield 3-hydroxy-6-cyano-2 : 5-dimethylpyrazine as needles, m. p. 219°, undepressed when mixed with the specimen described above.

3-Cyano-6-ethoxy-2 : 5-dimethylpyrazine (500 mg.) was heated under reflux for 10 hours with 50% sulphuric acid (20 c.c.); carbon dioxide was evolved during the reaction. The cold solution was neutralised with ammonia and extracted with ether. The dried (Na_2SO_4) extract was evaporated, and the residue crystallised from benzene (charcoal), to give 3-hydroxy-2 : 5-dimethylpyrazine as needles, m. p. 208—209°, undepressed when mixed with an authentic specimen.

3-Cyano-6-ethoxy-2 : 5-dimethylpyrazine (0·7 g.) was boiled under reflux for 10 hours with 5N-potassium hydroxide (15 c.c.); ammonia was evolved. The cold solution was acidified with hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with boiling alcohol, the extract concentrated, and the solid separating recrystallised twice from alcohol, from which 3-hydroxy-2 : 5-dimethylpyrazine-6-carboxylic acid (0·45 g.) separated as needles, m. p. 265° (decomp.), undepressed when mixed with the specimen described above.

3-*Cyano*-6-*ethoxy*-2 : 5-*dimethylpyrazine oxide*.—A solution of 3-cyano-6-ethoxy-2 : 5-dimethylpyrazine (0·32 g.) in acetic acid (3 c.c.) was treated with hydrogen peroxide (100 vol.; 3 c.c.) and kept at 55° for 20 hours. The cold solution was poured into water, and the solid was collected, washed with water and dried. Crystallisation from light petroleum (b. p. 40—60°) gave 3-*cyano*-6-*ethoxy*-2 : 5-*dimethylpyrazine oxide* (0·18 g.) as needles, m. p. 104° (Found : C, 56·0; H, 5·7; N, 21·5. $C_9H_{11}O_2N_3$ requires C, 56·0; H, 5·7; N, 21·8%). The oxide liberates iodine from an acidified potassium iodide solution.

3-*Chloro*-6-*cyano*-2 : 5-*dimethylpyrazine*.—3-Hydroxy-6-cyano-2 : 5-dimethylpyrazine (200 mg.) was treated with phosphoryl chloride (7 c.c.), and the mixture heated under reflux for 30 minutes and then evaporated under reduced pressure. The residual oil was triturated with a little ethanol until crystallisation occurred. Recrystallisation from aqueous ethanol gave 3-*chloro*-6-*cyano*-2 : 5-*dimethylpyrazine* as

plates (0·75 g.), m. p. 79—80° (Found : C, 50·4; H, 3·9; N, 24·6; Cl, 20·9. $C_7H_6N_3Cl$ requires C, 50·15; H, 3·6; N, 25·1; Cl, 21·2%).

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