194. *Pyrazine Derivatives. Part IX. The Conversion of* DL-*Phenylglycine Anhydride into 3-Hydroxy-2 : 5-diphenylpyrazine.*

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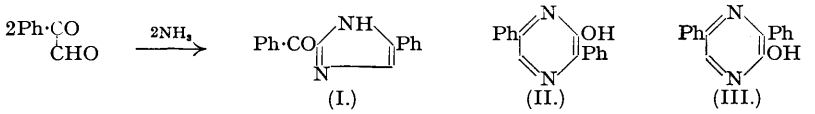
Treatment of DL-phenylglycine anhydride with phosphoryl chloride gives a mixture from which 3-hydroxy-2 : 5-diphenylpyrazine (II) and 3 : 6-dichloro-2 : 5-diphenylpyrazine have been isolated. 3-Hydroxy-2 : 5-diphenylpyrazine has also been obtained in good yield (*a*), together with the isomeric 2-benzoyl-4(5)-phenylglyoxaline (I), by treatment of phenylglyoxal with ammonium formate and (*b*) by the action of nitrous acid upon 3-amino-2 : 5-diphenylpyrazine.

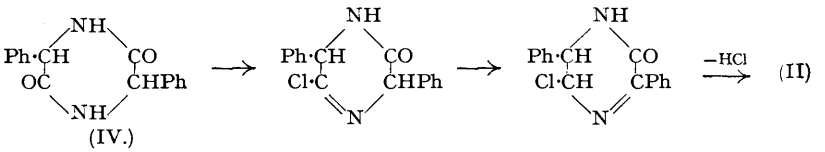
The limitations of the methods which are available for the synthesis of 3-hydroxy-2 : 5-dialkylpyrazines have been discussed by Baxter, Newbold, and Spring (*J.*, 1947, 370), and a variety of new methods have been described in earlier Parts of this series (*J.*, 1947, 370, 1179, 1183; 1948, 1855, 1862; this vol., p. 300). In a general study of antibacterial compounds, isolated from *Aspergillus flavus* and other micro-organisms, it became necessary to extend these methods to the synthesis of 3-hydroxy-2 : 5-diarylpyrazines and, in the first place, we have limited this study to the preparation of 3-hydroxy-2 : 5-diphenylpyrazine. The literature concerning this compound is very confused. By the action of ammonia on phenylglyoxal, Pinner (*Ber.*, 1905, **38**, 1531) obtained two isomeric products, $C_{16}H_{12}ON_2$, m. p.s 202° and 280°. The latter was considered to be 2-benzoyl-4(5)-phenylglyoxaline (I) and the former 3-hydroxy-2 : 5-diphenylpyrazine (II). The lower-melting isomer (cf. Müller and Pechmann, *Ber.*, 1889, **22**, 2556; Pinner, *Ber.*, 1902, **35**, 4131) was shown to be identical with a compound obtained by Engler and Hassenkamp (*Ber.*, 1885, **18**, 2240) by the action of ammonia upon ω-dibromoacetophenone. It had also been obtained previously by Japp and Miller (*J.*, 1887, 29), by treatment of benzil with hydrogen cyanide, and by Minovici (*Ber.*, 1899, **32**, 2206), by the action of hydrogen chloride on mandelonitrile, and was likewise formulated by Japp and Knox (*J.*, 1905, 701) as 2-keto-3 : 6-diphenyl-1 : 2-dihydropyrazine (equivalent to 3-hydroxy-2 : 5-diphenylpyrazine).



Gastaldi (*Gazzetta*, 1921, **51**, 233) obtained 3-hydroxy-2 : 5-diphenylpyrazine, m. p. 284°, by a route involving reaction of the hydrogen sulphite derivative of oximinoacetophenone with potassium cyanide followed by treatment of the mixture with hydrochloric acid, whereupon a product, formulated as 3 : 6-dicyano-2 : 5-diphenylpyrazine, was obtained. Alkaline hydrolysis of this gave 3-hydroxy-2 : 5-diphenylpyrazine-6-carboxylic acid, decarboxylation of which yielded 3-hydroxy-2 : 5-diphenylpyrazine, m. p. 284°, identical with the compound described by Pinner as 2-benzoyl-4(5)-phenylglyoxaline. Gastaldi's argument is dependent upon the structure of the intermediate dicyanide formulated by him as 3 : 6-dicyano-2 : 5-diphenylpyrazine; this structure has been supported by Sharp and Spring (*J.*, 1948, 1862) by the

synthesis of 3 : 6-dicyano-2 : 5-dimethylpyrazine by an alternative method starting from ethyl 2 : 5-dimethylpyrazine-3 : 6-dicarboxylate, the product proving to be identical with the dicyanide obtained from oximinoacetone by Gastaldi's method.

An unambiguous synthesis of 3-hydroxy-2 : 5-diphenylpyrazine from DL-phenylglycine anhydride (3 : 6-diketo-2 : 5-diphenylpiperazine) (IV) has now been effected. Treatment of the anhydride with phosphoryl chloride gives a mixture of 3-hydroxy-2 : 5-diphenylpyrazine (II), m. p. 285°, and 3 : 6-*dichloro*-2 : 5-*diphenylpyrazine*. This is the first example, within our experience, of the direct conversion of a diketopiperazine into a hydroxypyrazine, and it is presumably to be attributed to the ready loss of the elements of hydrogen chloride from an intermediate monochloro-dihydropyrazine derivative, thus :

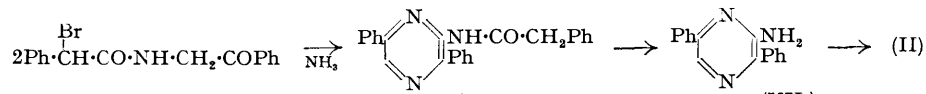


(IV.)

The diketopiperazines which have been previously similarly treated give mixtures of 3-chloro- and 3 : 6-dichloro-2 : 5-disubstituted pyrazines (Baxter and Spring, *J.*, 1947, 1179), whereas in the case of phenylglycine anhydride the corresponding 3-chloro-2 : 5-diphenylpyrazine was not isolated. However, the latter may well be a product since the resinous material remaining after the isolation of the dichloro-compound gave a further quantity of 3-hydroxy-2 : 5-diphenylpyrazine when heated with potassium hydroxide.

The 3-hydroxy-2 : 5-diphenylpyrazine obtained by the use of this method is identical with the compound described by Gastaldi and also with the higher-melting product obtained by the action of ammonia upon phenylglyoxal (or better by the action of ammonium formate upon phenylglyoxal). The isomeric lower-melting compound, m. p. 197—198°, obtained from the latter reaction, may be either 2-benzoyl-4(5)-phenylglyoxaline (I) or 2-hydroxy-3 : 5-diphenylpyrazine (III).

An attempt to synthesise the latter for comparison purposes was unsuccessful since reaction of ammonia with ω-bromophenylacetamidoacetophenone (V) gave 3-phenylacetamido-2 : 5-



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

diphenylpyrazine (VI) and not the expected 2-hydroxy-3 : 5-diphenylpyrazine (Newbold, Spring, and Sweeny, this vol., p. 300). This reaction, however, led to an independent synthesis of 3-hydroxy-2 : 5-diphenylpyrazine in which 3-amino-2 : 5-diphenylpyrazine (VII), obtained from (VI) by alkaline hydrolysis, is treated with nitrous acid. 3-Amino-2 : 5-diphenylpyrazine could not be obtained by the action of sodamide upon 2 : 5-diphenylpyrazine.

Although we have not succeeded in preparing 2-hydroxy-3 : 5-diphenylpyrazine, this structure has been excluded for the compound, m. p. 197—198°, as the latter gives a 2 : 4-*dinitrophenylhydrazone* from which we conclude that it is 2-benzoyl-4(5)-phenylglyoxaline (I).

Experimental.

3-Hydroxy-2 : 5-diphenylpyrazine and 2-Benzoyl-4(5)-phenylglyoxaline.—(*a*) Phenylglyoxal hydrate (50 g.) in warm water (500 c.c.) was treated with ammonia (*d* 0·88; 50 c.c.), and the mixture was stirred for 30 minutes. The mixture was neutralised by the careful addition of dilute hydrochloric acid, and the orange-coloured solid was collected, washed with cold water, and extracted with hot 95% alcohol (200 c.c.). The residual solid (12 g.) was crystallised from glacial acetic acid and then from pyridine from which 3-hydroxy-2 : 5-diphenylpyrazine separated as pale yellow needles, m. p. 286°. It is soluble in 3N-sodium hydroxide (Found : C, 77·2; H, 5·1; N, 11·1. Calc. for $C_{16}H_{12}ON_2$: C, 77·4; H, 4·8; N, 11·3%). A suspension of 3-hydroxy-2 : 5-diphenylpyrazine (0·6 g.) in glacial acetic acid (4 c.c.) was treated with a solution of bromine (0·6 g.) in glacial acetic acid (7 c.c.), and the mixture was warmed until solution was complete. The solid which separated on cooling was recrystallised from alcohol, giving the bromo-derivative as yellow felted needles, m. p. 246° (Found : C, 58·5; H, 3·0; N, 8·6. Calc. for $C_{16}H_{11}ON_2Br$: C, 58·7; H, 3·4; N, 8·6%).

The alcoholic extract, obtained as described above, was evaporated, the solid (18 g.) dissolved in hot 3N-sodium hydroxide, and the filtered solution cooled. The crystalline solid which separated was recrystallised from aqueous pyridine, giving 2-*benzoyl*-4(5)-*phenylglyoxaline* as soft iridescent yellow plates, m. p. 197—198° (Found : C, 77·8; H, 5·1; N, 11·3. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%).

The 2 : 4-*dinitrophenylhydrazone* separates from dilute acetic acid as small orange-red needles, m. p. 265° (Found : C, 61·5; H, 4·2; N, 19·4. $C_{22}H_{16}O_4N_6$ requires C, 61·7; H, 3·7; N, 19·6%).

A suspension of 2-benzoyl-4(5)-phenylglyoxaline (0·5 g.) in glacial acetic acid (3 c.c.) was shaken with a solution of bromine (1 c.c.) in acetic acid (5 c.c.) until solution was complete. The solution was diluted with water and the solid was collected, washed with water, and recrystallised from alcohol giving the *dibromo*-derivative as pale yellow needles, m. p. 248° (Found : C, 47·5; H, 2·6; N, 6·5. $C_{16}H_{10}ON_2Br_2$ requires C, 47·3; H, 2·5; N, 6·9%).

(*b*) A mixture of phenylglyoxal (4·02 g.) and ammonium formate (11·3 g.) was heated to 175° for 2 hours. The mixture was extracted with boiling water and then with boiling alcohol (10 c.c.). The residual solid was recrystallised from a large volume of alcohol from which 3-hydroxy-2 : 5-diphenylpyrazine separated as bright yellow plates (1·2 g.), m. p. 285—286° either alone or when mixed with the specimen described above. The monobromo-derivative separated from alcohol as yellow needles, m. p. 246° undepressed with the specimen prepared by method (*a*).

Evaporation of the alcohol mother liquor gave a solid (1·8 g.) which was crystallised, first from aqueous pyridine, and then from a little alcohol giving 2-benzoyl-4(5)-phenylglyoxaline as golden-yellow plates, m. p. 197—198° either alone or when mixed with the specimen prepared by method (*a*). The dibromo-derivative, m. p. and mixed m. p. 248°, separated from alcohol as yellow needles.

3-*Hydroxy*-2 : 5-*diphenylpyrazine and* 3 : 6-*Dichloro*-2 : 5-*diphenylpyrazine*.—DL-Phenylglycine anhydride (cf. Kossel, *Ber.*, 1891, **24**, 4145; Ovakimian, Kuna, and Levene, *J. Biol. Chem.*, 1940, **135**, 91) was prepared by heating DL-phenylglycine methyl ester (24 g.) at 140° for 16 hours. After cooling, the product was triturated with ether, and the solid (15 g.) recrystallised from ethylene glycol monoethyl ether from which the diketopiperazine separated as needles, m. p. 292—293° (sinters at 287°) (Found : C, 72·5; H, 5·7. Calc. for $C_{16}H_{14}O_2N_2$: C, 72·2; H, 5·3%). DL-Phenylglycine anhydride (10 g.) was heated under reflux with phosphoryl chloride (50 c.c.) for 2 hours. The excess of phosphoryl chloride was removed under reduced pressure, and the residue was triturated with ice water. The solid was collected and extracted with boiling alcohol (500 c.c.). The insoluble solid (filtrate *A*) was recrystallised from glacial acetic acid, giving 3-hydroxy-2 : 5-diphenylpyrazine as yellow prisms (0·53 g.), m. p. 283°, raised to 285° by recrystallisation from aqueous dioxan; its m. p. was not depressed when it was mixed with the specimen described above (Found : C, 77·0; H, 4·9; N, 11·7. Calc. for $C_{16}H_{12}ON_2$: C, 77·4; H, 4·8; N, 11·3%). The bromo-derivative separated from acetic acid as yellow felted needles, m. p. and mixed m. p. 245° (Found : C, 58·9; H, 3·5. Calc. for $C_{16}H_{11}ON_2Br$: C, 58·7; H, 3·4%).

The alcoholic filtrate *A* was concentrated to 200 c.c. and cooled. The solid separating (filtrate *B*) was recrystallised from alcohol from which 3 : 6-*dichloro*-2 : 5-*diphenylpyrazine* (2·96 g.) separated as needles, m. p. 159—160° (Found : C, 63·8; H, 3·5. $C_{16}H_{10}N_2Cl_2$ requires C, 63·8; H, 3·3%). This compound was readily soluble in acetone.

The filtrate *B* was evaporated, and the amorphous solid residue digested with methanol (50 c.c.), and the solid collected. This was recrystallised from glacial acetic acid, yielding a second crop of 3 : 6-dichloro-2 : 5-diphenylpyrazine (0·6 g.), m. p. 157—158° undepressed when mixed with the specimen described above. The methanolic mother liquor was evaporated to dryness and the resultant resin heated at 200° with powdered potassium hydroxide (10 g.) for 6 hours. The mixture was diluted with water and acidified with hydrochloric acid. The yellow solid was collected and boiled with glacial acetic acid, and the solution was filtered from silica. The filtrate deposited 3-hydroxy-2 : 5-diphenylpyrazine as yellow prisms (0·41 g.), m. p. and mixed m. p. 284°.

3-*Hydroxy*-2 : 5-*diphenylpyrazine*.—Sodium nitrite (0·1 g.) was added in small portions with stirring to concentrated sulphuric acid (1·5 c.c.) at 0°. The mixture was gradually heated to 60°. The clear solution was cooled to 0°, and treated with a solution of 3-amino-2 : 5-diphenylpyrazine (Newbold, Spring, and Sweeny, this vol., p. 300) (0·25 g.) in concentrated sulphuric acid (3 c.c.) added dropwise with stirring, the temperature being kept at or slightly below 0°. When the addition was complete, sodium nitrite (0·05 g.) was added, and the solution kept at 0° for 1 hour. The solution was poured on crushed ice (25 g.), and the mixture stirred until evolution of nitrogen ceased. The precipitated solid was collected and crystallised from glacial acetic acid giving 3-hydroxy-2 : 5-diphenylpyrazine (0·15 g.) as yellow-green prisms, m. p. 286° either alone or when mixed with the specimens described above.

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