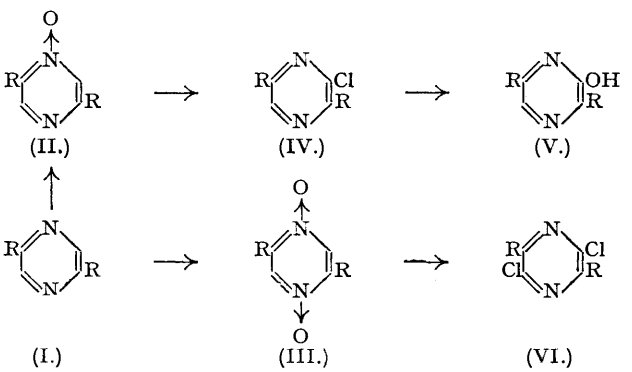
222. *Pyrazine Derivatives. Part IV. Pyrazine* N-*Oxides and their Conversion into Chloropyrazines.*

By G. T. Newbold and F. S. Spring.

2 : 5-Dialkylpyrazines are readily oxidised to a mixture of the corresponding mono- and di-*N*-oxides. The mono- and di-*N*-oxides are smoothly converted into 2-chloro- and 2 : 5-dichloro-3 : 6-dialkylpyrazines respectively. Hydrolysis of the 2-chloro-3 : 6-dialkylpyrazine gives the corresponding 2-hydroxy-3 : 6-dialkylpyrazine. By this route, 3 : 6-di-*sec.*-butylpyrazine yields a 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine identical with the racemate described by us in Parts II and III (this vol., p. 373, and preceding paper).

Treatment of 2 : 5-dimethylpyrazine (I, R = Me) with hydrogen peroxide in aqueous acetic acid gives 2 : 5-*dimethylpyrazine* N-*oxide* (II, R = Me) in 62% yield and 2 : 5-*dimethylpyrazine di*-N-*oxide* (III, R = Me) in 24% yield. Treatment of 2 : 5-dimethylpyrazine *N*-oxide with phosphoryl chloride gives 2-chloro-3 : 6-dimethylpyrazine (IV, R = Me) in 85% yield. Alkaline hydrolysis of the latter as described in the preceding paper yields 2-hydroxy-3 : 6-dimethylpyrazine (V, R = Me). This route to 2-hydroxy-3 : 6-dimethylpyrazine starting from 2 : 5-dimethylpyrazine is superior to that described by Baxter, Newbold, and Spring (this vol., p. 370).



2 : 5-Dimethylpyrazine di-*N*-oxide is converted by the action of phosphoryl chloride into 2 : 5-dichloro-3 : 6-dimethylpyrazine (VI, R = Me), identical with that described in the preceding paper. The yield, however, is low and is not increased by the use of sulphuryl chloride instead of phosphoryl chloride.

Treatment of 2 : 5-di-*sec.*-butylpyrazine (I, R = *sec.*-C_4H_9) with hydrogen peroxide gives a mixture of the corresponding mono- and di-*N*-oxides. 2 : 5-*Di*-sec.-*butylpyrazine di*-N-*oxide* (III, R = *sec.*-C_4H_9) is obtained in 64% yield, and on treatment with phosphoryl chloride it is converted into 2 : 5-dichloro-3 : 6-di-*sec.*-butylpyrazine (VI, R = *sec.*-C_4H_9), identical with that obtained from *iso*leucine anhydride. The mono-*N*-oxide (II, R = *sec.*-C_4H_9) was not isolated in a pure state; when treated with phosphoryl chloride it is converted into 2-chloro-3 : 6-di-*sec.*-butylpyrazine (IV, R = *sec.*-C_4H_9). The latter was characterised by hydrolysis to 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (V, R = *sec.*-C_4H_9), identical with the preparation described in the preceding paper and with that described in Part II (*loc. cit.*).

Experimental.

2 : 5-*Dimethylpyrazine Di*-N-*oxide*.—A solution of 2 : 5-dimethylpyrazine (5·5 g.) in glacial acetic acid (20 c.c.) was treated with hydrogen peroxide solution (40 c.c.; 100-vol.) and maintained at 56° for 16 hours. The solution was evaporated to small bulk under reduced pressure, and the residue was cooled in ice–water and made alkaline with sodium hydroxide solution. The mixture was extracted with chloroform (10 × 25 c.c.), the extract dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The solid residue was digested with boiling chloroform (25 c.c.), the mixture cooled, and the solid collected (filtrate *A*). Crystallisation from a large volume of chloroform gave 2 : 5-*dimethylpyrazine di*-N-*oxide* as needles (1·7 g.); it has no definite m. p., darkening profoundly at approximately 280°, and is not molten at 360°. The di-*N*-oxide is readily soluble in cold water but sparingly soluble in cold organic solvents. It is less soluble in 3N-sodium hydroxide solution than in water. It sublimes readily at 200°/0·5 mm. (Found: C, 51·3; H, 5·8. $C_6H_8O_2N_2$ requires C, 51·4; H, 5·7%).

2 : 5-*Dimethylpyrazine* N-*Oxide*.—The filtrate *A* and the mother liquors from the crystallisation of the di-*N*-oxide were combined, concentrated, and cooled, and some di-*N*-oxide was removed by filtration. The filtrate was evaporated to dryness and the solid residue (3·9 g.; m. p. 100°) was crystallised from benzene to give 2 : 5-*dimethylpyrazine* N-*oxide* as small colourless needles, m. p. 105—108°; it rapidly sublimes at 100°/0·001 mm. (Found: C, 58·0; H, 6·3. $C_6H_8ON_2$ requires C, 58·1; H, 6·45%). 2 : 5-Dimethylpyrazine *N*-oxide (0·6 g.) was heated with hydrogen peroxide solution (5 c.c.; 100-vol.) and glacial acetic acid (5 c.c.) for 18 hours at 56°. The reaction mixture was treated as described above to give 2 : 5-dimethylpyrazine di-*N*-oxide (0·5 g.), darkening at approximately 280° and not molten at 360° (Found: C, 51·5; H, 5·9%).

2-*Chloro*-3 : 6-*dimethylpyrazine*.—2 : 5-Dimethylpyrazine *N*-oxide (2·75 g.) was added in small portions to phosphoryl chloride (15 c.c.) with cooling and shaking. The mixture was cautiously warmed until solution was complete and the solution heated under reflux for 10 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured on crushed ice. The mixture was neutralised with sodium carbonate and extracted with chloroform (6 × 25 c.c.), and the combined extracts were dried ($NaSO_4$). The chloroform was evaporated and the residual oil distilled under reduced pressure to give a main fraction, b. p. 75—80°/12 mm. (2·7 g.; 85%), which on redistillation yielded 2-chloro-3 : 6-dimethylpyrazine as a colourless oil, b. p. 77°/12 mm.; $n_D^{19°}$ 1·5275 (Found: C, 50·8; H, 4·8; N, 19·4. Calc. for $C_6H_7N_2Cl$: C, 50·5; H, 4·9; N, 19·6%).

Hydrolysis of 2-chloro-3 : 6-dimethylpyrazine as described in the preceding paper gave a 50% yield of 2-hydroxy-3 : 6-dimethylpyrazine which after sublimation had m. p. 210—211°, undepressed on admixture with a specimen prepared *via* 2-amino-3 : 6-dimethylpyrazine (Baxter, Newbold, and Spring, *loc. cit.*).

2 : 5-*Dichloro*-3 : 6-*dimethylpyrazine*.—(*a*) 2 : 5-Dimethylpyrazine di-*N*-oxide (0·5 g.) was treated with phosphoryl chloride (2·5 c.c.) and heated under reflux for 30 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue triturated with ice–water. The solid was collected and purified by sublimation to yield 2 : 5-dichloro-3 : 6-dimethylpyrazine (100 mg.), m. p. 70—72°, not depressed by the preparation described in the preceding paper (Found: C, 41·0; H, 3·5. Calc. for $C_6H_6N_2Cl_2$: C, 40·7; H, 3·4%).

(*b*) The di-*N*-oxide (0·5 g.) was refluxed for 1 hour with sulphuryl chloride (10 c.c.). The excess of reagent was removed by distillation to give 2 : 5-dichloro-3 : 6-dimethylpyrazine (90 mg.), m. p. 71—73°, undepressed when mixed with the specimen described above.

2 : 5-*Di*-sec.-*butylpyrazine Di*-N-*oxide*.—2 : 5-Di-*sec.*-butylpyrazine (4·2 g.) in glacial acetic acid (30 c.c.) and hydrogen peroxide solution (30 c.c.; 100-vol.) was heated at 56° for 17 hours. The solution was evaporated to small bulk under reduced pressure, and the residue made alkaline with sodium hydroxide solution and extracted with chloroform (6 × 20 c.c.). The combined extracts were dried (K_2CO_3) and evaporated to dryness under reduced pressure.. The residue was recrystallised from benzene–light petroleum (b. p. 40—60°) to give 2 : 5-*di*-sec.-*butylpyrazine di*-N-*oxide* as needles, m. p. 159—161° (yield 64%). 2 : 5-Di-*sec.*-butylpyrazine di-*N*-oxide is insoluble in water; it dissolves in 5N-hydrochloric acid and is precipitated on basification of the solution (Found: C, 64·2; H, 9·0. $C_{12}H_{20}O_2N_2$ requires C, 64·3; H, 8·9%).

2 : 5-*Dichloro*-3 : 6-*di*-sec.-*butylpyrazine*.—A mixture of the di-*N*-oxide (1·6 g.) and phosphoryl chloride (20 c.c.) was gently warmed and then heated under reflux for 30 minutes. Excess of phosphoryl chloride was removed under reduced pressure and the residue poured into ice–water. After neutralisation with sodium carbonate the solid was extracted with chloroform, and the dried (Na_2SO_4) extract

evaporated to yield an oil which solidified on cooling. The solid was purified by sublimation at 50°/0·5 mm., and the sublimate crystallised from aqueous ethanol to yield 2 : 5-dichloro-3 : 6-di-*sec.*-butylpyrazine (46% yield) as laminæ, m. p. 59—61°, undepressed when mixed with the specimen described in the preceding paper (Found : C, 54·8; H, 6·9; N, 10·9. Calc. for $C_{12}H_{18}N_2Cl_2$: C, 55·2; H, 6·9; N, 10·7%).

2-*Chloro*-3 : 6-*di*-sec.-*butylpyrazine*.—The mother liquors from the crystallisation of 2 : 5-di-*sec.*-butylpyrazine di-*N*-oxide were evaporated. The viscous liquid (1·0 g.), which would not solidify, was heated under reflux with phosphoryl chloride (10 c.c.) for 30 minutes and the reaction mixture worked up in the usual manner to give 2-chloro-3 : 6-di-*sec.*-butylpyrazine (0·6 g.) as a colourless oil, b. p. 118—120°/14 mm.; $n_D^{20°}$ 1·5037 (Found : N, 12·1. Calc. for $C_{12}H_{19}N_2Cl$: N, 12·4%). Treatment of the chloro-compound (0·4 g.) with potassium hydroxide using the conditions described in the preceding paper gave 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (0·15 g.) as small needles which after sublimation had m. p. and mixed m. p. 121—123°.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, November 27th*, 1946.]