

74. *The Stereoisomeric 2 : 3 : 5 : 6-Tetramethylpiperazines. Part V.*

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It has already been shown (J., 1929, 2889) that when 2 : 3 : 5 : 6-tetramethylpyrazine is reduced under various conditions, four of the five theoretically possible 2 : 3 : 5 : 6-tetramethylpiperazines are formed. Three of these bases, the α -, β -, and γ -isomerides, were obtained in quantity and further investigated (J., 1931, 1160; 1932, 1336; 1933, 143), but only very small amounts of the δ -compound were present in the reduction products and the fifth isomeride could not be isolated. 2 : 3 : 5 : 6-Tetramethylpiperazine is now prepared technically by the Shell Chemical Company by the reduction of tetramethylpyrazine with hydrogen under pressure and at a high temperature, either with or without a catalyst; it was anticipated that the investigation of large quantities of this material might lead to the isolation of the missing isomeride, and that possibly the δ -base might be obtained in amount sufficient for further study. About 1700 g. of this product were therefore submitted to examination; it was found to consist almost entirely (99—99.5%) of the α - and the β -base, but 1.2 g. of the δ -dihydrochloride and 3.7 g. of the dinitroso-derivative of a new base (ϵ) were isolated, together with a minute amount of unreduced tetramethylpyrazine. It is remarkable that the mixture apparently contains none of the γ -isomeride, which is the main product of the catalytic reduction at the ordinary temperature (J., 1929, 2892).

EXPERIMENTAL.

The 2 : 3 : 5 : 6-tetramethylpiperazine (1720 g.) was first separated, by draining at room temperature, into a solid (1390 g.; *A*), and a liquid fraction (329 g.; *B*). The solid portion at 40—45° furnished a liquid (65 g.; *C*), which solidified almost completely at room temperature, and a solid, m. p. 44—45° (1325 g.; *D*) (α -tetramethylpiperazine has m. p. 45°; *loc. cit.*, p. 2894). The liquid portion at 0° gave a liquid (197 g.; *E*) and a solid (132 g.; *F*). The liquid *E* was fractionally distilled and collected at 176—178°, 178—180°, and 180—182°. Each fraction gave a dinitroso-derivative, m. p. 130—140°, and all were therefore neutralised with hydrochloric acid, and the solutions evaporated: α -tetramethylpiperazine dihydrochloride separated in a pure state, and successive crops proved identical until a residue was obtained which did not crystallise easily and gave a dinitroso-derivative melting below 100°. This residue was converted entirely into dinitroso-derivative, which, after crystallisation from alcohol, yielded that of the β -base (m. p. 102°). A small residue undistilled in the original fractionation also gave some pure β -dinitroso-derivative.

Fractions *C*, *F*, and *D* (115 g. only) were treated in the same way and furnished further quantities of the α -dihydrochloride and the β -dinitroso-compound. In all, 511 g. of α -hydrochloride and 196 g. of the β -dinitroso-derivative were obtained. Evaporation of the mother-liquors of the dinitroso-derivatives gave fractions melting indefinitely from 83—85° up to 100°, and from mixed m. p. determinations all appeared to be similar. As it was thought that these consisted of mixtures of the α - and the β -compound, synthetic mixtures were prepared for comparison; it was found, however, that no mixture melted below 98—103.5° (this was given by a mixture of 10% α -, 90% β -), and therefore there must be some other base present. The whole of the residual dinitroso-derivative was accordingly hydrolysed and converted into a dihydriodide, which crystallised well: fractionation from water finally gave four fractions, each of which was reconverted into a dinitroso-derivative and further fractionated from alcohol and acetone. From the most soluble fraction of the dihydriodide, a little dinitroso- δ -tetramethylpiperazine was isolated, and from the least soluble a little of the corresponding α -derivative: the remainder of the fractions was separately hydrolysed and converted into the dibenzoates. That obtained from the least soluble dihydriodide furnished two fractions: (*a*) sparingly soluble in water, m. p. 236—238° (dinitroso-derivative, m. p. 157°), the α -base; (*b*) a more soluble fraction which, after crystallising from alcohol, had m. p. 163—165° and gave a dinitroso-derivative which, crystallised from alcohol and acetone, finally had m. p. 116°, the new ϵ -base. The remaining benzoates, after fractionation, conversion into dinitroso-derivatives, and fractionation, yielded mainly the β -base, together with a little more δ - and ϵ -.

The whole of the mother-liquors of dinitroso-derivatives which could not be further separated, was hydrolysed (14 g. of hydrochloride obtained) and reconverted into benzoates: the mixture was apparently so complex that separation proved impossible, and as all the tetramethyl

piperazines had now been obtained and the mixture could not therefore contain any new compound, experiments were abandoned

ϵ -2 : 3 : 5 : 6-Tetramethylpiperazine dihydrochloride, prepared from the dinitroso-derivative, crystallised from aqueous alcohol in small prisms (Found : Cl, 33.0. $C_8H_{18}N_2 \cdot 2HCl$ requires Cl, 33.0%). With alkali a solid base (or hydrate) was precipitated, m. p. 60°.

Dinitroso- ϵ -2 : 3 : 5 : 6-tetramethylpiperazine crystallised from alcohol or acetone in yellow prisms, m. p. 116—117° (Found : C, 48.1; H, 8.2; N, 27.9. $C_8H_{16}O_2N_4$ requires C, 48.0; H, 8.0; N, 28.0%). This m. p. was depressed by the addition of the α - or the β -derivative.

Dibenzoyl- ϵ -2 : 3 : 5 : 6-tetramethylpiperazine was easily prepared by the Schotten-Baumann method, and crystallised in needles from acetone (easily soluble) or light petroleum (sparingly soluble), m. p. 146—147° (Found : N, 8.0. $C_{22}H_{26}O_2N_2$ requires N, 8.0%).

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