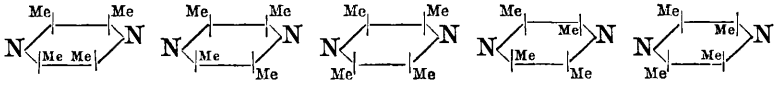
CCCXCI.—*The Stereoisomeric* 2 : 3 : 5 : 6-*Tetramethylpiperazines. Part I.*

By FREDERIC BARRY KIPPING.

2 : 3 : 5 : 6-TETRAMETHYLPIPERAZINE,  , should be capable of existence in five optically inactive stereoisomeric forms, which may be indicated thus :—



As only two (or possibly three) of these isomerides have been described, attempts have been made to prepare other members of the series.

After reducing 2 : 3 : 5 : 6-tetramethylpyrazine with sodium and alcohol, Wolff (*Ber.*, 1893, **26**, 724) isolated α-tetramethylpiperazine (dinitroso-derivative, m. p. 154°), β-tetramethylpiperazine (dinitroso-derivative, m. p. 99°), and a trace of a third isomeride (dinitroso-derivative, m. p. 82—86°). Stoehr (*J. pr. Chem.*, 1897, **55**, 49), repeating Wolff's work, obtained the α- and β-compounds but found no trace of a third isomeride: his results have now been confirmed by the present author.

As the reduction of this pyrazine seemed to be the only convenient method of preparing the corresponding piperazines, other reducing agents have been tried. Four of the five possible isomerides have thus been prepared.

Direct hydrogenation of tetramethylpyrazine hydrate with platinum oxide–platinum as the catalyst was unsuccessful, no hydrogen being absorbed by solutions in alcohol and in ethyl acetate, only small amounts when acetic acid was used as solvent, and little more when hydrogen chloride was present. Anhydrous tetramethylpyrazine hydrochloride, however, was rapidly and quantitatively reduced in absolute alcohol (compare Hamilton and Adams, *J. Amer. Chem. Soc.*, 1928, **50**, 2260, who found that, whereas pyridine was a poison to platinum catalysts, pyridonium salts were easily reduced). The reduction product consisted of a mixture of the β-isomeride already described and a new γ-isomeride (*dinitroso*-derivative, m. p. 174°). With palladium-black as catalyst, the reduction was much slower and did not proceed to completion and the products were again the β- and γ-isomerides. The passage of a mixture of tetramethylpyrazine vapour and hydrogen over nickel at 170—180° produced no reduction.

Reduction with aluminium amalgam in neutral solution gave a mixture of α-, β- and γ-tetramethylpiperazines. Sodium amalgam in aqueous acetic acid or hydrochloric acid gave mixtures of the α- and β-bases only.

Tin and hydrochloric acid reduced tetramethylpyrazine to a mixture of the α-, β- and γ-bases and a very small quantity of a fourth δ-isomeride (*dinitroso*-derivative, m. p. 189°).

In order to separate the isomerides in the reduction products, the hydrochlorides (or in some cases the hydriodides) were fractionally crystallised from water, alcohol, or mixtures of these solvents, each fraction being converted into its nitroso-derivative, the melting point of which was used as the criterion of purity. The bases were

easily recovered from the nitroso-derivatives by hydrolysis with hydrochloric acid.

The benzoyl and toluenesulphonyl derivatives of the various isomerides were then prepared for purposes of comparison and reference. In the formation of toluenesulphonyl derivatives, striking differences in behaviour were exhibited by the stereoisomerides. The γ-base gave a *monotoluenesulphonyl* derivative readily (but not quantitatively) by the Schotten–Baumann method, but did not form a ditoluenesulphonyl compound under any conditions. The α- and β-bases, on the other hand, reacted with *p*-toluenesulphonyl chloride only if they were anhydrous; a mono- and a di-derivative of the β-base were thus prepared, but the mono-derivative of the α-base could not be obtained. The δ-base was not available in sufficient quantity to allow of such experiments being made.

This behaviour is perhaps related to the extreme ease of hydrate formation of these bases (compare Graymore, this vol., p. 587); the γ-base, however, also gives a hydrate very readily.

EXPERIMENTAL.

Tetramethylpyrazine.—The *iso*nitroso-derivative of methyl ethyl ketone (Diels and Jost, *Ber.*, 1902, **35**, 3292) was converted into tetramethylpyrazine as follows (compare Kipping and Pope, J., 1926, 1077; Gabriel and Pinkus, *Ber.*, 1893, **26**, 2206). The *iso*nitroso-derivative (50 g.) was slowly added to a solution of stannous chloride (205 g.) in concentrated hydrochloric acid (295 c.c.) maintained at 5—10° and stirred mechanically. The product was diluted with water (450 c.c.), and 33% sodium hydroxide solution (900 c.c.) run in, the temperature being kept at 40—50°. Mercuric chloride (136 g.), dissolved in hot water (300 c.c.), was then added, and the mixture distilled in steam. Tetramethylpyrazine hydrate (26 g.) crystallised from the distillate on cooling (compare Guttnecht, *Ber.*, 1879, **12**, 2291; Treadwell, *Ber.*, 1881, **14**, 1469; Künne, *Ber.*, 1895, **28**, 2040). The anhydrous base was prepared from the hydrate by distillation: after removal of all the water (together with some of the base), the pure base boiled at 189—190° and melted at 85—86°.

The hydrochloride was prepared by evaporation to dryness of a solution of the base in hydrochloric acid or better by precipitation with dry hydrogen chloride of a solution of the anhydrous base in ether.

The anhydrous hydrochloride melted at 156° (Wolff, *Ber.*, 1887, **20**, 428, gives 91°. This is clearly the m. p. of the hydrate) (Found :

C, 55·0; H, 7·5; Cl, 21·0. Calc. for $C_8H_{12}N_2,HCl$: C, 55·6; H, 7·5; Cl, 20·6%). It is easily soluble in alcohol, water, acetone and acetic acid, fairly so in chloroform, and almost insoluble in ether and ethyl acetate. It sublimes readily in a vacuum at 100°. After standing in moist air for a day, the salt melted at 87—88° (Found : Cl, 17·1. Calc. for $C_8H_{12}N_2,HCl,2H_2O$: Cl, 17·05%).

Reduction of Tetramethylpyrazine. (a) *With sodium and alcohol.* To a solution of tetramethylpyrazine (33·3 g.) in absolute alcohol (650 c.c.), sodium (107 g.) was gradually added, dissolution being completed by heating. The product was diluted with water and distilled in steam, and the distillate neutralised with hydrochloric acid. Evaporation to dryness yielded 52·5 g. of hydrochloride, which was extracted with two lots of 250 c.c. of hot absolute alcohol. The residue (15 g.) gave a nitroso-derivative, m. p. 154—156° without recrystallisation, and was therefore Stoehr's α-tetramethylpiperazine hydrochloride. The alcoholic extracts were evaporated gradually and the successive crops of crystals were converted into nitroso-derivatives, all of which melted between 93° and 101°; careful fractionation of each portion resulted in the preparation of Stoehr's β-base (nitroso-derivative, m. p. 101—102°). No trace whatever was found of an isomeride giving a nitroso-derivative, m. p. 82—86°, as described by Wolff.

(b) *With hydrogen and a platinum catalyst.* The following method was adopted, as in no other case could anything approaching a quantitative reduction be obtained. A solution of tetramethylpyrazine hydrochloride (30 g.) in absolute alcohol with the addition of acetic acid (20 c.c.) and platinum oxide (0·3 g.) ("Organic Syntheses," VIII, 92) was shaken in hydrogen at just over atmospheric pressure for 8 hours, about 11 l. of hydrogen being absorbed. The solution was filtered from catalyst and concentrated somewhat, and sodium hydroxide gradually added until all unchanged tetramethylpyrazine had been precipitated as its hydrate (5 g.). This was removed by filtration, the filtrate made strongly alkaline and distilled in steam, and the distillate neutralised with hydriodic acid. The preparation was repeated until 87 g. in all of tetramethylpyrazine hydrochloride had been reduced. The tetramethylpiperazine hydriodide (130 g.) obtained was fractionally crystallised from water, aqueous alcohol, and alcohol in the order named, as the fractions increased in solubility in water. Each fraction was converted into the hydrochloride and subsequently into the nitroso-derivative, and the latter crystallised to constant melting point. Two nitroso-derivatives were thus obtained : (*a*) From the less soluble hydriodide fractions, a nitroso-derivative, m. p. 173—174°, which gave a new γ-tetramethylpiperazine (for analysis, etc., see

later); (*b*) from the more soluble hydriodide fractions, Stoehr's β-nitroso-derivative, m. p. 101—102°. No evidence could be obtained of the existence of any other isomeride in the reduction product.

(c) *With aluminium amalgam.* Aluminium (15 g.) was amalgamated (Mann and Pope, *Proc. Roy. Soc.*, 1925, **107**, 86) and tetramethylpyrazine hydrate (15 g.) in 95% alcohol (250 c.c.) was added at about 50°. A gentle reaction took place and when, after 4—5 hours, almost all the aluminium had dissolved the solution was filtered, neutralised with hydrochloric acid, and evaporated to dryness. The syrupy product partly crystallised on addition of alcohol, and the crystals gave a nitroso-derivative, m. p. 157° (α-base). The mother-liquor was distilled with alkali and neutralised with hydriodic acid, and the product fractionated from aqueous acetone. The less soluble portion gave a nitroso-derivative, m. p. 173—174° (γ-base), and the more soluble fraction one of m. p. 100° (β-base). The yields in this reduction were poor and small amounts of another base (insoluble in water) were present; as this could not be a tetramethylpiperazine (possibly it was a partly reduced pyrazine), it was not investigated.

(d) *With sodium amalgam.* Reduction of tetramethylpyrazine hydrate with 5% sodium amalgam in aqueous acetic and hydrochloric acids was carried out in the usual way, and the product examined as in the reduction with sodium. The bases produced in this manner were solely the α- and β-isomerides.

(e) *With tin and hydrochloric acid.* A mixture of tetramethylpyrazine hydrate (20 g.), concentrated hydrochloric acid (100 c.c.), and tin (50 g.) was boiled under reflux until the metal had dissolved. After being made alkaline, the product was distilled in steam, and the distillate neutralised with hydrochloric acid and concentrated. On cooling, crystals (2·5 g.) separated from which the base was isolated by distillation with alkali. On addition of saturated potassium carbonate solution to the distillate a solid base separated which after crystallisation from acetone had m. p. 85° and gave a nitroso-derivative, m. p. 157°, clearly Stoehr's α-isomeride. The acetone mother-liquor, neutralised with hydrochloric acid, evaporated, and treated with sodium nitrite, gave a nitroso-derivative (0·05 g.), which after crystallisation from acetone melted at 188—189°. This is the nitroso-derivative of a fourth tetramethylpiperazine, the δ-isomeride.

The hydrochloride in the original mother-liquor was converted into hydriodide, which on fractionation yielded the β- and γ-bases together with some unchanged tetramethylpyrazine. In further similar experiments, 0·4 g. of dinitroso-δ-tetramethylpiperazine was obtained from 20 g. of tetramethylpyrazine.

The Stereoisomeric Tetramethylpiperazines and their Derivatives.—In the preparation of these substances the dinitroso-derivatives were first made and crystallised to constant melting point.

α-2 : 3 : 5 : 6-Tetramethylpiperazine (compare Wolff and Stoehr, *locc. cit.*) is a colourless solid, b. p. 177—178°, m. p. 45°. Its hydrate ($2H_2O$) has m. p. 84—85° and crystallises easily from acetone. This (and the other isomerides) is readily soluble in water, but may be precipitated almost completely by the addition of a little potassium carbonate solution.

The dihydrochloride crystallises in prisms from aqueous alcohol and does not melt below 300° (Found, after drying in a vacuum at 15° : Cl, 32·8. Calc. for $C_8H_{18}N_2,2HCl$: Cl, 33·0%). It is almost insoluble in absolute alcohol.

Dinitroso-α-2 : 3 : 5 : 6-tetramethylpiperazine forms slightly yellow needles which crystallise easily from alcohol, m. p. 157°. It is exceedingly readily soluble in hot acetone, but only very slightly soluble in light petroleum.

Di-p-toluenesulphonyl-α-2 : 3 : 5 : 6-tetramethylpiperazine. The anhydrous base (1·5 g.) was dissolved in dry pyridine, *p*-toluenesulphonyl chloride (4·1 g.) added, and the solution boiled gently for about 3 hours; a precipitate gradually formed. Most of the pyridine was then distilled away, the residue treated with water, and the precipitated solid crystallised from hot pyridine and washed with acetone. (From the aqueous liquor, by treatment with nitrous acid, about 1·1 g. of dinitroso-α-tetramethylpiperazine were recovered.) This *product* melts at 308—309°, is easily soluble in hot pyridine, sparingly soluble in xylene, and almost insoluble in all the other usual solvents (Found : N, 6·5; S, 14·6. $C_{22}H_{30}O_4N_2S_2$ requires N, 6·2; S, 14·22%).

Dibenzoyl-α-2 : 3 : 5 : 6-tetramethylpiperazine, prepared by the Schotten–Baumann method, crystallises easily from alcohol in colourless plates, m. p. 247—248° (compare Wolff and Stoehr, *locc. cit.*).

β-2 : 3 : 5 : 6-Tetramethylpiperazine, prepared from its nitroso-derivative, is a colourless liquid, b. p. 183°. It forms no solid hydrate. The dihydrochloride crystallises from alcohol, in which it is much more soluble than the α-isomeride, in colourless prisms which do not melt at 300° (Found, after drying in a vacuum at 15° : Cl, 32·85. Calc. for $C_8H_{18}N_2,2HCl$: Cl, 33·0%). The dihydriodide also is fairly soluble in alcohol.

Dinitroso-β-2 : 3 : 5 : 6-tetramethylpiperazine crystallises from alcohol (or aqueous alcohol) in yellow prisms, m. p. 101—102°. It is more readily soluble in alcohol, acetone and light petroleum than the α-isomeride.

p-*Toluenesulphonyl*-β-2 : 3 : 5 : 6-*tetramethylpiperazine*. When the anhydrous base (4·1 g.) in pyridine was mixed with *p*-toluenesulphonyl chloride (11·5 g.), also dissolved in pyridine, heat was produced and the mixture became dark-coloured. After standing over-night, the precipitate which had formed was filtered off (8·1 g.) (A), and the pyridine removed from the mother-liquor by distillation. On treatment of the residue with water a dark-coloured solid (4·7 g.) (B) remained.

Portion (A), m. p. *ca.* 275°. This substance contained ionic chlorine and was therefore treated with dilute sodium hydroxide solution and washed well. After repeated crystallisation, *mono*-p-*toluenesulphonyl*-β-*tetramethylpiperazine*, m.p. 81—82°, was obtained (Found: N, 9·7; S, 10·7. $C_{15}H_{24}O_2N_2S$ requires N, 9·5; S, 10·7%). It crystallised from alcohol or aqueous alcohol in small colourless needles or prisms and from light petroleum in prisms. Passage of dry hydrogen chloride through an ethereal solution caused precipitation of the *hydrochloride*, which crystallised from alcohol in colourless prisms, m. p. 278° (decomp.) (Found: Cl, 10·6. $C_{15}H_{24}O_2N_2S,HCl$ requires Cl, 10·65%).

Portion (B). This was washed with petroleum to remove any unchanged *p*-toluenesulphonyl chloride; the residue crystallised from aqueous pyridine in small colourless plates, m. p. 222°, of *di*-p-*toluenesulphonyl*-β-*tetramethylpiperazine* (Found: N, 6·3; S, 14·4. $C_{22}H_{30}O_4N_2S_2$ requires N, 6·2; S, 14·2%).

In further preparations a substance was isolated which separated from alcohol–acetone in clusters of needles, m. p. 238—239°. Treatment with dilute alkali solution yielded mono-*p*-toluenesulphonyl-β-tetramethylpiperazine, and when this was mixed in acetone solution with 1 mol. of *p*-toluenesulphonic acid the substance of m. p. 238—239° was regenerated. The latter is therefore the *p*-toluenesulphonate of the mono-*p*-toluenesulphonyl derivative.

Dibenzoyl-β-2 : 3 : 5 : 6-tetramethylpiperazine, prepared by the Schotten–Baumann method, crystallises easily from acetone–light petroleum and melts at 175—176° (compare Wolff and Stoehr, *locc. cit.*).

γ-2 : 3 : 5 : 6-Tetramethylpiperazine, prepared in the usual way from its nitroso-derivative, is a colourless solid, m. p. 67—68°, b. p. 195—196°. Addition of potassium carbonate to its aqueous solution produced a jelly-like precipitate which was doubtless a hydrate, but it was not further investigated.

The *dihydrochloride* crystallises from aqueous alcohol in large plates containing (after being dried in a vacuum at 15°) one molecule of water (Found: Cl, 29·9; H_2O, 8·2. $C_8H_{18}N_2,2HCl,H_2O$ requires Cl, 30·5; H_2O, 7·8%. Found, after drying in a vacuum at

100°: Cl, 33·2. $C_8H_{18}N_2$,2HCl requires Cl, 33·0%). It does not melt below 300°.

The *dihydriodide* crystallises from water in cubes or octahedra and is almost insoluble in alcohol (Found: I, 63·6. $C_8H_{18}N_2$,2HI requires I, 63·8%).

Dinitroso-γ-2 : 3 : 5 : 6-tetramethylpiperazine crystallises from alcohol or acetone in yellow prisms, m. p. 173—174° (Found: C, 47·7; H, 7·9. $C_8H_{16}O_2N_4$ requires C, 48·0; H, 8·0%). It has about the same solubility as the α-isomeride in alcohol, but is less soluble in acetone.

Mono-p-toluenesulphonyl-γ-2 : 3 : 5 : 6-tetramethylpiperazine could be prepared in aqueous solution in small yield only and was preferably made in pyridine as before. In all cases, even when a large excess of the acid chloride was used, only the mono-derivative could be obtained. It crystallised from aqueous alcohol or light petroleum in colourless plates, m. p. 138—139° (Found: C, 60·9; H, 8·1. $C_{15}H_{24}O_2N_2S$ requires C, 60·8; H, 8·1%). The passage of dry hydrogen chloride through an ethereal solution precipitated the *hydrochloride*, which, after crystallisation from aqueous alcohol, had m. p. 332° (decomp.) (Found: Cl, 10·7. $C_{15}H_{24}O_2N_2S$,HCl requires Cl, 10·65%).

Benzoyl-γ-2 : 3 : 5 : 6-tetramethylpiperazine. Treatment of the γ-base with benzoyl chloride by the Schotten–Baumann method yielded a product which on fractionation from acetone gave two substances melting at 162° and 65° respectively. The low-melting fraction was dissolved in benzene, traces of the high-melting substance were removed, and hydrogen chloride was passed through the filtrate. A gummy substance was precipitated which crystallised from alcohol and did not melt at 300° (Found: Cl, 12·5. $C_{15}H_{22}ON_2$,HCl requires Cl, 12·55%). This *hydrochloride* was dissolved in water and treated with alkali; the precipitated *monobenzoyl-γ-2 : 3 : 5 : 6-tetramethylpiperazine* crystallised from light petroleum in small colourless prisms, m. p. 85° (Found: N, 11·35. $C_{15}H_{22}ON_2$ requires N, 11·4%).

The high-melting fraction was crystallised successively from benzene, ethyl acetate and alcohol, in all of which it was easily soluble, and finally obtained in colourless prisms, m. p. 163—164° (Found: N, 7·7, 7·7. $C_{22}H_{26}O_2N_2$ requires N, 8·0%). It is therefore *dibenzoyl-γ-tetramethylpiperazine.*

δ-*2 : 3 : 5 : 6-Tetramethylpiperazine.* Treatment of an aqueous solution of the hydrochloride of this base with alkali gave a precipitate of fine needles (probably a hydrate), m. p. 53—55° (without crystallisation). The *dihydrochloride* crystallised from water in small colourless prisms and did not melt below 300°. It was almost

insoluble in alcohol (Found: Cl, 32·9. $C_8H_{18}N_2,2HCl$ requires Cl, 33·0%).

Dinitroso-δ-2 : 3 : 5 : 6-*tetramethylpiperazine* crystallises from acetone, in which it is much less soluble than the other isomerides, in yellow prisms, m. p. 189—190° (mixed m. p. with γ-isomeride, 145—150°) (Found by micro-methods: C, 48·0; H, 8·7; N, 27·7. $C_8H_{16}O_2N_4$ requires C, 48·0; H, 8·0; N, 28·0%).

Summary.

Four of the five theoretically possible 2 : 3 : 5 : 6-tetramethylpiperazines have been prepared by reducing 2 : 3 : 5 : 6-tetramethylpyrazine under various conditions. Their properties, as would be expected, are very similar except with regard to their behaviour with *p*-toluenesulphonyl chloride. In this case the α-isomeride yields a di-derivative, the γ- a mono-, and the β- both. Only small quantities of the δ-base were available and were insufficient for study.

Further work is in progress on these bases with a view to a determination of their configuration.

In conclusion I wish to express my thanks to Sir William Pope for his interest in this work.

THE UNIVERSITY CHEMICAL LABORATORY,
CAMBRIDGE. [*Received, October 23rd*, 1929.]