173. *The Stereoisomeric 2 : 3 : 5 : 6-Tetramethylpiperazines. Part III. The Reduction Products of 2 : 3 : 5 : 6-Tetramethylpyrazine Methiodide.*

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From the figures given (J., 1931, 1160), it is clear that, if any group is attached to one of the nitrogen atoms of 2 : 3 : 5 : 6-tetramethylpiperazine, the plane and the centre of symmetry of formula (III) are destroyed and this then represents a *dl*-substance; formulæ (I) and (IV), however, still retain a plane of symmetry and represent *meso*-compounds. It has already been shown (*loc. cit.*) that, of the four known isomerides, β-2 : 3 : 5 : 6-tetramethylpiperazine has the configuration represented by (II), and in order to determine those of the remaining isomerides it is clearly of importance to prepare mono-*N*-substitution derivatives, $RN<(CHMe)_4>NH$, and, if possible, to show that one of these is resolvable into optical antipodes, whereas the parent base is a *meso*-compound: the base exhibiting these properties must then have the configuration (III).

As attempts to prepare such derivatives of the α-base had failed (J., 1929, 2894) and the δ-base was not available in sufficient quantities for investigation, it seemed probable that the reduction of 2 : 3 : 5 : 6-tetramethylpyrazine monomethiodide would yield a mixture of pentamethylpiperazines, each of which could be correlated with a tetramethyl base, and used for a determination of the configuration of the latter. Furthermore, the pentamethyl base corresponding with the missing tetramethylpiperazine might be formed (*loc. cit.*, p. 2890).

The methiodide was therefore reduced with hydrogen in the presence of platinum (compare Hamilton and Adams, *J. Amer. Chem. Soc.*, 1928, **50**, 2260), and about 250 g. of pentamethylpiperazine monohydriodide prepared. By the fractionation of this product from alcohol, nearly 220 g. of a less soluble *hydriodide* were obtained in a pure state, the base of which gave a p-*toluenesulphonyl* derivative, m. p. 124°. As the same compound was produced by the methylation of 1-*p*-toluenesulphonyl-γ-2 : 3 : 5 : 6-tetramethylpiperazine, it is clear that the base corresponding with this *p*-toluenesulphonyl derivative is γ-2 : 3 : 4 : 5 : 6-*pentamethylpiperazine* (J., 1931, 1161).

The oily mother-liquors of the γ-hydriodide were converted into hydrochloride, which was fractionated; each fraction was converted into the phenylthiourea, which was found to be the most suitable derivative for following the course of the fractionation. All the fractions appeared to be the same and to be homogeneous, m. p.

120—121°; after hydrolysis, however, a test portion of the base recovered from this thiourea gave about a 25% yield of *p*-toluenesulphonyl-γ-2 : 3 : 4 : 5 : 6-pentamethylpiperazine. Since γ-2 : 3 : 4 : 5 : 6-*pentamethylpiperazine phenylthiourea* has m. p. 154°, the thiourea of m. p. 120—121° is apparently a mixture of the former with an isomeride, which crystallises unchanged from various solvents.

Efforts to separate the mixture of bases by the fractionation of their hydrobromides, and by fractional formation of the thioureas, also proved useless, and finally the whole of the mixed bases was converted into the *p*-toluenesulphonyl derivative. Fractionation yielded a less soluble product, m. p. 124°, the γ-derivative, and a new compound, m. p. 99—100°, which was formed in small yield only, a fact which, combined with its greater solubility, accounts for its not having been isolated when only small amounts were prepared. The *thiourea* corresponding with this new *p*-toluenesulphonyl derivative had m. p. 122—123°.

It was thought that this new base (which will be called A) might be *dl*-β-2 : 3 : 4 : 5 : 6-pentamethylpiperazine, as a mixture of the β- and the γ-isomeride is obtained by the catalytic reduction of 2 : 3 : 5 : 6-tetramethylpyrazine. 1 - *p* - Toluenesulphonyl - *dl* - β-2 : 3 : 5 : 6-tetramethylpiperazine was therefore converted into p - *toluenesulphonyl* - dl - β - 2 : 3 : 4 : 5 : 6 - *pentamethylpiperazine* by methylation; this had m. p. 100—101°, but mixed m. p.'s showed that it is not identical with the *p*-toluenesulphonyl derivative of A. Further, dl-β-2 : 3 : 4 : 5 : 6-*pentamethylpiperazine phenylthiourea* prepared from the *p*-toluenesulphonyl derivative had m. p. 95° and was different from the thiourea derived from A.

The configuration of β-2 : 3 : 5 : 6-tetramethylpiperazine (J., 1931, 1160) is such that the two nitrogen atoms are differently situated in the molecule, and so the 2 : 3 : 4 : 5 : 6-pentamethyl base will be different from the 1 : 2 : 3 : 5 : 6-compound, whereas in the case of the other isomerides no such difference would appear: the possibility still remains, then, that the base A is the latter substance. From the base A and from *dl*-β-2 : 3 : 5 : 6-tetramethylpiperazine, by methylation, 1 : 2 : 3 : 4 : 5 : 6-hexamethylpiperazines were therefore prepared; both yielded *monomethiodides*, m. p. (decomp.) 275°, which when mixed again melted at the same temperature. The crystalline forms and solubilities of the isomerides, however, appeared to be different, but the quantity of the base from pure A was too small for solubility determinations. No salts of the hexamethylpiperazines had m. p.'s suitable for mixed melts, and the identity or otherwise of the two compounds could not be definitely decided.

α-2 : 3 : 5 : 6-Tetramethylpiperazine on methylation and treat-

ment with methyl iodide gave a *dimethiodide*, m. p. 273°, and the base A therefore cannot be an α-pentamethylpiperazine. Attempts to prepare *dl*-β-1 : 2 : 3 : 5 : 6-pentamethylpiperazine by suitable "blocking" of the nitrogen atoms failed.

The product of the reduction of 2 : 3 : 5 : 6-tetramethylpyrazine methiodide is therefore mainly γ-2 : 3 : 4 : 5 : 6(or 1 : 2 : 3 : 5 : 6)-pentamethylpiperazine mixed with small quantities of an isomeric compound which has not been correlated with any tetramethyl base.

EXPERIMENTAL.

2 : 3 : 5 : 6-Tetramethylpyrazine methiodide (compare Wolff, *Ber.*, 1887, **20**, 429) was obtained by heating tetramethylpyrazine with a slight excess of methyl iodide at 100° during several hours. The dark-coloured product separated from alcohol in yellow prisms, m. p. 212° (Found: I, 45·6. Calc. for $C_9H_{15}N_2I$: I, 45·7%). It is easily soluble in water, alcohol and chloroform, less readily so in acetone, and almost insoluble in light petroleum, ether and benzene.

Reduction of the Methiodide and Fractionation of the Product.—The methiodide was reduced in 50 g. batches by dissolving it in rectified spirit, with the addition of a little water, and shaking in hydrogen, with platinum oxide–platinum (0·5 g.) as the catalyst. After 4—6 hours, when about 12 litres of hydrogen had been absorbed, the colourless solutions from five such batches were evaporated under reduced pressure to a syrup (no alkaline vapours were evolved), which crystallised easily on the addition of absolute alcohol, and was exhaustively fractionated from this solvent. The less soluble fractions consisted of γ-2 : 3 : 4 : 5 : 6-pentamethylpiperazine monohydriodide (see below) (217 g.). The mother-liquors on evaporation resisted crystallisation and the base was therefore converted into its hydrochloride, and this salt fractionated from aqueous alcohol, alcohol, and acetone successively. The phenylthiourea prepared from each fraction in nearly theoretical yield by the addition of the equivalent quantity of aqueous sodium hydroxide and phenyl *iso*-thiocyanate had m. p. 110—124°, and 120—121° after successive crystallisations from light petroleum, alcohol, light petroleum, and acetone (Found: C, 66·2; H, 8·6. $C_{16}H_{25}N_3S$ requires C, 66·0; H, 8·6%). The combined fractions were hydrolysed with hydrochloric acid, and the hydrochloride formed was crystallised from alcohol and aqueous acetone (Found: Cl, 30·9. $C_9H_{20}N_2,2HCl$ requires Cl,

γ-derivative (m. p. 154°). The hydrochlorides and phenylthioureas being useless for effecting a separation, the bases were converted into hydrobromides, which crystallised easily from aqueous alcohol; fractions of this salt again gave thioureas, m. p. 121°. An attempt to separate the bases by the fractional formation of their thioureas by shaking with successive small quantities of phenyl *iso*thiocyanate gave specimens of the thiourea all of which melted between 119° and 123° and appeared to be identical.

The whole of the mixture of bases was then converted into the *p*-toluenesulphonyl derivative, which was separated, with the aid of light petroleum and alcohol, into a less soluble fraction, m. p. 124° (the γ-isomeride), and a new derivative, m. p. 99—100° (of the base A). Mixtures of this with *p*-toluenesulphonyl-*dl*-β-2 : 3 : 4 : 5 : 6-pentamethylpiperazine (see later) melted indefinitely at about 80° and there is therefore no doubt that the two substances are different.

The *p*-toluenesulphonyl derivative of A (0·1 g.) was heated with hydrochloric acid at 120° during 4 hours, and the base isolated as hydrochloride by distillation in steam; it yielded a thiourea, m. p. 122—123°, a value almost identical with that of the mixture with the γ-isomeride.

The pyridine distilled from the preparation of the *p*-toluenesulphonyl derivative was dissolved in water and successive quantities of phenyl *iso*thiocyanate were added until no more thiourea was formed; all the fractions of thiourea thus prepared melted at 122—123°, and probably consisted of the nearly pure derivative of A.

The hydrochloride of A was methylated with formalin, the resulting base obtained in ethereal solution and treated with methyl iodide. The *monomethiodide* of the hexamethylpiperazine so formed was crystallised from acetone–methyl alcohol and had m. p. 275° (decomp.) (Found: I, 41·4. $C_{11}H_{25}N_2I$ requires I, 40·7%). This m. p. was not depressed by the addition of the methiodide of *dl*-β-1 : 2 : 3 : 4 : 5 : 6-hexamethylpiperazine, but so much decomposition occurred that there was no evidence of identity.

γ-2 : 3 : 4 : 5 : 6-*Pentamethylpiperazine hydriodide*, obtained as described above, crystallises from water or alcohol in prisms, m. p. 161—162° (Found: I, 44·5. $C_9H_{20}N_2,HI$ requires I, 44·7%): it is very easily soluble in water and in hot alcohol.

γ-2 : 3 : 4 : 5 : 6-*Pentamethylpiperazine* forms a *monohydrate* which is easily soluble in alcohol and ethyl acetate, and fairly so in benzene and ether, probably with decomposition of the hydrate. It crystallises (best) from acetone in prisms, m. p. 73—74°. Water is lost over calcium chloride in a desiccator and the (liquid) free base is gradually produced; the hydrate was therefore dried for analysis by standing over the free base (Found: C, 60·8; H, 12·4. $C_9H_{20}N_2,H_2O$ requires

C, 62·1; H, 12·6%). The free base, in a moist atmosphere, took up 8·8%: the monohydrate requires 10·3%, and the difference is doubtless due to volatilisation of the base. The free base has b. p. 201—202° and crystallises in prisms, m. p. 4—5°; it is exceedingly hygroscopic.

γ-2 : 3 : 4 : 5 : 6-*Pentamethylpiperazine dihydrochloride* crystallises, by the addition of acetone to an aqueous-alcoholic solution, in minute, hygroscopic, colourless needles, m. p. *ca.* 300°. It is almost insoluble in alcohol but very readily soluble in water (Found: Cl, 31·0, 31·1. $C_9H_{20}N_2$,2HCl requires Cl, 31·0%).

γ-2 : 3 : 4 : 5 : 6-*Pentamethylpiperazine dihydriodide* crystallises from absolute alcohol in prisms, m. p. 240° (decomp.), and is readily soluble in alcohol, methyl alcohol and water, almost insoluble in acetone and ethyl acetate (Found in material dried in a vacuum at 120°: I, 61·8. $C_9H_{20}N_2$,2HI requires I, 61·6%).

γ-2 : 3 : 4 : 5 : 6-*Pentamethylpiperazine phenylthiourea* crystallises from light petroleum (b. p. 100—120°) in small colourless prisms, m. p. 154° (Found: C, 66·0; H, 8·7. $C_{16}H_{25}N_3S$ requires C, 66·0; H, 8·6%). It is easily soluble in alcohol and benzene, but much more sparingly so in light petroleum.

p-*Toluenesulphonyl*-γ-2 : 3 : 4 : 5 : 6-*pentamethylpiperazine* crystallises from light petroleum in needles and from alcohol, in which it is much more soluble, in prisms, m. p. 124° (Found: C, 61·8; H, 8·5. $C_{16}H_{26}O_2N_2S$ requires C, 62·0; H, 8·4%). The same substance was also obtained by methylation of 1-*p*-toluenesulphonyl-γ-2 : 3 : 5 : 6-tetramethylpiperazine (J., 1929, 2896) with methyl iodide or with formalin, thus proving that the tetra- and the penta-methyl base have the same configuration. The *hydrochloride* crystallises from alcohol in colourless prisms, m. p. 250° (Found in salt dried at 100° in a vacuum: Cl, 10·3. $C_{16}H_{26}O_2N_2S$,HCl requires Cl, 10·25%).

1-Nitroso-γ-2 : 3 : 4 : 5 : 6-pentamethylpiperazine was prepared in the usual way and isolated by extraction with ether and distillation under reduced pressure. It is a pale yellow oil, b. p. 155—157°/15 mm., very readily soluble in light petroleum, alcohol, ether, carbon disulphide, and less soluble in hot than in cold water. It solidified when cooled, m. p. 24—25°, but could not be recrystallised satisfactorily. A benzene solution treated with hydrogen chloride gave an oily precipitate which solidified easily and was washed with ether (Found: Cl, 16·3. $C_9H_{19}ON_3$,HCl requires Cl, 16·05%). This *hydrochloride* is almost insoluble in acetone but readily soluble in water and alcohol.

γ-1 : 2 : 3 : 4 : 5 : 6-*Hexamethylpiperazine dihydrochloride* was obtained from the hydrochloride of the pentamethyl base by boiling it with 40% formalin; it crystallised from alcohol (Found: Cl, 28·9,

29·4. $C_{10}H_{22}N_2$,2HCl requires Cl, 29·2%). The free base had b. p. 211—212°.

The hexamethyl base just described yielded a *monomethiodide* which crystallised from methyl alcohol–acetone in colourless needles, m. p. 272—274° (decomp.) (Found : I, 40·7. $C_{11}H_{25}N_2I$ requires I, 40·7%). It was also obtained from γ-2 : 3 : 5 : 6-tetramethylpiperazine dihydrochloride by treatment successively with formalin and methyl iodide. Attempts to make the dimethiodide by heating the monomethiodide with methyl iodide in a sealed tube at 150° were unsuccessful, as no interaction occurred (Found : I, 41·0%).

p-Toluenesulphonyl-*dl*-β-2 : 3 : 4 : 5 : 6-pentamethylpiperazine was prepared by methylation of 1-*p*-toluenesulphonyl-β-2 : 3 : 5 : 6-tetramethylpiperazine with methyl iodide or formalin ; it crystallises from alcohol or light petroleum in small prisms, m. p. 100—101°, and it was not identical with the sulphonyl derivative of the base A (p. 1337).

dl-β-2 : 3 : 4 : 5 : 6-*Pentamethylpiperazine phenylthiourea*. The toluenesulphonyl derivative just described was hydrolysed by heating it with concentrated hydrochloric acid at 120° during 8 hours and the base was isolated and converted into the *thiourea* in the usual way. It crystallised from light petroleum (b. p. 100—120°) in prisms, m. p. 95°, and was markedly different from the corresponding derivative of the base A (Found : C, 66·0 ; H, 8·5. $C_{16}H_{25}N_3S$ requires C, 66·0 ; H, 8·6%).

dl-β-1 : 2 : 3 : 4 : 5 : 6-Hexamethylpiperazine, obtained from the corresponding tetramethyl base with formalin, had b. p. 203—204°. With a methyl-alcoholic solution of methyl iodide, a *monomethiodide* separated at once, m. p. 275° (decomp.) after washing with acetone (Found : I, 40·8. $C_{11}H_{25}N_2I$ requires I, 40·7%).

4-*Nitroso*-1-p-*toluenesulphonyl*-dl-β-2 : 3 : 5 : 6-*tetramethylpiperazine* was obtained from an acetic acid solution of the *p*-toluenesulphonyl derivative and nitrous acid ; it crystallised from alcohol in small prisms, m. p. 153—154° (Found : C, 55·3 ; H, 7·1. $C_{15}H_{23}O_3N_3S$ requires C, 55·4 ; H, 7·1%). It is easily soluble in hot acetone, moderately so in hot alcohol, and almost insoluble in cold alcohol.

4-Amino-1-*p*-toluenesulphonyl-*dl*-β-2 : 3 : 5 : 6-tetramethylpiperazine was obtained by reduction of the last-mentioned compound with aluminium amalgam and aqueous alcohol. It crystallises from hot alcohol in colourless needles, m. p. 140—141°. It is easily soluble in benzene and chloroform, and fairly so in ether : it is insoluble in water, but dissolves in dilute acids. The passage of hydrogen chloride through the ethereal solution yielded an oily *hydrochloride*, which crystallised easily and was washed with acetone (Found : Cl, 10·1. $C_{15}H_{25}O_2N_3S$,HCl requires Cl, 10·2%).

α-1 : 2 : 3 : 4 : 5 : 6-*Hexamethylpiperazine.* Unlike the β- and the γ-tetramethylpiperazine, the α-isomeride is not methylated by boiling formalin, even after 8 hours or more. The dihydrochloride (3 g.) was therefore heated with 40% formalin (10 c.c.) at 160—180° during 6 hours, and the product crystallised from alcohol (Found : Cl, 29·2. $C_{10}H_{22}N_2,2HCl$ requires Cl, 29·2%). The anhydrous base had b. p. 198—200°. With methyl iodide, under the same conditions which lead to the production of monomethiodides with the β- and the γ-base, this base yields a *dimethiodide*, m. p. 272—273° (decomp.) (Found : I, 55·6. $C_{12}H_{28}N_2I_2$ requires I, 55·8%). It is very sparingly soluble in alcohol, methyl alcohol and acetone, but easily soluble in hot water, from which it separates in small cubes or octahedra.

α-Hexamethylpiperazine in acetone solution with ethyl iodide slowly deposited needles of the *monoethiodide* (Found : I, 39·0. $C_{12}H_{27}N_2I$ requires I, 38·9%). This substance is the only mono-*N*-derivative of the α-series of bases which has been prepared.

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