CLI.—*The Stereoisomeric 2 : 3 : 5 : 6-Tetramethylpiperazines. Part II. The Configuration of the so-called β-Isomeride.*

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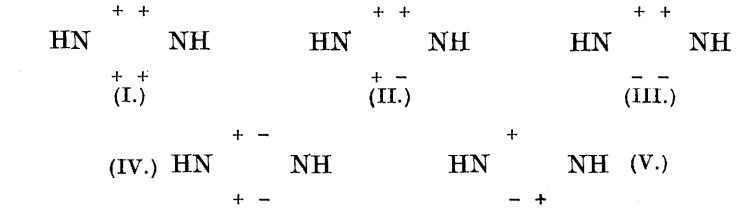
AN examination of the formulæ of the five theoretically possible optically inactive 2 : 3 : 5 : 6-tetramethylpiperazines (J., 1929, 2889) reveals the fact that, of these, two (II and V) are externally compensated, whereas the remaining three all have planes of symmetry and are therefore *meso*-compounds; the + sign being used to represent a methyl group above the plane of the ring, this is clear from the following figures:



Furthermore, isomerides (II) and (V) differ from each other in that the two nitrogen atoms of (V) are identically situated, whereas those of (II) have a different environment in the molecule. Hence, if two different groups, A and B, are introduced in the 1 : 4- and 4 : 1-positions respectively in formula (II), the two substances so depicted should be different; the compound represented by (V), however, must yield the same product in each case.

It is now shown that the so-called β-isomeride (*loc. cit.*, p. 2894) must have the configuration represented by (II), as it was found to be externally compensated, and to give isomeric 1 : 4-derivatives of the type just mentioned. Attempts to resolve the base with *d*-camphor-10-sulphonic acid, and *p*-toluenesulphonyl-β-2 : 3 : 5 : 6-tetramethylpiperazine with *d*-camphor-10-sulphonic acid, *d*-α-bromocamphor-π-sulphonic acid and *d*-hydroxymethylenecamphor, were unsuccessful: crystalline salts were obtained in each case, but fractional crystallisation of these failed to effect a separation.

The d-*base* was finally obtained by condensation of the *dl*-compound with *d*-hydroxymethylenecamphor, followed by crystallisation of the product; after three recrystallisations from alcohol, pure d-β-2 : 3 : 5 : 6-*tetramethylpiperazinebis*-d-*methylenecamphor* was obtained. Decomposition of this with bromine in the usual way (Pope and Read, J., 1912, **101**, 2337) yielded d-β-2 : 3 : 5 : 6-*tetra*-

methylpiperazine, which showed $[\alpha]_{5461}$ + 20·1° as *dihydrochloride*; the *d*-dinitroso-derivative prepared from this gave $[\alpha]_{5461}$ + 135°.

The l-*base* could not be obtained conveniently from the mother-liquors of the methylenecamphor derivative, but it was found that l-β-2 : 3 : 5 : 6-*tetramethylpiperazine mono*-d-α-*bromocamphor*-π-*sulphonate* was obtained by crystallisation of the salt of the *dl*-base from acetone. *l*-β-2 : 3 : 5 : 6-Tetramethylpiperazine dihydrochloride showed $[\alpha]_{5461}$ − 21·8° and the *l*-dinitroso-derivative gave $[\alpha]_{5461}$ − 135·5°.

Isomeric derivatives of the base of the type mentioned above were then prepared by the introduction of the A and B groups in a different order. It is assumed here, for the purpose of nomenclature, that the group first introduced takes up the 1-position. 1-*p*-Toluenesulphonyl-*dl*-β-2 : 3 : 5 : 6-tetramethylpiperazine (J., 1929, 2895) was converted, by boiling it with benzenesulphonyl chloride in pyridine solution, into 4-*benzenesulphonyl*-1-p-*toluenesulphonyl*-dl-β-2 : 3 : 5 : 6-*tetramethylpiperazine*, m. p. 175—176°; 1-*benzenesulphonyl*-dl-β-2 : 3 : 5 : 6-*tetramethylpiperazine* was similarly converted, by treatment with *p*-toluenesulphonyl chloride, into 1-*benzenesulphonyl*-4-p-*toluenesulphonyl*-dl-β-2 : 3 : 5 : 6-*tetramethylpiperazine*, m. p. 186°. Mixtures of these two isomerides melted indefinitely at 158—160°, and there is therefore no doubt that the two substances are different.

EXPERIMENTAL.

β-2 : 3 : 5 : 6-*Tetramethylpiperazine* d-*camphor*-10-*sulphonate* was obtained crystalline by the treatment of the residue from the evaporation of an aqueous solution of equimolecular quantities of the acid and base, with a mixture of benzene and light petroleum. Three crystallisations from benzene raised the melting point only 2°, the final value being 89—90° (Found : S, 8·4. $C_8H_{18}N_2,C_{10}H_{16}O_4S$ requires S, 8·6%). The salt separated from benzene in clusters of needles and was readily soluble in water, chloroform, and alcohol, but almost insoluble in light petroleum. All fractions exhibited substantially the same rotatory power, $[\alpha]^{15°}_{5780}$ + 31·2°, $[\alpha]^{15°}_{5461}$ + 35·7° in chloroform (c = 1·87) and $[\alpha]^{15°}_{5461}$ + 17·35°, $[M]_{5461}$ + 65·1° in water (c = 1·81). The last value is also practically identical with that for salts of the acid with inactive bases. The base recovered from the last fraction was optically inactive.

1-*p*-Toluenesulphonyl-β-2 : 3 : 5 : 6-tetramethylpiperazine *d*-camphor-10-sulphonate was prepared by warming 1-*p*-toluenesulphonyl-β-2 : 3 : 5 : 6-tetramethylpiperazine (1 mol.) with the acid (1 mol.) in aqueous solution : on cooling, the salt separated in prisms, m. p. 182—187°. After seven recrystallisations from

water the salt melted at 190°, but the rotatory powers of all fractions were practically identical, $[\alpha]_{5461}^{15°}$ + 24·8° in alcohol (c = 1·19). The sulphonyl derivative recovered from the last fraction was inactive.

1-p-*Toluenesulphonyl*-β-2 : 3 : 5 : 6-*tetramethylpiperazine* d-α-*Bromocamphor-π-sulphonate.*—A mixture of equimolecular proportions of the acid and base in water gave a gummy product, which crystallised after standing on the water-bath for some time; m. p. 142—143°. It separated from water, in which it was sparingly soluble, in small needles and from alcohol, in which it dissolved readily, in a similar form. After three recrystallisations from alcohol the melting point had not changed and the specific rotations of all fractions were substantially the same (Found : Br, 13·0. $C_{15}H_{24}O_2N_2S,C_{10}H_{15}O_4BrS$ requires Br, 13·15%). $[\alpha]_{5461}^{15°}$ + 63·2° in alcohol (c = 1·18). The sulphonyl derivative liberated from the last fraction showed a slight dextrorotation in alcohol, and that from the mother-liquors a lævo-value, so some resolution appeared to have occurred. In view, however, of the successful experiments described later, it was considered unnecessary to continue work on this salt.

1-p-*Toluenesulphonyl*-β-2 : 3 : 5 : 6-*tetramethylpiperazine*-d-*methylenecamphor.*—*d*-Hydroxymethylenecamphor (1 mol.) and the *p*-toluenesulphonyl derivative (1 mol.) were warmed together in alcohol–acetic acid on the water-bath. A crystalline solid gradually separated, m. p. 175°. After four recrystallisations from alcohol the melting point had risen to 179°, and all fractions gave the same rotatory power (Found : C, 68·2; H, 8·2. $C_{26}H_{38}O_3N_2S$ requires C, 68·1; H, 8·3%). $[\alpha]_{5780}^{12°}$ + 287°, $[\alpha]_{5461}^{12°}$ + 339° in alcohol (c = 1·04). The sulphonyl derivative recovered from the last fraction by the bromine method was inactive.

β-2 : 3 : 5 : 6-*Tetramethylpiperazinebis*-d-*methylenecamphor.*—The hydrochloride of the *dl*-base (10 g.), *d*-hydroxymethylenecamphor (17 g.), potassium hydroxide (5·2 g.), and sodium acetate (3 g.) were boiled together in aqueous-alcoholic solution during about 5 hours. The crystalline material which separated from the cooled solution melted at 253° and was easily soluble in cold chloroform, and in hot alcohol and acetone : it was almost insoluble in light petroleum. After being washed with water, it was recrystallised from alcohol three times, finally separating in stout needles, m. p. 266°, which proved to be pure d-β-2 : 3 : 5 : 6-*tetramethylpiperazinebis*-d-*methylenecamphor* (Found : C, 77·2; H, 9·7. $C_{30}H_{46}O_2N_2$ requires C, 77·3; H, 9·9%). $[\alpha]_{5780}^{16°}$ + 549°, $[\alpha]_{5461}^{16°}$ + 642° in chloroform (c = 0·4). Material precipitated by the addition of water to the filtrate from the original preparation, after one recrystallisation from aqueous alcohol, showed $[\alpha]_{5780}^{16°}$ + 610°, $[\alpha]_{5461}^{16°}$ + 742° (c = 0·5).

This is doubtless impure *l*-β-2 : 3 : 5 : 6-tetramethylpiperazinebis-*d*-methylenecamphor.

The pure derivative of the *d*-base (3 g.; 1 mol.) was dissolved in warm carbon tetrachloride, and bromine (2·32 g.; 2 mols.) in carbon tetrachloride was slowly added. The reddish precipitate which was formed was filtered off; when it was boiled with alcohol, the hydrobromide of the *d*-base was obtained, $[\alpha]_{5461}^{16°}$ + 14·3° in water (c = 4·85). d-β-2 : 3 : 5 : 6-*Tetramethylpiperazine dihydrochloride* was obtained from this by distillation with alkali, and neutralisation of the distillate with hydrochloric acid, and gave $[\alpha]_{5780}^{16°}$ + 18°, $[\alpha]_{5461}^{16°}$ + 20·1° in water (c = 3·76). These values refer to material dried in a vacuum at room temperature (Found: Cl, 32·0; loss at 100° in a vacuum, 3·6. $C_8H_{18}N_2,2HCl,\frac{1}{2}H_2O$ requires Cl, 31·7; H_2O, 4·0%. Found for completely dried material: Cl, 32·9. $C_8H_{18}N_2,2HCl$ requires Cl, 33·0%).

Dinitroso-*d*-β-2 : 3 : 5 : 6-tetramethylpiperazine, prepared in the usual way from the hydrochloride, had m. p. 108—109° and $[\alpha]_{5780}^{17°}$ + 115°, $[\alpha]_{5461}^{17°}$ + 135° in alcohol (c = 0·72).

β-2 : 3 : 5 : 6-*Tetramethylpiperazine* d-α-*Bromocamphor-π-sulphonate*.—A mixture of equimolecular proportions of the acid and the *dl*-base was evaporated to dryness in aqueous solution. The resulting crystalline salt was easily soluble in water, acetone, alcohol, and chloroform, fairly soluble in benzene, and almost insoluble in light petroleum. It was crystallised once from chloroform–light petroleum and then had m. p. 103—105°, and $[\alpha]_{5780}^{15°}$ + 60·3°, $[\alpha]_{5461}^{15°}$ + 70·9°, $[M]_{5461}$ + 322° in water (c = 1·0). This solvent was unsatisfactory and the salt was subsequently crystallised from acetone, from which it separated in small needles, finally consisting of pure l-β-2 : 3 : 5 : 6-*tetramethylpiperazine mono*-d-α-*bromocamphor-π-sulphonate*, m. p. 129—130° (Found: Br, 17·4. $C_8H_{18}N_2,C_{10}H_{15}O_4BrS$ requires Br, 17·6%). $[\alpha]_{5461}^{15°}$ + 65·5°, $[M]_{5461}$ + 297° in water (c = 1·36). The base was liberated from this by distillation with alkali and obtained in the form of its dihydrochloride, which showed $[\alpha]_{5780}^{16°}$ − 18·5°, $[\alpha]_{5461}^{16°}$ − 21·8° in water (c = 2·43).

Dinitroso-*l*-β-2 : 3 : 5 : 6-tetramethylpiperazine had m. p. 108—109° and gave $[\alpha]_{5780}^{17°}$ − 115·5°, $[\alpha]_{5461}^{17°}$ − 135·5° in alcohol (c = 0·79). It separated from aqueous alcohol in pale yellow needles. A mixture of this substance with an equal weight of the dextrorotatory isomeride melted at 103°, and addition of the *dl*-substance produced no further change in melting point.

Isomeric 1 : 4-*Derivatives of* β-2 : 3 : 5 : 6-*Tetramethylpiperazine*.

1-*Benzenesulphonyl*-dl-β-2 : 3 : 5 : 6-*tetramethylpiperazine*.—The anhydrous base (1·2 g.) was dissolved in dry pyridine, and benzene-

sulphonyl chloride (1·5 g.) added. After standing over-night, most of the pyridine was removed by distillation, and acetone added to the residue. The crystalline material which separated on further standing was washed with acetone, dissolved in hot water, and decomposed with ammonia. An oil was precipitated, which crystallised almost at once, and after recrystallisation from aqueous alcohol and light petroleum had m. p. 132·5°. The *hydrochloride* was precipitated from a benzene solution by hydrogen chloride: it had m. p. 270—272° and was easily soluble in water and hot alcohol. It separated from the latter in small prisms (Found: Cl, 11·15. $C_{14}H_{22}O_2N_2S,HCl$ requires Cl, 11·15%).

In further preparations of the benzenesulphonyl derivative a substance, m. p. 177°, was recovered from the acetone–pyridine mother-liquors. It crystallised from aqueous pyridine in colourless prisms, was unchanged by ammonia, and was doubtless the *dibenzenesulphonyl* derivative (Found: S, 15·7. $C_{20}H_{26}O_4N_2S_2$ requires S, 15·2%).

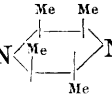
1-*Benzenesulphonyl*-4-p-*toluenesulphonyl*-dl-β-2 : 3 : 5 : 6-*tetramethylpiperazine*.—1-Benzenesulphonyl-*dl*-β-2 : 3 : 5 : 6-tetramethylpiperazine was boiled in pyridine solution with excess of *p*-toluenesulphonyl chloride during 5 hours: the solvent was then evaporated, and the residue treated with water. The solid so produced was boiled with alcohol and separated into two parts, one being much more soluble than the other. The soluble portion, m. p. 232—235°, on treatment with ammonia regenerated 1-benzenesulphonyl-*dl*-β-2 : 3 : 5 : 6-tetramethylpiperazine and was evidently the *p*-toluenesulphonate of this. The less soluble portion crystallised from aqueous pyridine, or from xylene, in small prisms, m. p. 186°. It was unchanged by ammonia (Found: C, 57·8; H, 6·6; N, 6·4. $C_{21}H_{28}O_4N_2S_2$ requires C, 57·8; H, 6·4; N, 6·4%).

4-*Benzenesulphonyl*-1-p-*toluenesulphonyl*-dl-β-2 : 3 : 5 : 6-*tetramethylpiperazine*.—This substance was prepared in pyridine solution in a similar manner to that used for its isomeride described above, but after addition of water to the residue from the pyridine solution, the precipitate was filtered off after standing only about a minute. The filtrate slowly deposited further solid which, after recrystallisation from alcohol, had m. p. 219—220°, and on treatment with ammonia yielded 1-*p*-toluenesulphonyl-*dl*-β-2 : 3 : 5 : 6-tetramethylpiperazine. It was therefore the benzenesulphonate of this compound. The first-formed precipitate was unattacked by ammonia and separated from aqueous pyridine in small needles, m. p. 175—176° (Found: C, 57·75, 57·7; H, 6·7, 6·8; N, 6·45. $C_{21}H_{28}O_4N_2S_2$ requires C, 57·8; H, 6·4; N, 6·4%).

Both this compound and its isomeride described above are

sparingly soluble in most solvents with the exception of pyridine and hot xylene. Mixtures of the two melted indefinitely at 158—160°, thus proving their non-identity.

Summary.

The configuration of the so-called β-2 : 3 : 5 : 6-tetramethylpiperazine has been shown to be  , from the facts that (1) it has been resolved into antimeric forms and (2) 4-benzenesulphonyl-1-*p*-toluenesulphonyl-*dl*-β-2 : 3 : 5 : 6-tetramethylpiperazine and 1-benzenesulphonyl-4-*p*-toluenesulphonyl-*dl*-β-2 : 3 : 5 : 6-tetramethylpiperazine are different substances. The dihydrochloride of the *d*-base was obtained from the bis-*d*-methylenecamphor derivative, and that of the *l*-isomeride from the mono-*d*-α-bromocamphor-π-sulphonate. The isomeric 1 : 4-derivatives were easily obtained by the introduction of the *p*-toluenesulphonyl and benzenesulphonyl radicals in a different order.

Work is being continued on the α- and γ-bases with a view to a determination of their configurations.

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