LII.—*The Isomerism of Reduced Derivatives of Quinoxaline. Part II. The Stereoisomeric 2 : 3-Dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxalines.*

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LIKE 2 : 3-diphenylquinoxaline (J., 1923, **123**, 1570), 2 : 3-dimethylquinoxaline (Gabriel and Sonn, *Ber.*, 1907, **40**, 4852), on reduction with sodium and ethyl alcohol, yields a mixture of two 2 : 3-disubstituted 1 : 2 : 3 : 4-tetrahydroquinoxalines, $C_6H_4<\begin{matrix}NH\cdot CHMe\\ NH\cdot CHMe\end{matrix}$. These two bases may be separated by taking advantage of the fact that the oxalate and the picrate of the externally compensated base are both less soluble than the corresponding salts of the *meso*-base.

The *meso*-base has been examined and characterised by the preparation of a number of simple derivatives. The externally compensated base has been resolved by means of *d*- and *l*-tartaric acids, which have, in this case, proved more useful than the stronger acids derived from optically active camphor. Whilst enantiomorphism in the crystalline form of the optically active bases has again been demonstrated, the analogy to the stereoisomerism of the tartaric acids is not so complete in this case as in the former, since the externally compensated base now described is probably a pseudo-racemic mixture, the melting points of all mixtures of the two optically active bases being between the melting point of the optically active bases and that of the externally compensated base. The rotatory powers of the bases are markedly higher than those of the corresponding 2 : 3-diphenyl derivatives previously described and the acyl derivatives possess considerable rotatory powers opposite in sign to those of the optically active bases from which they are prepared.

The following is a summary of the constants of the more important compounds now described :

	M. p.	$[M]^{20°}_{5461}$.
l-2 : 3-Dimethyltetrahydroquinoxaline	94·5°	−181·4°
d-2 : 3-Dimethyltetrahydroquinoxaline	94·5	+181·9
dl-2 : 3-Dimethyltetrahydroquinoxaline	101—102	—
meso-2 : 3-Dimethyltetrahydroquinoxaline	111—112	—
1-Benzoyl derivative of *l*-base	233—234	+983·3
1-Benzoyl derivative of *d*-base	233—234	−981·7
1-*p*-Toluenesulphonyl derivative of *l*-base	172—173	+211·3

EXPERIMENTAL.

meso-2 : 3-*Dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline.*

2 : 3-Dimethylquinoxaline was prepared in considerable quantities from diacetyl and *o*-phenylenediamine as described by Gabriel and

Sonn (*loc. cit.*). It was purified by steam distillation, and crystallised from the hot distillate in long, prismatic needles which probably contain three molecules of water of crystallisation (Found : H_2O, 24·6. $C_{10}H_{10}N_2,3H_2O$ requires H_2O, 25·5%). The anhydrous compound melts at 104·5—105·5° (compare Gabriel and Sonn).

The most satisfactory method of reducing the above base is by means of sodium in boiling absolute ethyl-alcoholic solution. The base (10 g.) was dissolved in boiling ethyl alcohol (300 c.c.) and sodium (25 g.) introduced in small lumps, a further small quantity of alcohol being used if necessary to facilitate the solution of the last portions of sodium. The alcoholic solution from two experiments was allowed to cool and acidified with concentrated hydrochloric acid (170 c.c.), the sodium chloride filtered off, and the filtrate and washings were evaporated to dryness. The residue was dissolved in dilute hydrochloric acid and the reduced mixed bases were precipitated by means of excess of sodium hydroxide, filtered off, washed with water, and dried in a vacuum desiccator; a further small quantity of the mixed bases was obtained by extraction of the alkaline solutions with ether (total yield, 175 g. from 190 g. of 2 : 3-dimethylquinoxaline).

In the earlier experiments, it had been proved that when equivalent quantities of the reduced mixed bases and picric acid were mixed in alcoholic solution, the picrate of what was subsequently shown to be *dl*-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline was very much less soluble than that of the *meso*-base. Under certain conditions, however, which were not fully investigated, the base liberated from the less soluble picrate was contaminated with a deep red base, indicating that oxidation had taken place. Subsequently it was found possible to separate the two bases in a state of greater purity and more easily by means of oxalic acid, the oxalate of the externally compensated base being again the less soluble in ethyl alcohol.

12·4 G. (1 mol.) of the mixed bases dissolved in boiling ethyl alcohol (120 c.c.) were mixed with 9·7 g. (1 mol.) of crystalline oxalic acid dissolved in 40 c.c. of hot alcohol. The crystalline oxalate (p. 346) which separated was filtered off when the solution had stood for some hours. The alcoholic filtrate was evaporated to dryness, the residue suspended in water, basified with ammonia, and the base extracted thoroughly with benzene. The base obtained on evaporation of the benzene solution was repeatedly crystallised from benzene–ligroin and finally from alcohol until its melting point was no longer altered. It was obtained in almost colourless plates, m. p. 111—112°. Under these conditions, this internally compensated base forms approximately 75% of the reduction product

of 2 : 3-dimethylquinoxaline (Found : C, 73·9; H, 8·9. $C_{10}H_{14}N_2$ requires C, 74·0; H, 8·7%).

meso-2 : 3-*Dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* was examined crystallographically by Dr. G. M. Bennett of the University of Sheffield, to whom I am very greatly indebted for the crystallographic reports in the present paper. It crystallises in the monoclinic system with $a : b : c = ? : 1 : 0{\cdot}625$; $\beta = 91°\ 5'$. Large, flat, rhomb-shaped crystals were obtained from acetone, developed on $a(100)$ and bounded by the form $m(011)$, but they were somewhat irregular and the angular values are only approximate :

	$a(100)$.	$m(011)$.	$m'(01\bar{1})$.
ϕ	0° 0′	*88° 16′	*268° 16′
ρ	90° 0′	*32° 2′	32° 2′

There is a perfect cleavage in the plane $a(100)$. The extinction on a is along the diagonal, which confirms the position of the plane of symmetry, and the crystals are biaxial.

meso-1 : 4-*Diacetyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*, $C_6H_4\begin{matrix}NAc\cdot CHMe\\ |\\ NAc\cdot CHMe\end{matrix}$, was prepared by heating the base with an excess of acetic anhydride on the water-bath for 1 hour. It crystallises from hot water in long, colourless needles, m. p. 145—146° (Found : C, 68·2; H, 7·3. $C_{14}H_{18}O_2N_2$ requires C, 68·25; H, 7·4%).

meso-1 : 4-*Dibenzoyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* was prepared by the Schotten-Baumann method, using a considerable excess of benzoyl chloride. It crystallises from ethyl alcohol in thin, colourless prisms, m. p. 218·5—219·5° (Found : C, 77·4; H, 6·4; N, 7·6. $C_{24}H_{22}O_2N_2$ requires C, 77·8; H, 6·0; N, 7·6%).

The following compounds were obtained by treating the base with the acyl chloride in pyridine and isolating the product in the usual manner.

meso-1-*Benzoyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* is much more soluble in alcohol than the dibenzoyl derivative, a small quantity of which is always obtained at the same time. It crystallises from alcohol in colourless, massive prisms, m. p. 137—138° (Found : C, 77·0; H, 6·9; N, 11·1. $C_{17}H_{18}ON_2$ requires C, 76·6; H, 6·8; N, 10·5%). It yields a colourless hydrochloride sparingly soluble in water and an almost colourless nitroso-compound which begins to decompose without melting at about 140°.

meso-1 : 4-*Di*-m-*nitrobenzoyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* crystallises from chloroform–ethyl alcohol in very pale yellow needles, m. p. 243—244° (Found : C, 62·6; H, 4·5. $C_{24}H_{20}O_6N_4$ requires C, 62·6; H, 4·4%).

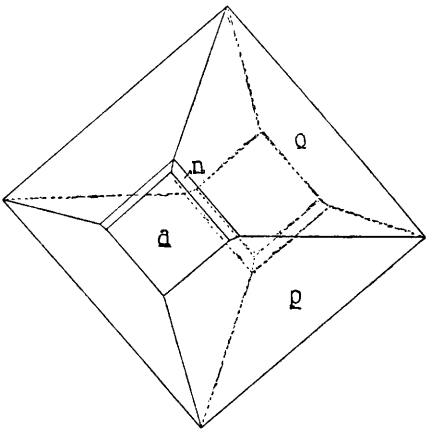
meso-1-p-*Nitrobenzoyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinox-*

aline crystallises from ethyl alcohol in red needles, m. p. 167° (Found: C, 65·55; H, 5·55. $C_{17}H_{17}O_3N_3$ requires C, 65·5; H, 5·5%).

meso-1-p-*Toluenesulphonyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* crystallises from ethyl alcohol in colourless prisms, m. p. 183—184° (Found: C, 64·55; H, 6·3. $C_{17}H_{20}O_2N_2S$ requires C, 64·5; H, 6·4%).

meso-1 : 4-*Diphenylcarbamyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* was prepared by keeping the base and an excess of phenylcarbimide in purified and dry acetone solution for some 12 hours. The product was repeatedly crystallised from purified acetone and obtained in colourless, soft needles, m. p. 190—191° (Found: C, 71·9; H, 5·9; N, 14·2. $C_{24}H_{24}O_2N_4$ requires C, 72·0; H, 6·0; N, 14·0%).

FIG. 1.



meso-1-*Carbamyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* was prepared by adding potassium cyanate (2 g.) gradually to a warm solution of the base (2 g.) in the calculated quantity of *N*/2-hydrochloric acid. The crystalline precipitate which separated in almost theoretical quantity was dried and recrystallised from benzene. Well-developed crystals were obtained, m. p. 162—163° (Found: C, 64·6; H, 7·25; N, 20·5. $C_{11}H_{15}ON_3$ requires C, 64·4; H, 7·4; N, 20·5%). Dr. Bennett's crystallographic report is:

This substance crystallises in the holohedral class of the monoclinic system with $a : b : c = 0{\cdot}9131 : 1 : 0{\cdot}9429$; $\beta = 92° 16'$. It is thus pseudo-cubic and the habit of the crystals from benzene solution is octahedral, the forms developed being $a(100)$, $n(311)$, $o(111)$, $p(\bar{1}11)$, $o'(1\bar{1}1)$ as shown in Fig. 1. The following mean angular values were obtained from three selected crystals:

	$a(100)$.	$n(311)$.	$o(111)$.	$p(\bar{1}11)$.	$o'(1\bar{1}1)$.	$p(1\bar{1}\bar{1})$.
ϕ	0° 0′	21° 38′	*52° 2′	126° 40′	* 4° 20′	354° 58′
ρ	90° 0′	90° 0′	90° 0′	90° 0′	*38° 7′	36° 42′

No marked cleavage was observed. Optical examination confirms the fact that the crystals are biaxial. The extinction on the face

a coincides with the diagonal of the face and an optic bisectrix emerges perpendicular to *a*.

Resolution of Externally Compensated 2 : 3-Dimethyltetrahydroquinoxaline into its Optically Active Components.

The crystalline oxalate * (p. 343) was suspended in water and treated with an excess of a solution of ammonia. Thorough extraction with benzene then removed a base, which was recrystallised from ligroin (b. p. 40—60°) until its melting point was unchanged. The almost colourless crystals had m. p. 101—102°, and the melting points of mixtures of this and the *meso*-base were always below 100°.

That the base having m. p. 101—102° is the externally compensated base, *dl*-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, was proved in a preliminary experiment by resolving 2 g. of the base by means of an equimolecular quantity of *d*-α-bromocamphor-π-sulphonic acid in aqueous solution, ethyl alcohol being added in small quantities to prevent the too rapid crystallisation of any salt at the ordinary temperature. After some hours, a salt (*d*A,*l*B) was obtained and from this, without further purification, the base was liberated. This base, after one crystallisation from ligroin (b. p. 40—60°), had $[\alpha]_{5461} = -84{\cdot}5°$ in 0·5% ethyl-alcoholic solution; the base liberated from the mother-liquor from the above salt had $[\alpha]_{5461} = +45{\cdot}3°$ under similar conditions. Whilst this experiment served to prove that the base having m. p. 101—102° is the externally compensated base, the resolution could not be repeated. No fewer than twelve experiments were performed in which every effort was made to maintain the conditions of the successful experiment, but in all cases the crystalline salt yielded a base which was optically inactive. With *d*-camphor-β-sulphonic acid under analogous conditions, positive indications of the partial resolution of this base were repeatedly obtained, but the rotatory power of the base from the repeatedly recrystallised, less soluble salt was very much smaller than that observed in the first successful experiment. Similarly, attempts to resolve the base by means of *d*-α-bromocamphor-β-sulphonic acid, *d*-benzoylalanine and *d*-hydroxymethylenecamphor were tried without success.

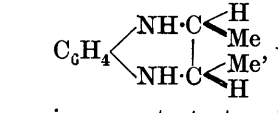
The resolution of the base by means of *d*- and *l*-tartaric acids was immediately successful. The following describes a typical experiment. *d*-Tartaric acid (20·0 g.; 1 mol.) was dissolved in boiling water (350 c.c.), and the base (21·4 g.; 1 mol.) dissolved in the boiling solution, which was then left to cool in the ice-chest for some

* In the first experiments the *dl*-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline was liberated from the less soluble picrate. The base so obtained was identical in all respects with that obtained from the less soluble oxalate.

hours. The salt (16·9 g.; 80% of the theoretical quantity) crystallised in long, colourless needles and yielded a base which in a 0·6% ethyl-alcoholic solution had $[\alpha]_{5461} = -90·4°$. The crystalline salt was therefore the *d*A,*l*B salt. The crude base (13·0 g.) obtained from the mother-liquor was treated with an equivalent quantity (12·0 g.) of *l*-tartaric acid (obtained by resolving racemic acid in the manner described by Marckwald, *Ber.*, 1896, **29**, 42) under exactly similar conditions to the above. The salt (15·5 g.), *l*A,*d*B, was similar in properties to the salt previously obtained, and yielded a base which in 0·6% ethyl-alcoholic solution had $[\alpha]_{5461} = +97·2°$. The base recovered from the mother-liquor from the *l*A,*d*B salt amounted to 4·85 g., so that practically the whole of the base originally taken was accounted for.

In order to obtain the optically pure *l*-base, the various specimens of recrystallised *l*-base whose rotatory powers in ethyl alcohol varied from $[\alpha]_{5461} = -96·2°$ to $-90·4°$ were mixed and added gradually to rather more than the equivalent quantity of pure *d*-tartaric acid, dissolved in sufficient boiling water, so that the whole remained dissolved at the boiling point. This solution was rapidly filtered and the filtrate left to crystallise. Pure l-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* d-*tartrate*, $C_{10}H_{14}N_2,C_4H_6O_6,2H_2O$, separated, on cooling, in characteristic, long, colourless needles which were separated in the usual manner. The anhydrous salt begins to decompose at about 149° (Found: H_2O, 10·5. $C_{14}H_{20}O_6N_2,2H_2O$ requires H_2O, 10·4%. Found in anhydrous material: C, 54·0; H, 6·7. $C_{14}H_{20}O_6N_2$ requires C, 53·8; H, 6·5%). The salt cannot be conveniently recrystallised, as its solutions darken somewhat rapidly. Its rotatory power was determined in ethyl-alcoholic solution at 20°: $c = 1·03$, $l = 4$, $\alpha_{5461} = -2·07°$, $[\alpha]_{5461} = -50·2°$.

Pure d-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* l-*tartrate* was obtained in a similar manner from the recrystallised specimens of the not quite completely resolved *d*-base and pure *l*-tartaric acid. It had analogous properties (Found in anhydrous material: C, 54·1; H, 6·8. $C_{14}H_{20}O_6N_2$ requires C, 53·8; H, 6·5%). Its rotatory power was determined in ethyl-alcoholic solution at 20°: $c = 1·004$, $l = 4$, $\alpha_{5461} = +2·00°$, $[\alpha]_{5461} = +49·9°$.

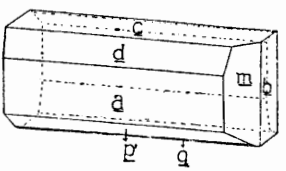
l- *and* d-2 : 3-*Dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxalines*,  , were obtained in each case from the corresponding pure tartrate. The salt was suspended in water, a slight excess of ammonia added, and the mixture extracted thoroughly with

benzene. The benzene solution after washing and drying was evaporated to dryness, and the residue extracted carefully with redistilled ligroin (b. p. 40—60°) in a Soxhlet apparatus. The pure base was obtained in massive, but distorted, almost colourless prisms. The pure bases have m. p. 94·5° and melting points of mixtures of the two bases lie between this melting point and the melting point of the externally compensated base (101—102°). The solubility of the active bases in organic solvents is high and distinctly greater than that of the externally compensated base. These bases are most conveniently recrystallised from ligroin [Found: (*l*-base) C, 74·1; H, 8·8; (*d*-base) C, 74·0; H, 9·1. $C_{10}H_{14}N_2$ requires C, 74·0; H, 8·7%]. The rotatory powers were determined in ethyl-alcoholic solution at 20°:

l-base: $c = 0{\cdot}6024$, $l = 4$, $\alpha_{5461} = -2{\cdot}70°$, $[\alpha]_{5461} = -112{\cdot}0°$.
d-base: $c = 0{\cdot}5902$, $l = 4$, $\alpha_{5461} = +2{\cdot}65°$, $[\alpha]_{5461} = +112{\cdot}3°$.

Although crystals of both the *l*- and the *d*-base were obtained after considerable trouble by the slow evaporation of their solutions in pure acetone, only those of the *d*-base, examined by Dr. Bennett, need be described.

FIG. 2.



d-2 : 3-Dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline crystallises in the sphenoidal class of the monoclinic system with $a : b : c = 1{\cdot}362 : 1 : 0{\cdot}892$; $\beta = 91°\ 56'$. The forms observed were *a*(100), *c*(001), *b*(010), *m*(110), *p*($\bar{1}$01), *q*($\bar{3}$05), *d*(601). Some crystals are simple combinations of *m* and *c*, but others show the definitely enantiomorphous habit depicted in Fig. 2, with elongation along the *b* axis. Owing to the imperfections of the crystals some of the following mean angular values (obtained from five crystals) are a little uncertain:

	a(100)	*d*(601)	*c*(001)	*q*($\bar{3}$05)	*p*($\bar{1}$01)	*m*(110)	*b*(010)
ϕ ...	0° 0′	13° 47′	*88° 4′	109° 15′	*121° 54′	0° 0′	0° 0′
ρ ...	90° 0′	90° 0′	90° 0′	90° 0′	90° 0′	*36° 18′	−0° 6′

There is no marked cleavage. The substance is biaxial. The extinction appears to be straight on *a* and *c*, and the optic axial plane coincides with *b*.

1-1-*Benzoyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*, $C_6H_4\langle^{NBz\cdot C(H)Me}_{NH-C(Me)H}$, was prepared by treating a solution of the *l*-base (1·5 g.) with a benzene solution of benzoyl chloride (3 g.) and

sodium hydroxide in the usual manner at the ordinary temperature. The product was recrystallised three times from benzene, its m. p., 233—234° (decomp.), not altering after the first crystallisation. It was obtained in small, colourless needles (Found: N, 10·5. $C_{17}H_{18}ON_2$ requires N, 10·5%). Its rotatory power was determined at 20° in ethyl alcohol, in which solvent the substance is only sparingly soluble: $c = 0{\cdot}2338$, $l = 4$, $\alpha_{5461} = +3{\cdot}46°$, $[\alpha]_{5461} = +369{\cdot}7°$.

d-1-*Benzoyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*, m. p. 233—234° (decomp.), was obtained in a precisely similar way from the *d*-base, and the compound has analogous properties (Found: C, 76·4; H, 6·7; N, 10·4. $C_{17}H_{18}ON_2$ requires C, 76·6; H, 6·8; N, 10·5%). Its rotatory power was determined in ethyl-alcoholic solution at 20°: $c = 0{\cdot}3596$, $l = 4$, $\alpha_{5461} = -5{\cdot}31°$, $[\alpha]_{5461} = -369{\cdot}1°$.

l-1-p-*Toluenesulphonyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*, $C_6H_4\langle \begin{matrix} N(SO_2{\cdot}C_7H_7){\cdot}C\langle \begin{matrix} H \\ Me \end{matrix} \\ NH\text{———}C\langle \begin{matrix} Me \\ H \end{matrix} \end{matrix}$, was prepared from the *l*-base (1·5 g.) and *p*-toluenesulphonyl chloride (3·7 g.) in pyridine solution. The product crystallised from alcohol in small, colourless plates, m. p. 172—173° (decomp.) (Found: N, 8·6. $C_{17}H_{20}O_2N_2S$ requires N, 8·9%). Its rotatory power was determined in ethyl alcohol at 20°: $c = 0{\cdot}5762$, $l = 4$, $\alpha_{5461} = +1{\cdot}54°$, $[\alpha]_{5461} = +66{\cdot}9°$.

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