XVI.—*The Stereochemistry of Reduced Quinoxalines. Part III. The Resolution of Externally Compensated α- and β-2 : 3 : 7-Trimethyl-1 : 2 : 3 : 4-tetrahydroquinoxalines.*

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2 : 3 : 7-TRIMETHYLQUINOXALINE (von Pechmann, *Ber.*, 1888, **21**, 1414) is easily reduced by sodium and ethyl alcohol to a mixture of the two stereoisomeric derivatives, $C_6H_3Me<^{NH\cdot CHMe}_{NH\cdot CHMe}$, which are conveniently separated by the method described in the present paper. The α-, or lower-melting, compound constitutes about 30% of the mixture.

Both these compounds are externally compensated bases and the

* For comparison with the above results the *ethyl* esters of dl- and d-α-*naphthalenesulphonylalanine* (Colles and Gibson, *loc. cit.*) were studied.

dl-α-Naphthalenesulphonylalanine was converted in the usual manner into its *ethyl* ester, which was obtained in 75% yield. Recrystallised from ethyl alcohol, it was obtained in hard rhombs, m. p. 104° (Found : C, 58·6; H, 5·4. $C_{15}H_{17}O_4NS$ requires C, 58·6; H, 5·5%). The amide was not obtained by the method described above.

d-α-Naphthalenesulphonylalanine was similarly converted into its *ethyl* ester, which crystallised from benzene–ligroin in colourless needles, m. p. 83·5—84° (Found : N, 4·6%). In ethyl alcohol it had $[\alpha]$ − 47·15° (c = 1·9842, l = 4, α = − 3·74°).

1·1186 G. of the ester were dissolved in 50 c.c. of ethyl alcohol, mixed with rather more than the calculated quantity of $N/2$-sodium hydroxide, and made up to 100 c.c. The rotatory power, α = − 0·87°, observed immediately after mixing showed that hydrolysis had barely commenced. After 22½ hours, the rotatory power was α = − 0·11° and after 67 hours a constant rotatory power of α = + 0·21° was observed. The acid recovered from the solution was recrystallised and had m. p. 140·5—141·5°, alone or mixed with pure *d*-α-naphthalenesulphonylalanine.

α-base is readily resolved into its optically active components by means of *d*- and *l*-tartaric acids under similar conditions to those adopted for the resolution of externally compensated 2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline (Gibson, J., 1927, 342). The melting points of the pure optically active α-bases being 61·5—62·5° and mixtures of the optically active bases having melting points below 60°, whereas the melting point of the externally compensated base is 71°, it follows that the last is a racemic compound. The *d*- and *l*-α-bases have distinctly higher rotatory powers than those of the optically active 2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoxalines (Gibson, *loc. cit.*).

The following is a summary of the constants of *racemic* α-2 : 3 : 7-trimethyl-1 : 2 : 3 : 4-tetrahydroquinoxaline, of its optically active components and of those derivatives which are described in the present paper :

	M. p.	$[M]_{5461}^{20°}$.
rac-α-2 : 3 : 7-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*	71°	—
dl-α-1 : 4-*Diacetyl*-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*	147	—
d-α-2 : 3 : 7-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*	61·5—62·5	+206·9°
l-α-2 : 3 : 7-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*	61·5—62·5	−206·9
d-α-1 : 4-*Di*-m-*nitrobenzoyl*-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*	—	−466·4
l-α-1 : 4-*Diacetyl*-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*	164·5—165·5	+427·2

The externally compensated β-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* forms the greater part of the reduction product of 2 : 3 : 7-trimethylquinoxaline, and being the less soluble, is the more easily isolated. No crystalline salt of this base was obtained with *d*-camphor-10-sulphonic acid, *d*-α-bromocamphor-π-sulphonic acid or *d*-tartaric acid. When the base was condensed with *d*-oxymethylenecamphor (Pope and Read, J., 1913, **103**, 1516; Gibson and Simonsen, J., 1915, **107**, 1157) a crystalline mixture was obtained. From this, the less soluble d-β-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxalino*-1-d-*methylenecamphor* (the 1 : 4-di-*d*-methylenecamphor derivative was not obtained) was obtained pure by repeated crystallisation from ethyl alcohol. It is probable that the diastereoisomeride, *l*-β-2 : 3 : 7-trimethyl-1 : 2 : 3 : 4-tetrahydroquinoxalino-1-*d*-methylenecamphor, was not obtained optically pure. Pure l-β-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxalino*-1-l-*methylenecamphor* was, however, prepared both from the externally compensated base and from the base obtained by hydrolysis of the more soluble fractions from the first resolution (see below).

These compounds are highly crystalline and have very high

rotatory powers, $[\alpha]_{5461}^{20°} = \pm 1309°$. Being derivatives of secondary bases, the difficulty with which they are hydrolysed probably accounts for the fact that they show no mutarotation even in the presence of acetic acid during 24 hours at the ordinary temperature. Pope and Read (J., 1912, **101**, 2387) have shown that there are two methods for effecting the hydrolysis of oxymethylenecamphor derivatives of primary and of secondary amines: (1) by titrating an alcoholic solution of the condensation product with bromine, and (2) in the case of the condensation product of secondary amines when the nitrogen is in a closed ring, by hydrolysis with hydrochloric acid (Pope and Read, J., 1913, **103**, 1580). Titration of an alcoholic solution of the condensation product with bromine was found to be unsatisfactory, since the reaction did not proceed normally, and consequently the hydrolysis of the two stereoisomeric condensation products with hydrochloric acid was carefully investigated.

The hydrolysis is conveniently effected by passing steam into a suspension of the condensation product in concentrated hydrochloric acid until oxymethylenecamphor ceases to distil. Under the most favourable conditions, *i.e.*, carrying out the steam distillation in the minimum time—usually 15 minutes—and superheating being avoided, the hydrolysis is attended with the formation of some small quantity of resinous and other by-products, but the base is easily separated in the usual way.

After purification, the base obtained from either condensation product showed but feeble optical activity and the experimental work indicates that very considerable racemisation of the base had occurred during the hydrolysis. For example, a part of the expected *d*-β-base, having a small optical activity, was converted into its diacetyl derivative and this was found to be a mixture. On recrystallisation from water, the aqueous filtrate had a marked dextrorotatory power. Another portion was converted into its oxalate in acetone solution; the base recovered from the less soluble oxalate had a small dextrorotatory power, whereas that obtained from the more soluble portion of the oxalate had a larger dextrorotatory power. Similarly, the expected *l*-β-base had only a small lævorotatory power. The corresponding diacetyl derivative yielded on crystallisation a specimen which was optically inactive and the mother-liquor from this showed a considerable lævorotation. The oxalate of the same specimen of base which separated from acetone solution gave optically inactive base, and the base recovered from the oxalate remaining in solution was definitely lævorotatory.

The hydrolysis of oxymethylenecamphor derivatives of this type by means of concentrated hydrochloric acid has not been extensively

studied and it appears that this is the first time it has been shown that the hydrolysis of such compounds may be attended with racemisation, even when the asymmetric centres in the compounds are not affected chemically during the reaction. If the hydrolysis by means of concentrated hydrochloric acid could be brought about at the ordinary temperature, as in the case of the dimethylpiperazino-*d*-methylenecamphors (Pope and Read, J., 1912, **101**, 2337), it is possible that racemisation of the base might not take place. The present work provides evidence that the hydrolysis of the diacetyl derivatives of the active bases is also attended with racemisation of the base.

Although the pure *d*- and *l*-β-bases have not been obtained, it is possible to conclude that the externally compensated β-base is a racemic compound. The inactive base has m. p. 97—98° and mixtures of the active bases have been obtained with melting points lower and higher than this value.

Experimental.

dl-α- *and* β-2 : 3 : 7-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxalines*.—The 2 : 3 : 7-trimethylquinoxaline (von Pechmann, *loc. cit.*) was purified by steam distillation and isolated from the distillate, saturated with ammonium sulphate, by extraction with benzene.

The reduction was carried out exactly as described in Part II (Gibson, *loc. cit.*). In the earlier experiments an attempt was made to separate the two tetrahydro-bases formed by means of oxalic acid and it was thus found possible to separate the higher-melting β-base in a state of purity, but the lower-melting α-base could not be obtained pure when the mother-liquors were worked up. The most convenient method for obtaining the two bases was as follows: The solid mixture (20 g.) was extracted in a Soxhlet apparatus with ligroin (b. p. 40—60°; 200 c.c.), and the cooled solution kept for some hours; a slightly yellowish base (9 g.) then crystallised. This consisted of the nearly pure β-*base*. It was purified by crystallisation from ligroin (b. p. 60—80°) until its melting point was unaltered and was thus obtained in colourless, flat plates, m. p. 97—98° (Found: C, 75·3; H, 8·9. $C_{11}H_{16}N_2$ requires C, 75·0; H, 9·1%). The oxalate crystallised from acetone, in which it was only sparingly soluble, in colourless nodules, m. p. 138—140°, decomp. 152—154°.

dl-β-1 : 4-*Diacetyl*-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* was prepared by heating the base with an excess of acetic anhydride for 1 hour on the water-bath. It crystallises from ligroin or water in colourless, glistening prisms, m. p. 131° (Found: C, 69·1; H, 7·5. $C_{15}H_{20}O_2N_2$ requires C, 69·2; H, 7·7%).

The ligroin filtrate from which the β-base had been removed was evaporated to dryness, the residue dissolved in alcohol (40 c.c.), and concentrated hydrochloric acid (20 c.c.) added. After some hours, the greater part of the β-base remaining in the mixture crystallised as the sparingly soluble hydrochloride. The filtrate was evaporated to dryness, the residue suspended in water, and ammonia added in slight excess. The liberated base was distilled in steam and isolated from the distillate by extraction with benzene. This dl-α-*base* crystallised from ligroin (b. p. 40—60°) in almost colourless prisms, m. p. 71°. The yield of the α-base was approximately 30% of the total reduction product (Found : C, 75·0; H, 8·7. $C_{11}H_{16}N_2$ requires C, 75·0; H, 9·1%).

dl-α-1 : 4-*Diacetyl*-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*, prepared from the base and acetic anhydride, crystallised from water in colourless prisms, m. p. 147° (Found : C, 69·1; H, 7·7. $C_{15}H_{20}O_2N_2$ requires C, 69·2; H, 7·7%).

Resolution of dl-α-2 : 3 : 7-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*.—To a boiling solution of *d*-tartaric acid (24 g.) in water (180 c.c.) the *dl*-α-base (24·6 g.) was added gradually, the liquid was boiled until a clear solution was obtained and was then cooled, and after 3 hours the crystals were separated and washed with a little water. The salt thus obtained (24·2 g.) was the crude *d*-tartrate of the *d*-α-base. The filtrate and washings were used for the separation of the *l*-α-base.

The above crude tartrate was decomposed with a slight excess of ammonia, the base was isolated and again converted into the *d*-tartrate under the same conditions as above, and the salt was separated and again treated in the same way; pure d-α-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* d-*tartrate* was then obtained. It crystallised from water in colourless needles containing $2H_2O$ (Found : N, 7·9; H_2O, 9·9. $C_{15}H_{22}O_6N_2,2H_2O$ requires N, 7·7; H_2O, 9·9%).

From the original mother-liquor and the washings from the first separation of the crude *d*-α-base *d*-tartrate, the base (12 g.) was liberated and dissolved in boiling water containing *l*-tartaric acid (11 g.). The salt (20 g.) which crystallised on cooling was reconverted into the free base (8·8 g.) and this was again combined with *l*-tartaric acid (8·1 g.) under the same conditions; the pure salt then crystallised from the solution on cooling.

l-α-2 : 3 : 7-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* l-*tartrate* crystallised from water in colourless needles containing $2H_2O$ (Found : N, 7·9. $C_{15}H_{22}O_6N_2,2H_2O$ requires N, 7·7%).

The *d*-α-base *d*-tartrate had $\alpha + 1{\cdot}96°$ ($c = 0{\cdot}9592$), whence

$[\alpha] = +51{\cdot}1°$,* and the *l*-α-base *l*-tartrate had $\alpha - 1{\cdot}77°$ ($c = 0{\cdot}8576$), whence $[\alpha] = -51{\cdot}6°$.

The pure d- and l-α-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxalines* were each obtained from the corresponding tartrate by treatment in aqueous suspension with a slight excess of ammonia; the base was extracted with benzene and after removal of the solvent the residue was extracted in a Soxhlet apparatus with ligroin (b. p. 40—60°). The bases crystallised in very faintly yellow prisms, m. p. 61·5—62·5° in each case [Found: (for *d*-base) N, 15·9; (for *l*-base) N, 15·7. $C_{11}H_{16}N_2$ requires N, 15·9%]. Some mixtures of the two bases had melting points lower than 60°. The *d*-α-base had $\alpha + 4{\cdot}29°$ ($c = 0{\cdot}9120$), whence $[\alpha] = +117{\cdot}5°$, and the *l*-α-base had $\alpha - 4{\cdot}29°$ ($c = 0{\cdot}9124$), whence $[\alpha] = -117{\cdot}5°$.

d-α-1 : 4-*Di*-m-*nitrobenzoyl*-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline* was prepared by heating the *d*-α-base with rather more than the theoretical quantity of *m*-nitrobenzoyl chloride in pyridine solution on the water-bath. The product was crystallised three times from ethyl alcohol and obtained as a microcrystalline, pale yellow powder. It gradually decomposed on heating without melting (Found: N, 12·1. $C_{25}H_{22}O_6N_4$ requires N, 11·8%). It gave $\alpha - 0{\cdot}91°$ ($c = 0{\cdot}2312$), whence $[\alpha] = -98{\cdot}4°$.

l-α-1 : 4-*Diacetyl*-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*, prepared from the *l*-α-base in the usual way, crystallised from water in colourless, flat prisms which contained water of crystallisation. It was obtained anhydrous by drying in a desiccator over sulphuric acid and then melted at 164·5—165·5° (Found: N, 11·3. $C_{15}H_{20}O_2N_2$ requires N, 10·8%). It had $\alpha = +5{\cdot}69°$ ($c = 0{\cdot}8656$), whence $[\alpha] = +164{\cdot}3°$.

Resolution of dl-β-2 : 3 : 7-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxaline*.—Attention has already been directed to the difficulties encountered in effecting the resolution of this base. The salts with the optically active acids already mentioned were uncrystallisable gums. The *dl*-β-base (83 g.) was dissolved in acetic acid (50%, 400 c.c.) and *d*-oxymethylenecamphor (85 g.) in alcohol (400 c.c.) was added. The mixture was heated on the water-bath for 15 minutes and on cooling a crystalline solid (133 g.) separated. The condensation product remaining in solution was precipitated by the addition of dilute sodium hydroxide solution.

The less soluble fraction was repeatedly crystallised from ethyl alcohol until its melting point was constant and in this way pure

* The rotations of the active compounds described in this paper were determined in ethyl-alcoholic solution at 20° in a 4-dcm. tube for the mercury-green (5461) line (except where stated otherwise).

d-β-2 : 3 : 7-*trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxalino*-1-d-*methylene-camphor*, $C_6H_3Me(NH{\cdot}CHMe{\cdot}CHMe)N{\cdot}CH{:}C(C_8H_{14})CO$, was obtained in well-formed, yellow prisms, m. p. 243—244° (Found: C, 78·4; H, 8·7. $C_{22}H_{30}ON_2$ requires C, 78·1; H, 8·9%). It had α_{5461} + 26·77° and α_{5780} + 21·30° (c = 0·5100), whence $[\alpha]_{5461}$ = + 1312° and $[\alpha]_{5780}$ = + 1044°. When acetic acid was added to the alcoholic solution no mutarotation was observed during 24 hours at the ordinary temperature.

By working up the earlier mother-liquors from the recrystallisation of the condensation product and also the product precipitated by dilute sodium hydroxide a more soluble fraction was obtained which, after several crystallisations from dilute alcohol and then from ligroin–benzene, softened at 110° and melted at 170—175° (Found: N, 7·9. $C_{22}H_{30}ON_2$ requires N, 8·3%). From its behaviour on heating it was believed that it was the optically impure diastereoisomeric condensation product. The analysis was somewhat difficult to carry out owing to the substance being hygroscopic. It had α_{5461} + 16·54° and α_{5780} + 13·65° (c = 0·8900), whence $[\alpha]_{5461}$ = + 448° and $[\alpha]_{5780}$ = + 383°.

As the more soluble fraction could not be purified, the crude substance (45 g.) recovered from the solution was heated to boiling with concentrated hydrochloric acid (500 c.c.) and steam passed through the solution until *d*-oxymethylenecamphor ceased to distil (15 minutes). The yellow solution which remained contained some resinous material which was easily separated. The solution was cooled, extracted with benzene to remove neutral products, and then treated with a slight excess of aqueous ammonia. The semi-solid which separated was extracted with benzene, and the latter solution, after being washed, dried with potassium hydroxide. The benzene solution after filtration from a further small quantity of resinous material was evaporated to dryness, and the base thus obtained purified by extraction with ligroin * (b. p. 40—60°); yield 15·4 g. This base had m. p. 96—99° and had a small lævorotatory power, α — 0·16° (c = 0·9596), whence [α] = — 4·17°.

l-β-2 : 3 : 7-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxalino*-1-l-*methylenecamphor* † was prepared from the feebly lævorotatory base referred to above and *l*-oxymethylenecamphor, the condensation and purification of the less soluble product being carried out exactly as for the stereoisomeric substance. After repeated crystallisation

* In later experiments it was found more convenient to purify the base by steam distillation.

† The same compound was obtained when the pure *dl*-β-base was condensed with *l*-oxymethylenecamphor.

from ethyl alcohol, the pure substance, m. p. 243—244°, was obtained in yellow prisms (Found : N, 8·35. $C_{22}H_{30}ON_2$ requires N, 8·3%) and its properties corresponded exactly with those of the stereoisomeride. It had α_{5461} — 25·63° and α_{5780} — 20·50° (c = 0·4902), whence $[\alpha]_{5461}$ = — 1307° and $[\alpha]_{5780}$ = — 1045°.

Hydrolysis of d-β-2 : 3 : 7-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoxalino*-1-d-*methylenecamphor and of its Stereoisomeride* —The hydrolysis of these substances was carried out under the onditions previously described, the base in each case being isolated by steam distillation.

The base separated from the *d*-oxymethylenecamphor derivative crystallised from ligroin in glistening, colourless, thin plates, m. p. 106—107·5°, and the melting point after admixture with the *dl*-β-base was depressed to 90—95° (Found : N, 15·6. $C_{11}H_{16}N_2$ requires N, 15·9%). This base in ethyl-alcoholic solution was only feebly dextrorotatory. The diacetyl derivative crystallised slowly from water in colourless prisms, and later, when the solution was stirred, needles separated, indicating that the diacetyl derivative was a mixture. This was confirmed by the melting point, since the substance softened at 108—109° and did not become clear until 123—124°. The aqueous filtrate was dextrorotatory, giving in a 4-dcm. tube at 20° α_{5461} = + 2·7°. When a concentrated acetone solution of the base was mixed with the calculated quantity of oxalic acid, also in acetone solution, and kept in the ice-chest, the oxalate crystallised slowly in rosettes of glistening needles differing in appearance from the oxalate of the *dl*-β-base. The needles softened at 138° and decomposed at 144°. The base which was obtained from the oxalate had m. p. 105—106° after crystallisation from ligroin, and showed a small but definite dextrorotation in ethyl-alcoholic solution at 20° : c = 2·2490, l = 4, α_{5461} = + 0·23°, whence $[\alpha]_{5461}$ = + 2·56°. From the oxalate of the base remaining in the mother-liquor, the recovered base, after recrystallisation from ligroin, had m. p. 105—107°, softening at 102°. It had α + 0·05° (c = 0·6096, l = 2), whence $[\alpha]$ = + 4·1°.

The base separated from the hydrolysis of the *l*-oxymethylenecamphor derivative was purified by distillation in steam and crystallisation from ligroin. It was obtained in glistening, thin plates, m. p. 105—106°, and when mixed with the *dl*-β-base it softened at 90° and melted at 94—95° (Found : N, 16·0. $C_{11}H_{16}N_2$ requires N, 15·9%). Its lævorotation in ethyl-alcoholic solution was very small. The diacetyl derivative, after crystallisation from ligroin and then from water, separated in hard, glistening prisms, m. p. 132—132·5°, and this was not depressed on admixture with the diacetyl derivative of the *dl*-β-base. It was optically inactive in ethyl-alcoholic solution. The aqueous filtrate was lævorotatory,

giving in a 4-dcm. tube at 20° $\alpha_{5461} = -1{\cdot}0°$. On hydrolysis of the acetyl derivative present in this aqueous solution with hydrochloric acid, complete racemisation took place, the base liberated being optically inactive in ethyl-alcoholic solution. The oxalate, prepared in acetone solution, was deposited slowly in hard nodules. The base obtained from this crystalline oxalate, after crystallisation from ligroin, had m. p. 95—99° and was optically inactive in ethyl-alcoholic solution. The base recovered from the oxalate remaining in the acetone solution had, after crystallisation from ligroin, m. p. 105—108°. It had $\alpha -0{\cdot}09°$ ($c = 1{\cdot}2492$), whence $[\alpha] = -3{\cdot}6°$.

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