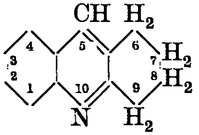
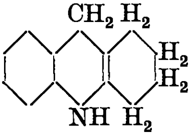
LVI.—*Tetrahydroacridine, Octahydroacridine, and their Derivatives. Part II. Resolution of the Octahydroacridines (A) and (B).*

By William Henry Perkin, jun., and William Greenwell Sedgwick.

In Part I of this investigation (Perkin and Sedgwick, J., 1924, **125**, 2437) it was shown that the reduction of tetrahydroacridine (I) with tin and hydrochloric acid leads at once to the formation of two octahydroacridines (A, m. p. 82°, and B, m. p. 72°), four atoms of hydrogen being absorbed. It is remarkable that, in spite of careful search, no intermediate product of reduction could be detected, because it was to be expected that the carbon-nitrogen conjugated system ·C̣:C̣·C̣:Ṇ· would, in the first place, absorb two atoms of hydrogen to yield a hexahydroacridine (II) containing the grouping, ⩾C·C̣:C̣·Ṇ·.

(I.)



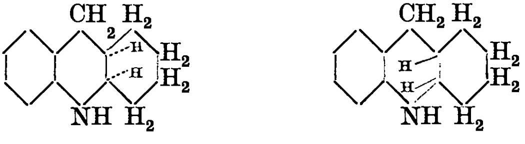


(II.)

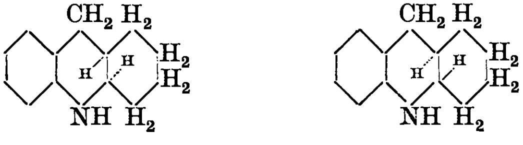
Experiment showed that, if less reducing agent is employed than is necessary to convert the whole of the tetrahydroacridine into octahydroacridine, the product is a mixture of octahydroacridine and unchanged tetrahydroacridine. If, as may be assumed to be the case, hexahydroacridine (II) is the intermediate stage, it is probable that this substance is more readily reduced than tetrahydroacridine and is therefore at once converted into octahydroacridine, the corresponding amount of tetrahydroacridine remaining unchanged. It was pointed out in the previous communication (p. 2440) that remarkable as the observation seemed at first, the formation of two octahydroacridines by the addition of four atoms of hydrogen to tetrahydroacridine (I) is strictly in accordance with structural theory.

If the model (compare Sachse, *Ber.*, 1890, **23**, 1363; Mohr, *J. pr. Chem.*, 1918, **98**, 315) be set up and examined, it is at once evident that the pairs (III) and (IV) should result from the addition

(III.)



(IV.)



of four hydrogen atoms to tetrahydroacridine and that both pairs should be resolvable into their *d*- and *l*-constituents. In order to prove that the configurations (III) and (IV) actually represent the two octahydroacridines (A) and (B), it was clearly necessary to demonstrate that both these substances can be resolved into active constituents. In our first experiments, resolution was attempted with the aid of bromocamphorsulphonic acid, but without immediate success. It was then discovered that the salts of (A) and (B) with the *d*- and *l*-camphorsulphonic acids are sufficiently well characterised to allow of satisfactory fractional crystallisation, and in this way resolution was achieved in both cases. When the pure salts were decomposed by alkali, they at once yielded the *d*- and *l*-modifications of the *octahydroacridines* (*A*) and (*B*) in a pure state.

The stages in these resolutions will be clearly understood from the following tables :

(I) *Resolution of* dl-*Octahydroacridine* (*A*, m. p. 82°).

d-Camphorsulphonic acid	*l*-Camphorsulphonic acid
↓	↓
l-*Octahydroacridine* (*A*) d-*camphorsulphonate* (m. p. 183°)	d-*Octahydroacridine* (*A*) l-*camphorsulphonate* (m. p. 182°)
NaOH ↓	NaOH ↓
l-*Octahydroacridine* (*A*), m. p. 85°, $[\alpha]_D$ −32°.	d-*Octahydroacridine* (*A*), m. p. 84·5°, $[\alpha]_D$ +34°.

Mean rotation $[\alpha]_D$ ±33°.

(II) *Resolution of* dl-*Octahydroacridine* (*B*, m. p. 72°).

d-Camphorsulphonic acid	*l*-Camphorsulphonic acid
↓	↓
l-*Octahydroacridine* (*B*) d-*camphorsulphonate* (m. p. 172°)	d-*Octahydroacridine* (*B*) l-*camphorsulphonate* (m. p. 172°)
NaOH ↓	NaOH ↓
l-*Octahydroacridine* (*B*), m. p. 73°, $[\alpha]_D$ −24°.	d-*Octahydroacridine* (*B*), m. p. 73°, $[\alpha]_D$ +22°.

Mean rotation $[\alpha]_D$ ±23°.

When the corresponding *d*- and *l*-modifications are mixed, the inactive forms are at once produced, but loss of activity also occurs gradually when the *d*- or *l*-modifications are heated at or above their melting points and the change to the inactive form is complete on distillation under reduced pressure. It is curious, both in the case of (A) and of (B), that the inactive modification melts at a somewhat lower temperature than the active constituents, suggesting that the *dl*-modification may be a mixture and not a true racemic compound. It is interesting also that, on boiling with acetic anhydride, *l*-octahydroacridine (A) is converted into the acetyl derivative of *dl*-octahydroacridine (A) (m. p. 86°) described in the previous communication (p. 2449).

So far, sufficient evidence is not available to enable definite configurations to be assigned to the octahydroacridines (A) and (B), but it is significant that, when tetrahydroacridone is reduced by sodium amalgam (*loc. cit.*, p. 2449), the product consists entirely of modification (A). The probability in this reduction is that the hydrogen atoms will add themselves on to the double linking in the direction indicated in (III) and we are for this reason inclined to assign the configuration (III) to octahydroacridine (A). In the earlier communication (p. 2450) it is shown that isatin condenses with *cyclo*hexanone to yield tetrahydroacridinecarboxylic acid (compare Borsche, *Ber.*, 1908, **41**, 2207) and that this acid yields, on reduction with sodium amalgam, a mixture of octahydroacridinecarboxylic acids (A) and (B), which, on distillation, decompose with elimination of carbon dioxide and formation of the octahydroacridines (A) and (B). These acids are doubtless also *dl*-modifications corresponding to (III) and (IV) and experiments on their resolution are in progress.

During the course of these resolution experiments, we thought it desirable to be able to confirm the results obtained with the octahydroacridines (A) and (B) by the investigation of another case of the same kind. We therefore condensed 1-methyl*cyclo*hexan-3-one with (i) *o*-aminobenzaldehyde and (ii) isatin. In (i) we obtained a substance melting at 71° which may be either 6- or 8-*methyltetrahydroacridine* and in (ii) a 6(or 8)-*methyltetrahydroacridinecarboxylic acid* (m. p. 296°) which, on heating, yielded the same parent substance melting at 71°. When this substance is reduced with tin and hydrochloric acid, it is converted into a mixture of 6(or 8)-*methyloctahydroacridines* (*A*, m. p. 92°) and (*B*, m. p. 80°), and again (compare above) only the modification (A) is produced when 6(or 8)-methyltetrahydroacridone (*loc. cit.*, p. 2442) is reduced with sodium amalgam. Of these modifications, the substance (A) has been resolved with the aid of the *d*- and *l*-camphorsulphonic acids and the active modifications have $[\alpha]_D + 20°$ and $- 28°$, respectively, or a mean rotation of $[\alpha] \pm 24°$.

EXPERIMENTAL.

The *l*-camphorsulphonic acid used in this research was prepared by sulphonating *l*-camphor with a mixture of sulphuric acid and acetic anhydride as described by Reychler (*Bull. Soc. chim.*, 1898, **111**, 120). The *d*-acid was supplied by the British Drug Houses. Both gave physical constants in good agreement with those quoted in the literature, melting, in the anhydrous form, at 193° and showing, in solution as ammonium salts, $[\alpha]_D \pm 19{\cdot}9°$. The octahydroacridine (A) (m. p. 82°) used in the following experiments was obtained partly by the reduction of tetrahydroacridone with sodium amalgam, and both the (A) and (B) modifications were prepared in quantity by the reduction of tetrahydroacridine and separated by the sulphuric acid method (compare Perkin and Sedgwick, *loc. cit.*, p. 2448).

Resolution of dl-*Octahydroacridine* (*A*) (m. p. 82°).—This *dl*-base (20 g.), dissolved in the minimum quantity of hot alcohol, was added to a concentrated solution of the equivalent quantity of *d*-camphorsulphonic acid (24·9 g.), and the mixture left over-night. The mother-liquor was then decanted from the crystalline mass of crude l-*octahydroacridine* (*A*) d-*camphorsulphonate*, the crystals (24 g.) were quickly washed with a little alcohol, dissolved in the minimum quantity of boiling alcohol, and allowed to recrystallise. This operation was repeated four times, the final product, l-*octahydroacridine* (*A*) d-*camphorsulphonate* (8 g.), separating in large, colourless prisms, m. p. 182° (Found: C, 65·4; H, 7·7. $C_{13}H_{17}N,C_{10}H_{15}O{\cdot}SO_3H$ requires C, 65·9; H, 7·9%; 0·6084 required 14·55 c.c. of *N*/10-NaOH for neutralisation, whereas the theoretical amount is 14·5 c.c.).

In order to separate the free base, the salt was dissolved in alcohol, and the solution carefully neutralised with *N*/10-sodium hydroxide, phenolphthalein being used as indicator; the precipitation was then completed by the addition of water, and the base extracted three times with ether. The ethereal extract was dried over sodium sulphate and concentrated; l-*octahydroacridine* (*A*) then separated slowly in well-defined plates, m. p. 85° (Found: C, 83·2; H, 9·1. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1%). 0·5 G. in 20 c.c. of alcohol ($c = 2{\cdot}5$) gave, in a 1-dcm. tube, $\alpha - 0{\cdot}80°$, whence $[\alpha]_D = -32°$.

d-*Octahydroacridine* (*A*) was isolated in the same manner by means of *l*-camphorsulphonic acid and melted at 84·5° (Found: C, 83·0; H, 9·0%). $[\alpha]_D$ in alcohol, $+ 34°$ ($c = 2{\cdot}5$) and in acetone, $+ 29°$ ($c = 2{\cdot}0$). Both active modifications undergo racemisation on distillation and when equal quantities were mixed and the mixture was crystallised from ether, the *dl*-base (A) obtained melted at 82·5°. The melting point of a mixture of approximately equal quantities was 83°. The mother-liquor from the first crystallisation of *l*-octahydroacridine (A) *d*-camphorsulphonate deposited, on further concentration, several crops of crystals of varying rotation. The last of these, on repeated recrystallisation, yielded ultimately a crop which was nearly pure d-*octahydroacridine* (*A*) d-*camphorsulphonate* (m. p. 180°), since the base, set free on neutralisation, had, in alcohol, $[\alpha]_D + 25°$.

Resolution of dl-*Octahydroacridine* (*B*) (m. p. 72°).—This *dl*-base (10 g.) was slowly dissolved in a warm concentrated aqueous solution of *d*-camphorsulphonic acid (15 g.), the excess of acid over that theoretically required to neutralise the base (12·4 g.) being necessary to effect complete solution. After 12 hours, the crystalline mass was collected, washed with alcohol, and dried between blotting paper, the filtrate (O) being preserved for subsequent treatment.

The crude l-*octahydroacridine* (*B*) d-*camphorsulphonate* crystallised from water with one molecule of the solvent, which was removed by drying in a desiccator over sulphuric acid or by heating in an air-oven.

The salt was then subjected to two crystallisations from alcohol; the ultimate yield of pure anhydrous *l*-octahydroacridine (B) *d*-camphorsulphonate was 4 g. and the salt melted at 172° with previous softening. 0·4693 G. of the salt required 11·1 c.c. of *N*/10-sodium hydroxide for neutralisation, whereas the theoretical amount is 11·2 c.c.

l-*Octahydroacridine* (*B*) was obtained from this salt by neutralisation with sodium hydroxide and separated from petroleum (b. p. 40—60°) in colourless plates, m. p. 73° (Found: C, 83·1; H, 9·5. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1%). $[\alpha]_D$ in alcohol ($c = 2·5$), $- 24°$; $[\alpha]_D$ in acetone ($c = 1·0$), $- 19°$.

The filtrate (O), after removal of the crystals which had separated on further standing, was neutralised with sodium hydroxide, and the precipitated base extracted with ether. The ethereal extract was evaporated in a vacuum desiccator, and the crystalline residue (4 g.) showed a small dextrorotation in alcoholic solution.

This material was combined with *l*-camphorsulphonic acid under the conditions already described, the salt purified by repeated crystallisation, and the d-*octahydroacridine* (*B*) precipitated by neutralisation with sodium hydroxide. The base melted at 73° and had $[\alpha]_D$ in alcohol ($c = 2$) $+ 22°$.

The salts of octahydroacridine (B) with the camphorsulphonic acids are more soluble than those of the isomeride (A), particularly in anhydrous alcohol. This property may be utilised as a method for the separation of the two isomerides, in which case the mixture resulting from the reduction of tetrahydroacridine with tin and hydrochloric acid (*loc. cit.*, p. 2448) is dissolved in a warm concentrated alcoholic solution of the equivalent quantity of *d*-camphorsulphonic acid and allowed to crystallise. The first crop of crystals consists of almost pure octahydroacridine (A) *d*-camphorsulphonate and can be used directly for the resolution of the base.

6(or 8)-*Methyltetrahydroacridine*.—In preparing this substance, a mixture of *o*-aminobenzaldehyde (3 g.) with 1-methyl*cyclo*hexan-3-one (5 g.) was heated in an oil-bath at 100° for about an hour and then at 130° for 1½ hours. On distilling the product under reduced pressure (15 mm.), water and unchanged methyl*cyclo*hexanone passed over below 120° and then *methyltetrahydroacridine* (3 g.) distilled at about 150° as a pale yellow oil which quickly solidified. The base crystallised from petroleum in colourless plates, m. p. 70—71° (Found : C, 85·0; H, 7·5. $C_{14}H_{15}N$ requires C, 85·3; H, 7·6%). The *picrate*, prepared by mixing solutions of the base and picric acid in hot alcohol, crystallised on cooling in yellow prisms, m. p. 182° (darkening).

6(or 8)-*Methyltetrahydroacridinecarboxylic Acid*.—A solution of isatin (10 g.) in potassium hydroxide (42 c.c. of 30%) was mixed with alcohol (80 c.c.) and 1-methyl*cyclo*hexanone (20 g.) and refluxed for 12 hours. The alcohol was evaporated in an open basin, the viscid residue mixed with water, the semi-crystalline scum removed by filtration, and the *methyltetrahydroacridinecarboxylic acid* precipitated as a fine, yellow, crystalline powder by the addition of 50% acetic acid.

The dried product is pure enough for most purposes and is very sparingly soluble in the usual solvents. It separates from much alcohol in minute, yellow needles, m. p. 296° (decomp.) (Found : C, 74·8; H, 6·6. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2%). The acid (10 g.) was heated in a distilling flask at its melting point until evolution of carbon dioxide had ceased and the dark liquid was then distilled under 15 mm. pressure; 6(or 8)-*methyltetrahydroacridine* passed over as a pale yellow oil which immediately crystallised. The recrystallised material melted at 70—72° and gave no depression of melting point when mixed with a specimen prepared by the *o*-aminobenzaldehyde process just described.

The 6(or 8)-*Methyloctahydroacridines*.—Methyltetrahydroacridine was reduced with tin and hydrochloric acid under the conditions described in the case of tetrahydroacridine (*loc cit.*, p. 2448), and the resulting two methyloctahydroacridines (A) and (B) were separated in a manner similar to that employed in the separation of the octahydroacridines (A) and (B) (*loc. cit.*). *Methyloctahydroacridine* (*A*) was also obtained by the reduction of methyltetrahydroacridone and separated from ether or petroleum in colourless prisms, m. p. 92°. It was resolved with the aid of *d*- and *l*-camphorsulphonic acids exactly as described in the case of the octahydroacridines (A) and (B). The *d*- and *l*-isomerides melt at 92° (Found for the *d*-isomeride : C, 83·4; H, 9·4. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5%). 0·09 G. of the *d*-modification, dissolved in 15 c.c. of alcohol ($c = 0·6$), gave in a 1-dcm. tube, $\alpha = +0·12°$, whence $[\alpha]_D + 20°$. 0·1 G. of the *l*-modification, dissolved in 20 c.c. of alcohol ($c = 0·5$), gave in a 2-dcm. tube, $\alpha - 0·28°$, whence $[\alpha]_D - 28°$; the mean rotation is therefore $[\alpha]_D \pm 24°$.

The *sulphate* of *dl*-methyloctahydroacridine (B) is more readily soluble than the sulphate of the modification (A), and the base melts at 80°; no attempt was made to resolve it into its active modifications.

One of us (W. G. S.) desires to express his thanks to the Salters' Institute of Industrial Chemistry for a Fellowship which has enabled him to engage in this investigation.

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