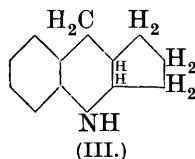
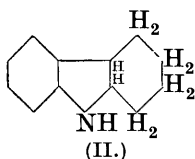
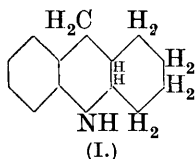


LXXXVII.—*Stereoisomerism in Polycyclic Systems.*  
*Part IV. Two Stereoisomerides of 2:3:4:5:12:13-*  
*Hexahydroquinindene.*

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 PLANT.

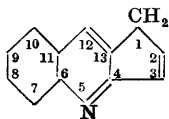
IN the earlier investigations it has been shown that octahydroacridine (I) (Perkin and Sedgwick, J., 1924, **125**, 2437; 1926, 438) and hexahydrocarbazole (II) (Gurney, Perkin, and Plant, J., 1927, 2676)\* each occur in two stereoisomeric modifications the existence of which can be accounted for by the Sachse-Mohr theory of multi-planar rings. It was found that when tetrahydrocarbazole is reduced to hexahydrocarbazole the product consists almost entirely of the *cis*-modification, only about 1–2% of the *trans*-form being present. In Part III it is pointed out that this may be ascribed to the fact that in the configuration of the reduced dicyclic system of the *trans*-modification there must be considerable strain. It is obvious, however, that in these cases the effect of the benzene ring must also be considered, and the factors which determine the relative strain in the various stereoisomerides of this type are clearly more complex than in a simple dicyclic system. With a view to gaining information bearing on this point, we have decided to examine the possibility of stereoisomerism in the case of 2:3:4:5:12:13-hexahydroquinindene (III).†



This substance is closely allied to hexahydrocarbazole, the possibility of stereoisomerism being again a feature of the dicyclic system composed of one 6-membered and one 5-membered ring, and it might be expected from previous experience in the case of the

\* These communications are regarded as Parts I, II, and III, respectively, of this series.

† It has been suggested by Dr. Smith that compounds containing the ring system present here should be considered as derived from the hypothetical parent substance, "quinindene,"



reduction of tetrahydrocarbazole that only a small quantity of the *trans*-form would occur in any reaction which might give rise to both stereoisomerides at the same time.

We have prepared considerable quantities of 2:3-dihydroquinindene (IV) from 2:3-dihydroquinindene-12-carboxylic acid (V) by the elimination of carbon dioxide (compare Borsche, *Annalen*,



1910, 377, 120), and have investigated its reduction by means of tin and hydrochloric acid in aqueous-alcoholic solution, under conditions similar to those used in the case of hexahydrocarbazole. An oily mixture of the *cis*- and *trans*-bases was obtained, and it was found that separation could best be brought about by converting the product into the mixture of the corresponding benzoyl derivatives and separating these by fractional crystallisation from alcohol and acetone. In this way two stereoisomeric 5-benzoyl-2:3:4:5:12:13-hexahydroquinindenes, (A), m. p. 174°, and (B), m. p. 161°, were isolated, but contrary to the experience in the case of the reduction of tetrahydrocarbazole, where only 1—2% of the *trans*-form is obtained, the proportion of (A) to (B) is about 1 to 3. The corresponding stereoisomeric 2:3:4:5:12:13-hexahydroquinindenes (VI and VII) have been isolated from these benzoyl compounds by hydrolysis, (A) melting at 67°, and (B) being an oil, b. p. 284°/



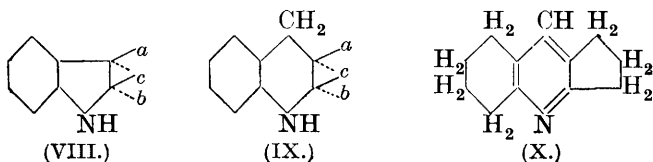
762 mm. Each base has been converted into its *acetyl* derivative, that from (A) melting at 102°, and that from (B) at 87°. The *picrate* of 2:3:4:5:12:13-hexahydroquinindene (A) melts at 193° (decomp.), and that of the stereoisomeride (B) at 158°. Both of the isomeric benzoyl derivatives have been shown to be unimolecular.

The nature of the reducing agent influences the course of the reaction, since in subsequent experiments, when 2:3-dihydroquinindene was reduced electrolytically and the product separated as before by means of the benzoyl derivatives, appreciable quantities of both forms, (A) and (B), were again isolated, but the proportion

of the benzoyl derivative (A) (m. p. 174°) to (B) (m. p. 161°) was now about 1 to 12. It is an interesting fact that our experiments seem to show that the electrolytic reduction of tetrahydrocarbazole gives no appreciable quantity of the *trans*-hexahydrocarbazole.

The two stereoisomeric 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindenes have here been designated (A) and (B), respectively. As will be pointed out later, considerations of strain and of the relative amounts of the two forms produced lead to no certain indication as to which is the *cis*- and which the *trans*-modification. There is no absolute method available for determining this point, since oxidation to some simple recognisable *cis*- and *trans*-forms of a monocyclic system, or synthesis from these, seems to be out of the question.

It is clear that the factors which determine the relative amounts of the two stereoisomerides in the cases so far investigated are numerous and complex. The nature of, and the strain in, the ring system undergoing reduction, the kind of reducing agent used, and the relative strains in each of the isomeric products will all presumably have some influence on the proportion of the stereoisomerides formed. A detailed study of the problem of the strain in the products is very interesting in view of the different nature of the results already obtained on reducing tetrahydrocarbazole and 2 : 3-dihydroquinindene to hexahydrocarbazole and 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene, respectively. Adopting the generally accepted views (i) that the normal position of the benzene ring is in one plane with the six hydrogen atoms symmetrically arranged in the same plane, (ii) that the 5-membered ring is also normally uniplanar, and (iii) that the *cyclohexane* ring has one of the well-known multiplanar configurations, it is possible with the aid of models to see that the *trans*-valencies, marked *a* and *b* in the dihydroindole skeleton (VIII), when projected on to a plane at right angles to the line joining the two carbon atoms to which they are attached, enclose a relatively large angle (about 110°), so that a *trans*-union of the remaining  $-(\text{CH}_2)_4-$  group to form hexahydrocarbazole results in a very highly strained configuration. The dihydroindole skeleton is itself strained and presumably uniplanar, and any attempt to facilitate the *trans*-union of the  $-(\text{CH}_2)_4-$  group by reducing the angle



between the *trans*-valencies *a* and *b* by free rotation results in an increased strain in this section. The corresponding projections of

the *cis*-valencies, *a* and *c*, are coincident, and the *cis*-hexahydrocarbazole molecule is far less strained than the *trans*-. There can be little doubt that the formation of only very small quantities of *trans*-hexahydrocarbazole during the reduction of tetrahydrocarbazole is due in a large measure to this fact.

Applying the same considerations to the case of 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene, it is found that the effect of the benzene ring is to alter the positions in the multiplanar, 6-membered ring so as to cause the two *trans*-valencies, *a* and *b* in fig. IX, to be so situated that, when projected on to a plane as before at right angles to the line joining the two carbon atoms to which they are attached, they enclose only a small angle. The study of the model indicates that the angle enclosed between the projections of the corresponding *cis*-valencies, *a* and *c*, is approximately the same as in the case of the *trans*-. It will be apparent, therefore, that both the *cis*- and the *trans*-union of the remaining  $-(\text{CH}_2)_3-$  group to complete the 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene molecule should be brought about with approximately equal ease. It is also apparent that the size of the angle enclosed between the projections of the various *cis*- and *trans*-valencies on to a plane perpendicular to that already considered will have a marked effect upon the strains in the completed molecules, but this angle varies only slightly in the systems under consideration. The effect of this factor will, of course, depend upon the number of carbon atoms in the groups  $-(\text{CH}_2)_n-$  which are attached to these valencies in order to complete the tricyclic system.

In the absence of quantitative data concerning the actual distribution of the total strain throughout these molecules, it is difficult at present to be more definite, but it is even possible that the *cis*-modification of 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene may be more strained than the *trans*-. These facts are interesting in view of the isolation of considerable quantities of both forms of 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene as the result of the reduction of 2 : 3-dihydroquinindene. We propose to extend these investigations to other polycyclic systems with a view to obtaining further data which may be useful for developing more definite ideas concerning some of the points raised above.

The reduction of dihydroquinindene has previously been investigated by von Braun, Petzold, and Schultheiss (*Ber.*, 1923, 56, 1347). By catalytic hydrogenation these authors obtained two products, one of which could be benzoylated, but the other could not. These substances are regarded by them as 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (III) and "2 : 3-trimethylene-5 : 6-tetramethylene-pyridine" (X), respectively; the former is described as an oil, b. p. 169—171°/18 mm., its benzoyl derivative is said to melt at 157° and

its picrate at 154°. It seems probable that this substance is identical with the 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (B) described in this communication.

#### EXPERIMENTAL.

A mixture of isatin (50 g.), cyclopentanone (90 g.), aqueous potassium hydroxide (200 c.c. of 30%), and alcohol (400 c.c.) was boiled under reflux for 8 hours, the alcohol removed by distillation, the residue diluted by water (about 2500 c.c.), and acidified, after filtering, with an excess of glacial acetic acid. The 2 : 3-dihydroquinindene-12-carboxylic acid (V), which rapidly separated, was used without further purification for the preparation of 2 : 3-dihydroquinindene, but it can be crystallised from glacial acetic acid and obtained in pale green prisms, m. p. 297° (decomp.) (Found : N, 6.5. Calc. : N, 6.6%. Compare Borsche, *loc. cit.*, who gives the m. p. 277—278°). The dry, crude acid was heated at a temperature just above its m. p. in a small distillation flask for about 10 minutes, until the evolution of carbon dioxide ceased, and the residue was then distilled under reduced pressure. The distillate was dissolved in ether and shaken with dilute aqueous sodium carbonate, the ethereal solution was dried over potassium carbonate, the solvent removed, and the residue crystallised from low-boiling petroleum, from which 2 : 3-dihydroquinindene separated in large, colourless prisms, m. p. 60° (compare Borsche, *loc. cit.*). The yield from 50 g. of isatin amounted to 23 g.

*Reduction of 2 : 3-Dihydroquinindene with Tin and Hydrochloric Acid.*—A mixture of 2 : 3-dihydroquinindene (17.5 g.), alcohol (70 c.c.), concentrated hydrochloric acid (70 c.c.), and granulated tin (70 g.) was boiled under reflux on the steam-bath for 5 hours and then filtered while still hot, the tin residues being washed with a little hot alcohol. After removal of the alcohol by distillation, the residue was cooled, treated gradually with an excess of concentrated aqueous sodium hydroxide (70 g. of NaOH), and extracted several times with ether. The extract was dried over potassium carbonate and the solvent removed, a mixture of products being obtained as an oil which did not solidify after standing for some time. The mixture was converted into the corresponding benzoyl derivatives by shaking with benzoyl chloride (20 g.) and an excess of dilute aqueous sodium hydroxide, the product soon separating in a solid condition. On crystallising this mixture from alcohol, a quantity of 5-benzoyl-2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (A) separated first in long, colourless prisms, m. p. 174° (Found : C, 82.1; H, 7.0; *M*, by Rast's method, 289. C<sub>19</sub>H<sub>19</sub>ON requires C, 82.3; H, 6.8%; *M*, 277). After a short time the second derivative also began to separate at a

point very easily detected, and the solution was then rapidly filtered. The mixture which crystallised from the filtrate was then recrystallised from acetone, 5-benzoyl-2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (B) separating first in large, stout, colourless prisms, m. p. 161° (Found : C, 82.4; H, 7.0%; *M*, by Rast's method, 261). After a time the other benzoyl derivative (m. p. 174°) also began to separate from this solution, and at this point the product was collected. Both of these stereoisomerides can be purified, if necessary, by further recrystallisation from either alcohol or acetone. After a certain quantity of each stereoisomeride had been isolated in this way, the mother-liquors were united and the mixture was obtained by dilution with water or by evaporation of the solvent, and again subjected to the above process of separation. The whole procedure can be repeated to bring about complete separation, and the amounts of the stereoisomerides (B) and (A) were found to be approximately in the ratio 3 : 1, although in different preparations the actual amounts varied a little. These benzoyl derivatives are only slowly hydrolysed by aqueous-alcoholic potassium hydroxide, prolonged boiling being necessary in order to separate the corresponding bases.

2 : 3 : 4 : 5 : 12 : 13 - Hexahydroquinindene (A). — 5 - Benzoyl - 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (A) (4 g.) was boiled under reflux with potassium hydroxide (25 g.) in aqueous alcohol for 24 hours, the alcohol was distilled off, and the residue was shaken with ether and water. Two clear layers were obtained in this case. The ethereal layer was shaken with dilute hydrochloric acid and no residue remained after evaporation of the ether, so that hydrolysis of the benzoyl derivative was complete. The solution of the base in dilute hydrochloric acid was made alkaline with ammonia and extracted with ether, the ethereal solution dried over potassium carbonate, and the solvent removed. The residual oil quickly solidified, and, after crystallisation from petroleum, 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (A) was obtained in large, colourless prisms, m. p. 67° (Found : C, 83.5; H, 8.6.  $C_{12}H_{15}N$  requires C, 83.2; H, 8.7%). By shaking this base (A) with benzoyl chloride and dilute aqueous sodium hydroxide the benzoyl derivative (m. p. 174°) was regenerated. After boiling the mixture of the base with an excess of acetic anhydride for 20 minutes, shaking it with water, and crystallising the product from dilute alcohol, 5-acetyl-2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (A) was obtained in long, colourless prisms, m. p. 102° (Found : N, 6.4.  $C_{14}H_{17}ON$  requires N, 6.5%). The *picrate* of 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (A) separated from alcohol in small, yellow prisms, m. p. 193° (decomp.).

2 : 3 : 4 : 5 : 12 : 13-*Hexahydroquinindene* (B).—A mixture of 5-benzoyl-2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (B) (7.5 g.) and potassium hydroxide (25 g. in aqueous alcohol) was boiled under reflux for 24 hours, the alcohol was distilled off, and the residue well shaken with ether and water. The ethereal layer, after being filtered from some unchanged benzoyl derivative, which is only slightly soluble in ether, was extracted with dilute hydrochloric acid, and then, after removal of the ether, a further quantity of unchanged benzoyl derivative was obtained. The total quantity of benzoyl compound recovered amounted to 3.5 g. The hydrochloric acid solution of the base was made alkaline with ammonia and extracted with ether, the ethereal solution was dried over potassium carbonate, and the solvent removed. The residual oily 2 : 3 : 4 : 5 : 12 : 13-*hexahydroquinindene* (B) has not been made to solidify, but, on distillation, it boiled at 284°/762 mm. (Found: C, 83.4; H, 8.7.  $C_{12}H_{15}N$  requires C, 83.2; H, 8.7%). By shaking the base (B) with benzoyl chloride and dilute aqueous sodium hydroxide the benzoyl derivative (m. p. 161°) was obtained. After a solution of the base in an excess of acetic anhydride had been boiled for 20 minutes and shaken with water, and the solid crystallised from low-boiling petroleum, 5-*acetyl*-2 : 3 : 4 : 5 : 12 : 13-*hexahydroquinindene* (B) separated in colourless plates, m. p. 87° (Found: C, 78.0; H, 8.0.  $C_{14}H_{17}ON$  requires C, 78.1; H, 7.9%). The *picrate* of 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (B) separated from alcohol in orange-coloured prisms, m. p. 158°.

*Electrolytic Reduction of 2 : 3-Dihydroquinindene*.—2 : 3-Dihydroquinindene (8 g.) was dissolved in dilute sulphuric acid (300 c.c. of 10%) and reduced electrolytically, lead electrodes and a current of 2.5 amps. (0.01 amp. per sq. cm. of cathode) being used, for 16 hours. The solution was then filtered, made alkaline with aqueous sodium carbonate, and extracted with ether. After the extract had been dried over potassium carbonate and the solvent removed, the residual oil was distilled under reduced pressure, and the distillate was collected at 155—160°/11 mm. This mixture of the 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindenes (A) and (B) was converted by benzoylation in the usual way into the two corresponding stereoisomeric benzoyl derivatives (A) and (B). On fractional crystallisation from alcohol a considerable amount of the isomeride (B) separated first in this case, since it was present to a greater extent than in the product from the reduction with tin and hydrochloric acid. After separating the two benzoyl derivatives, it was found that the proportion of (B) to (A) is here approximately 12 to 1.

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