CCCXLII.—*Stereoisomerism in Polycyclic Systems. Part V.*

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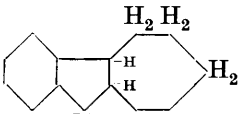
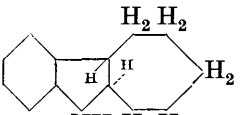
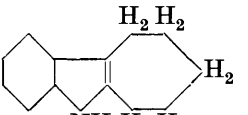
IT has been shown that although the reduction of tetrahydrocarbazole with tin and hydrochloric acid in aqueous alcohol leads almost entirely to the *cis*-modification of hexahydrocarbazole, the *trans*- being produced in only small amount (Gurney, Perkin, and Plant, J., 1927, 2676), yet the reduction of 2 : 3-dihydroquinindene under similar conditions gives relatively large quantities of both the *cis*- and the *trans*-form of 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (Perkin and Plant, this vol., p. 639). These facts were found to be in accordance with the deductions which could be drawn from a consideration of the relative strains in the various multiplanar configurations. The present communication deals with an extension of these considerations to some systems containing seven-membered rings. Owing to the fact that the multiplanar *cyclo*heptane ring can pass by free rotation into a strainless phase in which the *trans* valencies of two neighbouring carbon atoms, when projected on to a plane at right angles to the line joining these two atoms, enclose only a very small angle, it appears that there



cis- (I.)



trans- (II.)



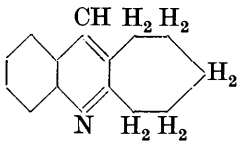
(III.)

should be relatively less strain in the *trans*-configuration of 2 : 3 : 4 : 5 : 11 : 12-*hexahydroheptindole* (II) than in *trans*-hexahydro-

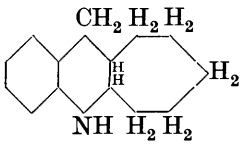
carbazole. It was thought, therefore, that the reduction of 2 : 3 : 4 : 5-*tetrahydroheptindole* * (III) with tin and hydrochloric acid in aqueous alcohol might lead to relatively large quantities of both the stereoisomeric hexahydro-derivatives (I) and (II).

2 : 3 : 4 : 5-Tetrahydroheptindole has been prepared by Fischer's indole synthesis from suberonephenylhydrazone, its reduction under the above conditions has been investigated, and the product has been found to consist almost entirely of a single form (presumably the *cis*-, since this is likely to be the less strained) of 2 : 3 : 4 : 5 : 11 : 12-hexahydroheptindole, not more than 5% of any stereoisomeride being present. This modification of hexahydroheptindole is basic, readily yielding a *picrate*, and *acetyl* and *benzoyl* derivatives. The isolation of the small quantity of the second form, which may possibly be present here as it was in the case of hexahydrocarbazole, was not attempted on account of the difficulty of obtaining the large amounts of suberone which would be required for such an investigation.

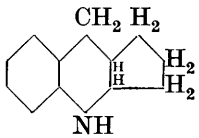
The results obtained in the above investigations suggested that a study of the reduction of 7 : 8 : 9 : 10-tetrahydroheptaquinoline † (IV) to 5 : 7 : 8 : 9 : 10 : 11 : 14 : 15-octahydroheptaquinoline (V) would be interesting. In this instance, as in the case of octahydroacridine (Perkin and Sedgwick, J., 1924, **125**, 2437) and of 2 : 3 : 4 : 5 : 12 : 13-hexahydroquinindene (VI) (Perkin and Plant, *loc. cit.*), there should be very little difference in the strains of the



(IV.)



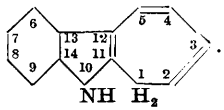
(V.)



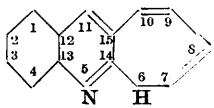
(VI.)

two stereoisomeric octahydro-derivatives, and relatively large quantities of the two forms should again be produced. We have pre-

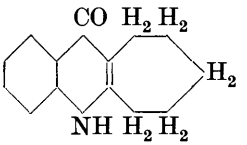
* This substance is regarded as derived from the hypothetical parent compound " heptindole,"

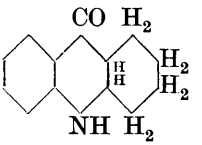


† This substance is regarded as derived from the hypothetical parent compound " heptaquinoline,"



pared 7 : 8 : 9 : 10-tetrahydroheptaquinoline by the elimination of carbon dioxide from 7 : 8 : 9 : 10-tetrahydroheptaquinoline-11-carboxylic acid (compare Borsche, *Annalen*, 1910, **377**, 122), and have found that on reduction by means of tin and hydrochloric acid in aqueous-alcoholic solution it yields an oily base. By benzoylation (see Experimental), this was shown to consist almost entirely of one of the two possible forms of 5 : 7 : 8 : 9 : 10 : 11 : 14 : 15-*octahydroheptaquinoline*, admixed with a small amount of the unreduced tetrahydro-compound. The failure to isolate more than one stereoisomeride in these two reduced systems containing 7-membered rings is surprising and difficult to explain. Previous work in this field has indicated that the constitution of the product is influenced by the nature of the reducing agent used and depends also upon the nature of the starting material. It was hoped, therefore, that the second stereoisomeride of 5 : 7 : 8 : 9 : 10 : 11 : 14 : 15-octahydroheptaquinoline would result from the reduction of 11-*keto*-5 : 7 : 8 : 9 : 10 : 11-*hexahydroheptaquinoline* (VII) with sodium amalgam. We have prepared this keto-derivative by condensing anthranilic acid with suberone, but have found that reduction under these conditions and subsequent benzoylation of the oily product yields a single benzoyl derivative identical with that obtained by the previous method.

(VII.) 



(VIII.)

In Part I of this series (J., 1924, **125**, 2437), the formation of the two stereoisomeric octahydroacridines (A, m. p. 82°, and B, m. p. 72°) by the reduction of tetrahydroacridine with tin and hydrochloric acid in aqueous alcohol is described. The more recent developments of this work have made it desirable to determine the relative amounts of the two modifications produced under these conditions, and we have now found that the ratio of octahydroacridine (A) to octahydroacridine (B) in the product is approximately 1 to 4. The reduction of tetrahydroacridone with sodium amalgam yielded entirely octahydroacridine (A) (Perkin and Sedgwick, *loc. cit.*), but it has been found during the course of the present work that the action of tin and hydrochloric acid on tetrahydroacridone in aqueous alcohol is to give a small quantity of a base which appears to be one of the two possible *hexahydroacridones* (VIII). This structure is confirmed by the fact that it gives an *oxime* (p. 2590).

EXPERIMENTAL.

2 : 3 : 4 : 5-*Tetrahydroheptindole.*—After equal weights of suberone and phenylhydrazine had been warmed together on the water-bath for 5 minutes and then cooled, the product solidified, and suberone-phenylhydrazone could be obtained from dilute alcohol in colourless needles, m. p. 72°. When a mixture of the crude hydrazone (18 g.), water (360 c.c.), and concentrated sulphuric acid (20 c.c.) was heated on the water-bath for 25 minutes with frequent shaking, 2 : 3 : 4 : 5-*tetrahydroheptindole* (11 g.) gradually separated in a practically pure condition. On crystallisation from alcohol it was isolated in colourless plates, m. p. 144° (Found : N, 7·4. $C_{13}H_{15}N$ requires N, 7·6%). The *picrate* was obtained from hot alcohol in dark crimson plates, m. p. 142°.

2 : 3 : 4 : 5 : 11 : 12-*Hexahydroheptindole.*—A mixture of 2 : 3 : 4 : 5-tetrahydroheptindole (10 g.), alcohol (30 c.c.), granulated tin (30 g.), and concentrated hydrochloric acid (30 c.c.) was boiled under reflux for 5 hours, filtered, the tin residues washed with a little hot alcohol, and the alcohol distilled off from the united filtrates. After being made alkaline with a concentrated aqueous solution of sodium hydroxide (30 g.) and cooled, the whole was filtered through asbestos, and both the solid and the filtrate were extracted with ether. The solid residue then remaining was dissolved in dilute hydrochloric acid, the solution was made alkaline with aqueous sodium hydroxide and again extracted with ether. When the united ethereal solutions were dried over potassium carbonate and the solvent removed, the residue solidified on cooling. On crystallising from alcohol, 2 : 3 : 4 : 5 : 11 : 12-*hexahydroheptindole* (2·9 g.) separated in colourless plates, m. p. 77°, unaltered by further recrystallisation (Found : C, 83·4; H, 9·2. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1%). After removal of the solvent from the alcoholic filtrate, the residue melted at 67—70°, and crystallisation of this from a small quantity of alcohol yielded a further quantity (3·3 g.) of the hexahydroheptindole, m. p. 72—74° (mixed m. p. 73—75°). The solvent was then again removed from the filtrate, and the residue extracted with dilute hydrochloric acid, which left a small quantity of a dark red, resinous material. After the acid solution had been made alkaline with ammonia, the base obtained (2·0 g., m. p. 45—55°) was treated in hot alcohol with picric acid (2·5 g.). The picrate (2·4 g., equivalent to 1·1 g. of base) which separated, m. p. 176° (decomp.), proved to be identical with the picrate of 2 : 3 : 4 : 5 : 11 : 12-hexahydroheptindole described below, and, on decomposition with aqueous sodium hydroxide, it yielded the base, m. p. 77°. The alcoholic filtrate from the picrate was shaken with ether and dilute aqueous sodium

hydroxide, and the ethereal solution extracted with dilute hydrochloric acid. The small amount (0·6 g.) of base obtained by making this acid solution alkaline with ammonia melted at 35—45°, and on benzoylation gave a product which, after crystallisation from methyl alcohol, yielded 0·2 g. of the benzoyl derivative described below. It is thus apparent that not more than a very small quantity of any second stereoisomeride can be present in the product of the reduction of 2 : 3 : 4 : 5-tetrahydroheptindole by the above method.

2 : 3 : 4 : 5 : 11 : 12-Hexahydroheptindole forms a sparingly soluble *hydrochloride*, but this dissolves in much water, and the base is reprecipitated by adding ammonia. When the product obtained by boiling a solution of the base in acetic anhydride for 15 minutes, cooling and shaking with water, was crystallised from dilute alcohol, 10-*acetyl*-2 : 3 : 4 : 5 : 11 : 12-*hexahydroheptindole* was obtained in long, silky, colourless needles, m. p. 87° (Found : N, 6·3. $C_{15}H_{19}ON$ requires N, 6·1%). When the base was shaken with benzoyl chloride and aqueous sodium hydroxide, 10-*benzoyl*-2 : 3 : 4 : 5 : 11 : 12-*hexahydroheptindole* resulted; it separated from alcohol in clusters of colourless prisms, m. p. 116° (Found : N, 4·9. $C_{20}H_{21}ON$ requires N, 4·8%). The *picrate* of the base was isolated from alcohol in yellow prisms, m. p. 176° (decomp.).

7-*Bromo*-2 : 3 : 4 : 5-*tetrahydroheptindole*.—When suberone (4 g.) and *p*-bromophenylhydrazine (6 g.) were mixed in a small quantity of hot alcohol, *suberone*-p-*bromophenylhydrazone* separated, on cooling, in colourless plates, m. p. 57°, which quickly decomposed on exposure to the air. The alcoholic mixture was added to water (500 c.c.) containing concentrated sulphuric acid (60 c.c.), and the whole was boiled for 10 minutes. The product separated as a dark red oil, which solidified on cooling, and, after crystallisation from alcohol, 7-*bromo*-2 : 3 : 4 : 5-*tetrahydroheptindole* was obtained in colourless plates, m. p. 129—130° (Found : N, 5·5. $C_{13}H_{14}NBr$ requires N, 5·3%). It is not basic, being precipitated from its solution in concentrated sulphuric acid by pouring into water. The reduction of this substance by means of tin and hydrochloric acid in aqueous alcohol was studied, but partial debromination occurred during the process.

Reduction of 7 : 8 : 9 : 10-*Tetrahydroheptaquinoline*.—A mixture of 7 : 8 : 9 : 10-tetrahydroheptaquinoline (12 g., prepared from suberone and isatin as described by Borsche, *loc. cit.*), alcohol (60 c.c.), concentrated hydrochloric acid (60 c.c.), and granulated tin (60 g.) was boiled under reflux for 9 hours, a further quantity (20 c.c.) of hydrochloric acid being added after 5 hours. The liquid was then filtered, the solid residue washed with alcohol, and as much alcohol as possible removed by distillation from the united liquors. The

residue was made alkaline by the addition of a concentrated aqueous solution of sodium hydroxide (80 g.), and extracted several times with ether. After the extract had been dried over potassium carbonate and the solvent removed, the residual oil, which could not be made to solidify, was shaken with dilute aqueous sodium hydroxide and benzoyl chloride (15 g.). The solid product was dissolved in a considerable quantity of ether, the solution shaken with dilute hydrochloric acid, which removed a quantity (2·3 g., isolated by making the acid solution alkaline) of unreduced 7 : 8 : 9 : 10-tetrahydroheptaquinoline, dried over calcium chloride, and the solvent distilled off. The solid residue (13·3 g.) melted at 133—137°, and after crystallisation from alcohol, *5-benzoyl-5 : 7 : 8 : 9 : 10 : 11 : 14 : 15-octahydroheptaquinoline* (9·3 g.) separated in colourless prisms, m. p. 145° (Found: C, 82·8; H, 7·6. $C_{21}H_{23}ON$ requires C, 82·6; H, 7·5%). By concentrating the alcoholic mother-liquor, a further quantity (1·1 g.) of the benzoyl compound was obtained, and it is clear that no appreciable quantity of a stereoisomeride of this benzoyl compound can be present.

5 : 7 : 8 : 9 : 10 : 11 : 14 : 15-*Octahydroheptaquinoline*.—A solution of the benzoyl derivative (m. p. 145°) in aqueous-alcoholic potassium hydroxide was boiled for 24 hours, the alcohol removed, and the residue shaken with ether and water. The base was removed from the unchanged benzoyl compound, which was also present in the ether, by extraction with dilute hydrochloric acid, recovered by adding ammonia, and taken up in ether. 5 : 7 : 8 : 9 : 10 : 11 : 14 : 15-*Octahydroheptaquinoline* was collected as a colourless oil, b. p. 203°/24 mm. (Found: C, 83·9; H, 9·2. $C_{14}H_{19}N$ requires C, 83·6; H, 9·4%). Its *picrate* separated from alcohol in orange-red prisms, m. p. 196°.

11-*Keto*-5 : 7 : 8 : 9 : 10 : 11-*hexahydroheptaquinoline*.—This substance was obtained by a process analogous to that used by Tiedtke (*Ber.*, 1909, **42**, 624) for the preparation of tetrahydroacridone. Anthranilic acid (3·5 g.) and suberone (4 c.c.) were heated together at 120° for an hour and then at 210° for 15 minutes. The solid was boiled for 1½ hours with benzene, in which it is sparingly soluble, collected, and crystallised from alcohol; 11-*keto*-5 : 7 : 8 : 9 : 10 : 11-*hexahydroheptaquinoline* then separated in colourless plates, m. p. 344—345° (Found: N, 6·5. $C_{14}H_{15}ON$ requires N, 6·6%).

The keto-compound (6 g.), dissolved in boiling alcohol (300 c.c.) to which a little sodium bicarbonate had been added, was treated gradually at 80° with sodium amalgam (450 g. of 4%), the whole being vigorously stirred and carbon dioxide being passed continuously. After 6 hours, the mixture was filtered, the solid washed with alcohol, and the alcohol removed from the united filtrates

under reduced pressure. The residue was shaken with ether and water, the ether layer dried over potassium carbonate, and the solvent removed. After distilling under reduced pressure, the residual oil did not solidify, and, on shaking with benzoyl chloride (4·5 g.) and dilute aqueous sodium hydroxide, it yielded 5-benzoyl-5 : 7 : 8 : 9 : 10 : 11 : 14 : 15-octahydroheptaquinoline, isolated from alcohol in colourless prisms, m. p. 145°. The mixture with the benzoyl compound obtained from the reduction product of 7 : 8 : 9 : 10-tetrahydroheptaquinoline also melted at 145°.

Reduction of Tetrahydroacridine with Tin and Aqueous-alcoholic Hydrochloric Acid.—A mixture of tetrahydroacridine (27 g.), alcohol (100 c.c.), concentrated hydrochloric acid (100 c.c.), and granulated tin (100 g.) was boiled under reflux for 5 hours, filtered, and the alcohol distilled off from the filtrate. The residue, after being made alkaline with sodium hydroxide (100 g. in concentrated aqueous solution), was extracted repeatedly with ether; from the extract, dried over potassium carbonate, a product was obtained which solidified on cooling and was crystallised from petroleum (b. p. 40—60°). Octahydroacridine (B) (6·7 g.) separated, and a further quantity (3·0 g.) was obtained by concentrating the mother-liquor. The petroleum was then completely removed, the residue heated to boiling for ½ hour with an excess of acetic anhydride, and the whole shaken with water (1500 c.c.) and left for several hours. The solid product was extracted with ether, and from the aqueous layer a small quantity (1·3 g.) of unchanged tetrahydroacridine was obtained by making it alkaline with ammonia and extracting it with ether. The extract containing the acetyl derivatives was shaken with dilute aqueous sodium carbonate, dried over calcium chloride, the solvent removed, and the residue crystallised from alcohol, 10-acetyloctahydroacridine (B) (7·0 g., m. p. 135—136°) being thus obtained; by distilling off the alcohol from the mother-liquor and crystallising the product from petroleum (b. p. 60—80°), a further quantity (1·7 g.) of the same substance was collected. After the mother-liquor was again evaporated to dryness, the residue was treated with potassium hydroxide (25 g.) in aqueous alcohol, and the whole boiled for 24 hours. The mixture, after removal of the alcohol, was diluted with water and shaken with ether; the ethereal layer was extracted with dilute hydrochloric acid and then evaporated, and the fact that no appreciable residue remained indicated complete hydrolysis of the acetyl derivatives. The aqueous acid solution was made alkaline with ammonia, and the basic product taken up in ether and dried with potassium carbonate. After removal of the ether, the residue (7·2 g.) solidified. It was dissolved in alcohol and treated with an alcoholic solution of picric acid (10 g.), whereupon the picrate of

octahydroacridine (A) (10·5 g., m. p. 198°) rapidly separated; the free (A) base was obtained from this by treatment with dilute aqueous sodium hydroxide and extraction with ether. The product remaining in the mother-liquor after removal of the picrate was clearly small and was essentially the picrate of octahydroacridine (B), for when the liquid was shaken with aqueous sodium hydroxide and ether, and the extracted base was crystallised from petroleum, octahydroacridine (B) (0·5 g., m. p. 72°) separated. The identities of the substances isolated were definitely established by mixed m. p. determinations with the products obtained as described by Perkin and Sedgwick (*loc. cit.*); the total amounts correspond to 17·3 g. of octahydroacridine (B) and 4·7 g. of octahydroacridine (A).

Hexahydroacridone.—A mixture of tetrahydroacridone (12 g.), alcohol (70 c.c.), concentrated hydrochloric acid (70 c.c.), and granulated tin (70 g.) was boiled for 6 hours, filtered, the alcohol removed, and the residue made alkaline with sodium hydroxide (70 g. in concentrated aqueous solution). After extraction with ether, drying with potassium carbonate, and removal of the solvent, the small quantity (about 0·5 g.) of solid obtained was crystallised from alcohol, from which *hexahydroacridone* separated in yellow plates, m. p. 180° (Found: C, 77·4; H, 7·7. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5%). The unreduced tetrahydroacridone was recovered by acidifying the mixture after the ether extraction with concentrated hydrochloric acid, collecting the hydrochloride, dissolving this in much water, and adding concentrated nitric acid. The nitrate of tetrahydroacridone gradually separated in a pure condition, and the free base was obtained from this with sodium hydroxide.

Hexahydroacridone, which is readily soluble in dilute hydrochloric acid, was treated in alcoholic solution with hydroxylamine hydrochloride and sodium acetate, the mixture boiled for 2 hours, the alcohol distilled off, and the residue shaken with water. The *oxime* separated from alcohol in pale yellow prisms, m. p. 215—216° (Found: N, 13·1. $C_{13}H_{16}ON_2$ requires N, 13·0%).

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