CCXLIII.—*Stereoisomerism in Substituted* 1 : 2 : 3 : 4-*Tetrahydroquinolines. Part I.*

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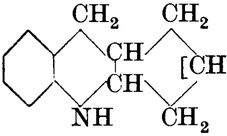
It has been shown that octahydroacridine (I; $n = 2$), hexahydrocarbazole (II), and 2 : 3 : 4 : 5 : 12 : 13-hexahydro-β-quinindene (I; $n = 1$) exist in two stereoisomeric modifications, depending upon the *cis*- and *trans*-unions respectively of the two reduced ring systems, and that the relative amounts of the two forms produced in any of these cases during the appropriate reduction process can be accounted for very satisfactorily by considering the strains in the various multiplanar configurations involved (Perkin and Plant, J., 1928, 639). It has been mentioned, however, that these considerations of strain are not the only factors concerned in the problem, and that the nature of the reducing agent can have some influence on the proportions of the stereoisomerides formed. In the previous work, attempts were made to eliminate this latter factor by using standard reducing conditions throughout, but, although the results obtained were in close agreement with the theoretical deductions, it is still uncertain how far these really determine the relative amounts of the products formed. In the 2 : 3-disubstituted tetrahydroquinolines of the type (III), where the fully reduced carbocyclic system of the substances (I; $n = 1$ or 2) is no longer present, these strain factors, which are discussed in detail in the communication referred to, do not enter. It became apparent, therefore, that a study of the products formed by reducing 2 : 3-disubstituted quinolines (IV) under various conditions might throw considerable light upon the importance to be attached to the views already mentioned.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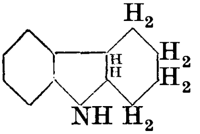
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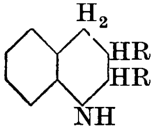
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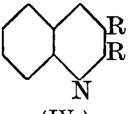
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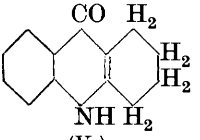
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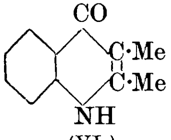
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Although it is clear that 2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (III; R = Me) can exist theoretically in *cis*- and *trans*-modifications, these do not appear to have been described hitherto. Consequently, the behaviour of 2 : 3-dimethylquinoline towards certain reducing agents has now been studied, and in each case the product has been separated into two stereoisomeric tetrahydro-derivatives. As it is not known which of these has the *cis*-configuration, or which the *trans*-, they have been called (A) and (B), the designation (A) being assigned to the higher-melting base in accordance with the procedure adopted in the related compounds.

2 : 3-Dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (A) is a base, m. p. 38—39°, which gives a *hydrochloride* (m. p. 240—243°), a *benzoyl* derivative (m. p. 92°), and a picrate (m. p. 178°), whilst the stereoisomeric base (B) is a liquid at ordinary temperatures, giving a hydrochloride (m. p. 169—170°), and a *benzoyl* derivative (m. p. 96—97°). It was found that with tin and alcoholic hydrochloric acid as the reducing agent, the ratio of the amounts of (A) and (B) present in the product was approximately 1 : 10; with zinc and alcoholic hydrochloric acid, 4 : 3; by electrolytic reduction, 8 : 3; and with sodium and alcohol, 1 : 1. The reduction of 2 : 3-dimethylquinoline with sodium and alcohol has previously been investigated by Ferratini (*Gazzetta*, 1893, **23**, ii, 112), who apparently considered the 2 : 3-dimethyltetrahydroquinoline formed (an oil, b. p. 254—255°/759 mm.) to be a single substance, giving a hydrochloride, m. p. 210—215°. It has now been found that, on dissolving the basic product in hot dilute hydrochloric acid, a solid separates, on cooling, and melts at 214—218°, but this is a mixture of the two stereoisomeric hydrochlorides already mentioned. The catalytic hydrogenation of 2:3-dimethylquinoline by hydrogen under pressure at about 150°, in the presence of nickel, has been studied by von Braun, Gmelin, and Schultheiss (*Ber.*, 1923, **56**, 1344), who state that their product consisted of a mixture of 2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (a liquid, b. p. 127—128°/13 mm., giving a benzoyl derivative, m. p. 94—95°, and a hydrochloride, m. p. 154°) and 2 : 3-dimethyl-5 : 6 : 7 : 8-tetrahydroquinoline. There can be little doubt that the former of these two products is identical with the base (B) now described, but the m. p. of its hydrochloride suggests that it was not quite pure.

Since the reduction of tetrahydroacridone (V) with sodium amalgam gave only one of the two modifications of octahydroacridine (I; $n = 2$) (Perkin and Sedgwick, J., 1924, **125**, 2437), it was thought that a study of the action of this reagent on 4-keto-2 : 3-dimethyl-1 : 4-dihydroquinoline (VI) would be interesting. It was found that, if a large excess of the reducing agent was employed, a mixture of the two dimethyltetrahydroquinolines (A) and (B) in the proportion of 4 : 3 again resulted, but if a smaller quantity of sodium amalgam was used, the product consisted very largely of 2 : 3-dimethylquinoline. These results suggest that the mechanism of the reduction of these keto-compounds involves the formation of the quinoline derivative as an intermediate step.

It was then decided to investigate the reduction of 2 : 3-diphenylquinoline (IV; R = Ph) to 2 : 3-diphenyl-1 : 2 : 3 : 4-tetrahydroquinoline (III; R = Ph), and it has been found that the use of certain reducing agents leads readily to a mixture of two stereoisomerides, which have again been designated (A) and (B). Thus, by employing zinc dust and alcoholic hydrochloric acid, or sodium and alcohol, relatively considerable amounts of the two forms were isolated, but, when the reduction was carried out with tin and alcoholic hydrochloric acid, or catalytically with the aid of colloidal platinum, no appreciable quantity of the (B) form appeared to be present, although good yields of the (A) modification were obtained in each case. These investigations are being continued in several directions.

EXPERIMENTAL.

2 : 3-*Dimethylquinoline.*—The following procedure was found to be satisfactory for the preparation of the relatively large amounts of 2 : 3-dimethylquinoline used in these experiments (compare Pfitzinger, *J. pr. Chem.*, 1897, **56**, 315; von Braun, Gmelin, and Schultheiss, *loc. cit.*). A mixture of isatin (100 g.), aqueous sodium hydroxide (2150 c.c. of 11·5%), and methyl ethyl ketone (150 g.) was heated under reflux on the steam-bath for 8 hours, excess of the ketone was removed by distillation, and the residue diluted with water (1200 c.c.) and then allowed to cool. After filtration, the solution was heated to boiling and acidified with acetic acid, and on cooling and standing, 2 : 3-dimethylquinoline-4-carboxylic acid, together with some 2-ethylquinoline-4-carboxylic acid, separated gradually. After 24 hours, the product was collected, recrystallised from water, and then distilled under the ordinary pressure from an oil-bath, the temperature of which was raised slowly from 310° to 350°. The mixture (40 g.) of 2 : 3-dimethylquinoline and 2-ethylquinoline obtained in this way was dissolved in boiling alcohol and treated with a hot alcoholic solution of picric acid (60 g.), whereupon, after 10 minutes' boiling and stirring, the picrate of 2 : 3-dimethylquinoline separated in a pure condition (m. p. 228°). It was collected by filtration of the hot mixture, and decomposed by dilute ammonia, the 2 : 3-dimethylquinoline being extracted with ether. After drying over potassium carbonate and removing the solvent, the base was crystallised from light petroleum and obtained in colourless prisms (20 g.), m. p. 68°. The hydrochloride was prepared by passing hydrogen chloride through a solution of the base in dry ether, and separated readily from absolute alcohol in colourless prisms, m. p. 244°.

Reduction of 2 : 3-*Dimethylquinoline.*

(a) *With Tin and Alcoholic Hydrochloric Acid.*—To effect complete reduction of the base a large excess of the reducing agent was required. A mixture of 2 : 3-dimethylquinoline (4 g.), alcohol (100 c.c.), granulated tin (55 g.), and hydrochloric acid (130 c.c.) was boiled under reflux for 60 hours, the acid being added in portions at intervals of about 10 hours. After filtering and washing the residue with boiling alcohol, the united liquids were heated on the steam-bath to remove as much alcohol as possible, made alkaline by the gradual addition of sodium hydroxide (130 g., in concentrated aqueous solution), and the whole was submitted to steam distillation for 4 hours. The distillate was shaken with ether, the ethereal solution was dried over potassium carbonate, and, after removal of the solvent, an oily mixture (3·5 g.) of the two 2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinolines remained. This was dissolved in dry ether and treated with dry hydrogen chloride, and after removing the ether, the mixed hydrochlorides were obtained as an almost colourless, hygroscopic mass. After several recrystallisations from absolute alcohol, the *hydrochloride* of 2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (A) was isolated in clusters of colourless prisms, m. p. 240—243° (Found : C, 66·9; H, 8·2; N, 7·2. $C_{11}H_{16}NCl$ requires C, 66·8; H, 8·1; N, 7·1%). A mixture with 2 : 3-dimethylquinoline hydrochloride (m. p. 244°) melted below 200°. The alcoholic mother-liquors from the hydrochloride (A) were evaporated to dryness, the residue was treated with an excess of warm aqueous potassium hydroxide, and the product was extracted with ether. After drying and distilling off the solvent, the residue was shaken with benzoyl chloride (3·5 g.) and dilute aqueous sodium hydroxide; the resulting 1-*benzoyl*-2 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoline* (B) crystallised from alcohol in colourless prisms, m. p. 96—97° (Found : C, 81·7; H, 7·4. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2%). After a mixture of the benzoyl compound (0·6 g.), potassium hydroxide (5 g.), water (5 c.c.), and alcohol (20 c.c.) had been boiled for 30 hours and the alcohol then removed by distillation, the corresponding base remained as an oil. By passing dry hydrogen chloride into its solution in dry ether and allowing the mixture to remain in a desiccator, the hydrochloride (B) was obtained in hygroscopic, colourless needles, m. p. 169—170°. From the amounts of the products obtained, it was estimated that the two bases (A) and (B) were present in the proportion of approximately 1 : 10 in the reduction product under these conditions.

2 : 3-Dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (A), obtained from its hydrochloride by the action of alkalis, separated from light petroleum in colourless prisms, m. p. 38—39°; its *benzoyl* derivative obtained by shaking the base with benzoyl chloride and dilute aqueous sodium hydroxide, separated from alcohol in colourless prisms, m. p. 92° (Found : N, 5·5. $C_{18}H_{19}ON$ requires N, 5·3%). A mixture with the benzoyl compound (B) melted at 69—73°.

The picrate of 2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (A) separated from alcohol in bright yellow prisms, m. p. 178°.

(b) *With Zinc and Alcoholic Hydrochloric Acid.*—It was found that for complete reduction a large excess of the reagent was again required. A mixture of 2 : 3-dimethylquinoline (3 g.), alcohol (105 c.c.), and zinc dust (55 g.) was boiled under reflux for 70 hours, whilst concentrated hydrochloric acid (100 c.c.) was added gradually in portions. The reaction mixture was then submitted to a process similar to that described above, in order to separate the bases present. Although the yield of mixed bases amounted to only 30% of that theoretically possible, the amounts of the products isolated indicated that in this mixture the tetrahydro-compounds (A) and (B) were present in the proportion of approximately 4 : 3.

(c) *Electrolytic Reduction.*—A solution of 2 : 3-dimethylquinoline (4 g.) in sulphuric acid (200 c.c. of 20%) was submitted to electrolytic reduction for 8 hours in the cathode compartment of a cell, lead electrodes and a current of 4 amps. (approximately 0·02 amp./cm.^{2} of cathode) being used, and the temperature being kept at 95—100° by immersing the cell in boiling water. The reduction was then complete, and, after filtering the solution and making it alkaline with concentrated aqueous potassium hydroxide, the free bases were removed by steam distillation, and investigated as before. It was estimated that the proportions of the bases (A) and (B) present were approximately as 8 to 3.

(d) *With Sodium and Alcohol.*—A solution of 2 : 3-dimethylquinoline (6 g.) in absolute alcohol (120 c.c.) was kept boiling under reflux and treated gradually with sodium (17 g.). After decomposing any unchanged sodium by adding a small quantity of alcohol, the mixture was diluted with water and some alcohol was removed on the water-bath. The residue was submitted to steam distillation, and the mixed bases were examined in the manner already described; it was found that the two tetrahydro-compounds (A) and (B) were present in approximately equal amounts. When the oily mixture of bases was dissolved in hot hydrochloric acid (*d* 1·08), a mixture of hydrochlorides, m. p. 214—218°, separated on cooling. This was probably similar to the product described by Ferratini (*loc. cit.*) as melting at 210—215°. On recrystallising this mixture from hydrochloric acid, the hydrochloride (A) (m. p. 240—243°) was obtained in a pure condition.

Reduction of 4-*Keto*-2 : 3-*dimethyl*-1 : 4-*dihydroquinoline.*

The initial material in these experiments was prepared by a method analogous to that described by Conrad and Limpach (*Ber.*, 1891, **24**, 2991). A mixture of aniline (18·6 g.) and ethyl acetoacetate (26 g.)

was kept over zinc chloride in an evacuated desiccator for 2 days, then dissolved in dry benzene (200 c.c.), treated cautiously with sodium wire (4·6 g.), and subsequently with methyl iodide (28·4 g.). After keeping for some time and warming on the steam-bath for a few minutes, water was added and the benzene solution was dried and evaporated. The residual ethyl β-anilino-α-methylcrotonate was heated rapidly to 240°, and the temperature was then raised gradually to 260°. The product soon separated as a solid, which was then treated with boiling dilute hydrochloric acid and charcoal. After filtering and cooling, the hydrochloride of 4-keto-2 : 3-dimethyl-1 : 4-dihydroquinoline was obtained; it separated from alcohol in colourless prisms, m. p. 248—249°, and was decomposed in hot aqueous solution by the addition of sodium acetate. The base can be crystallised from hot water, and obtained in colourless prisms, m. p. 319—320° (rapid heating) (Found : N, 8·1. Calc. : N, 8·1%).

A mixture of 4-keto-2 : 3-dimethyl-1 : 4-dihydroquinoline (6 g.) and alcohol (500 c.c.), to which a little sodium bicarbonate had been added, was heated to boiling under reflux, and, during vigorous stirring and passage of a continuous stream of carbon dioxide, sodium amalgam (750 g. of 4%) was added gradually during 5 hours, the whole being then kept vigorously stirred at the boiling point for a further 6 hours. The resulting mixture was filtered, and the residue well washed with boiling alcohol. After removal of the alcohol on the steam-bath, the remainder was submitted to steam distillation, and the oily mixture of 2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (A) and (B) was examined by the procedure already outlined. Approximately 4 parts of the (A) modification to 3 parts of the (B) were present.

When a smaller quantity of sodium amalgam (240 g.) was employed in this reaction, the oily product was found to consist very largely of 2 : 3-dimethylquinoline, since, on dissolving it in hot alcohol and adding picric acid, the characteristic picrate (m. p. 228°) of this latter base separated.

Reduction of 2 : 3-*Diphenylquinoline.*

The 2 : 3-diphenylquinoline used in these experiments was prepared by a process essentially the same as that described by Pfitzinger (*loc. cit.*, p. 299). It was found that if the crude material from the decarboxylation of 2 : 3-diphenylquinoline-4-carboxylic acid was dissolved in ether and shaken with dilute aqueous sodium hydroxide, the crystallisation of the final product was facilitated. Its hydrochloride separated as a hygroscopic solid when dry hydrogen chloride was passed through a solution of the base in dry ether, and, after crystallisation from absolute alcohol, it was obtained in colourless prisms. m. p. 215°.

(a) *With Tin and Alcoholic Hydrochloric Acid.*—A mixture of 2 : 3-diphenylquinoline (4 g.), alcohol (150 c.c.), and granulated tin (80 g.) was boiled under reflux for 70 hours, whilst concentrated hydrochloric acid (160 c.c.) was added in portions of 20 c.c. at intervals. After filtration and removal of the alcohol on the steam-bath, the residue was made alkaline with sodium hydroxide (160 g. in concentrated aqueous solution). The product was extracted with ether, the solution dried with potassium carbonate, and, after removal of the solvent, the residual oil rapidly solidified. It was crystallised from alcohol (150 c.c.), from which a pale yellow base (3·1 g.), m. p. 127—128°, separated. After further recrystallisation from alcohol, pure 2 : 3-*diphenyl*-1 : 2 : 3 : 4-*tetrahydroquinoline* (A) was obtained in colourless prisms, m. p. 130—131° (Found: C, 88·6; H, 6·8. $C_{21}H_{19}N$ requires C, 88·4; H, 6·7%). The compound did not dissolve in aqueous hydrochloric acid, but when dry hydrogen chloride was passed through a solution in ether, the hydrochloride of 2 : 3-diphenyl-1 : 2 : 3 : 4-tetrahydroquinoline (A) separated, and, after crystallisation from absolute alcohol, it was obtained as a colourless solid, m. p. 198—199°. The *nitrosoamine* of the compound (A) separated from alcohol in pale yellow prisms, m. p. 150° (Found: N, 8·9. $C_{21}H_{18}ON_2$ requires N, 8·9%). After boiling a solution of the compound (A) in an excess of acetic anhydride for 8 hours, diluting with water, and then neutralising with sodium carbonate, 1-acetyl-2 : 3-diphenyl-1 : 2 : 3 : 4-tetrahydroquinoline (A) was obtained. On crystallisation from alcohol it was isolated in small colourless prisms, m. p. 145°.

(b) *With Zinc and Alcoholic Hydrochloric Acid.*—A boiling mixture of 2 : 3-diphenylquinoline (5 g.), alcohol (130 c.c.), and zinc dust (60 g.) was treated during 25 hours with hydrochloric acid (110 c.c., added in portions). After filtering and washing the residue with boiling alcohol, the united liquors were heated on the steam-bath to remove as much alcohol as possible, and then treated cautiously with sodium hydroxide (110 g. in concentrated aqueous solution). When cold, the whole was thoroughly extracted with ether, the solvent removed from the dried ethereal solution, and the residue treated with boiling alcohol. There remained an insoluble product, which so far has not been obtained crystalline. The alcoholic solution was concentrated somewhat, filtered, and poured into water, whereby a colourless solid (3 g., melting below 100°) was precipitated. After drying over phosphoric oxide, this was dissolved in a little chloroform, and, on standing, 2 : 3-diphenyl-1 : 2 : 3 : 4-tetrahydroquinoline (A) separated in colourless prisms,

m. p. 127—128°. After evaporating the chloroform filtrate, dissolving the residue in dry ether, and passing in dry hydrogen chloride, a colourless product, melting indefinitely at 180—225°, was obtained. Recrystallisation of this from absolute alcohol yielded the *hydrochloride* of 2 : 3-diphenyl-1 : 2 : 3 : 4-tetrahydroquinoline (B) in colourless prisms, m. p. 239—242° (Found : C, 78·7; H, 6·3. $C_{21}H_{20}NCl$ requires C, 78·4; H, 6·2%). On adding dilute aqueous potassium hydroxide to the hot alcoholic solution of this hydrochloride, and cooling, 2 : 3-*diphenyl*-1 : 2 : 3 : 4-*tetrahydroquinoline* (B) was obtained in colourless prisms, which, after recrystallisation from alcohol, melted at 92° (Found : C, 88·7; H, 6·9. $C_{21}H_{19}N$ requires C, 88·4; H, 6·7%). The m. p. was greatly depressed by admixture with either the tetrahydro-compound (A) or 2 : 3-diphenylquinoline. The *nitrosoamine* of the compound (B) separated from alcohol in clusters of needles, m. p. 138° (Found : N, 8·9. $C_{21}H_{18}ON_2$ requires N, 8·9%). A mixture with the nitrosoamine of the stereoisomeride (A) melted indefinitely at 115—130°.

Although appreciable quantities of each form of 2 : 3-diphenyl 1 : 2 : 3 : 4-tetrahydroquinoline were formed in this reduction, it was not possible to make a useful estimate of the actual proportions on account of the difficulties introduced by the presence of the amorphous product mentioned above.

(c) *With Sodium and Alcohol.*—A solution of 2 : 3-diphenylquinoline (5 g.) in absolute alcohol (125 c.c.) was boiled under reflux, and treated gradually with sodium (20 g.). After about ¾ hour any excess of sodium was removed by the addition of alcohol, the whole was diluted with water, and as much alcohol as possible was removed on the steam-bath. On cooling, the product solidified, and, after collection and crystallisation from alcohol, 2 : 3-diphenyl-1 : 2 : 3 : 4-tetrahydroquinoline (A) (3·4 g.) was obtained. The mother-liquor was concentrated and then diluted with water; the precipitated solid was dried over phosphoric oxide, dissolved in dry ether, and treated with hydrogen chloride. The mixed hydrochlorides (1·8 g., m. p. 207—235°) were crystallised from absolute alcohol, from which the hydrochloride of 2 : 3-diphenyl-1 : 2 : 3 : 4-tetrahydroquinoline (B) (m. p. 239—242°) separated. The alcoholic mother-liquor yielded a small additional quantity of the compound (A) when it was made alkaline and the solid crystallised from alcohol. It was estimated that the tetrahydro-compounds (A) and (B) were present in the reduction product in the proportion of approximately 4 : 1.

(d) *Catalytic Reduction.*—A solution of 2 : 3-diphenylquinoline (2 g.) in glacial acetic acid (50 c.c.) was added to a colloidal platinum solution (50 c.c., prepared according to the directions of Skita and

Meyer, *Ber.*, 1912, **45**, 3579), and the mixture was vigorously stirred for 3 days in an atmosphere of hydrogen, during which time the theoretical quantity of hydrogen (320 c.c.) was absorbed. The resulting mixture was filtered, the product washed with water, and then crystallised from alcohol, from which 2 : 3-diphenyl-1 : 2 : 3 : 4-tetrahydroquinoline (A) (1·3 g.) separated in clusters of colourless prisms, m. p. 130—131°. The aqueous acetic acid filtrate, on being made alkaline and extracted with ether, yielded nothing crystalline, so that the reduction product consisted essentially of the single modification (A) of the tetrahydro-compound.

One of us (R. J. R.) wishes gratefully to acknowledge the receipt of a grant from the Department of Scientific and Industrial Research which has enabled him to take part in this investigation.

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