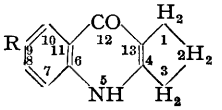
118. *Some Amino-derivatives of Dihydro-β-quinindene and Tetrahydroacridine.*

By V. Petrow.

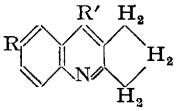
Amino-derivatives of dihydro-β-quinindene and tetrahydroacridine have been prepared. Nitration of 5-chlorotetrahydroacridine gives 5-chloro-9-nitrotetrahydroacridine, together with some of the 6-nitro-isomeride, identified after reduction and hydrolysis as 6-*amino*-1 : 2 : 3 : 4-*tetrahydroacridone*.

The object of the present study, carried out during 1942—1944, was the preparation of some amino-derivatives of dihydro-β-quinindene (II) and tetrahydroacridine (III) for biological examination. Both these compounds occupy structurally an intermediate position between the quinolines and the acridines, two classes of compound which have been extensively studied from the chemotherapeutic standpoint. Biological results obtained on some of the following compounds, however, were not sufficiently encouraging to warrant a further extension of the work.

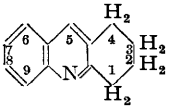
The dihydro-β-quinindenes (II; R′ = NH_2) were prepared essentially employing the method of Blount, Perkin, and Plant (*J.*, 1929, 1982). Ethyl *cyclo*pentanonecarboxylate was condensed with the appropriate anilines at room temperature, and the water-free anilino-derivatives added to boiling liquid paraffin. The resulting 12-*keto*-2 : 3 : 5 : 12-*tetrahydro*-β-*quinindenes* (I) were converted into the 12-*chloro*-2 : 3-*dihydro*-β-*quinindenes* (II; R′ = Cl) by heating with phosphorus oxychloride. Attempts to convert 12-*chloro*-9-*methoxy*-2 : 3-*dihydro*-β-*quinindene* (II; R = OMe; R′ = Cl) into the 9-amino-compound by passage of ammonia through its



(I.)



(II.)



(III.)

solution in phenol at 180°, a procedure successfully employed by Backenberg and Marais (*J.*, 1942, 382) with related 4-chloroquinaldines, led to formation of 12-*phenoxy*-9-*methoxy*-2 : 3-

dihydro-β-quinindene (II; R = OMe; R′ = OPh) in high yield. The desired *amino*-compounds (II; R′ = NH_2) were ultimately prepared in 50—60% yields by heating the chloro-compounds (II; R′ = Cl) in sealed tubes with saturated alcoholic ammonia at 220—240°, in the presence of a trace of a copper salt. In common with related 4-aminoquinaldines, acetylation of 12-*amino*-2 : 3-*dihydro*-β-*quinindene* (II; R = H; R′ = NH_2) gave a *diacetyl* derivative. The *monoacetyl* derivative was obtained by reaction of the base with a small excess of acetic anhydride in pyridine solution.

5-Aminotetrahydroacridine was prepared by the action of alcoholic ammonia (copper salt as catalyst) on 5-chlorotetrahydroacridine (Braun, Heymons, and Mans, *Ber.*, 1931, **64**, 227) at 220—240°. It was not obtained when ammonia was passed through a solution of the chloro-compound in phenol at 180°, the product being 5-*phenoxytetrahydroacridine*. Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169T) have since prepared 5-aminotetrahydroacridine by this method, employing *p*-cresol as a solvent. Acetylation of 5-aminotetrahydroacridine gave a bright yellow *diacetyl* derivative. The ultra-violet absorption curve of this compound was practically identical with that of the colourless 12-diacetylaminodihydro-β-quinindene (above), so it does not seem necessary to postulate a 5-iminoacridan type of structure for this compound to account for its yellow colour (cf. Wilkinson and Finar, *J.*, 1946, 115). The *monoacetyl* derivative was prepared by the same means as that recorded in the preceding paragraph.

Reduction of 5-chloro-7-nitro-1 : 2 : 3 : 4-tetrahydroacridine (Magidson and Travin, *J. Gen. Chem. Russ.*, 1937, **7**, 819) with reduced iron in acidulated aqueous alcohol gave 5-*chloro*-7-*amino*-1 : 2 : 3 : 4-*tetrahydroacridine*, characterised by preparation of an *acetyl* derivative. Reaction with alcoholic ammonia in a sealed tube yielded the 5 : 7-*diamino*-compound, which gave only a *diacetyl* derivative on acetylation. 5-*Chloro*-8-*amino*-1 : 2 : 3 : 4-*tetrahydroacridine* was similarly prepared from the corresponding nitro-compound (Magidson and Travin, *loc. cit.*), and characterised as the *acetyl* derivative. Conversion of 9-nitrotetrahydroacridone (Perkin and Sedgwick, *J.*, 1924, 2442) into the corresponding 5-*chloro*-9-*nitro*-1 : 2 : 3 : 4-*tetrahydroacridine* was unsatisfactory owing to considerable resinification. The latter compound was more conveniently prepared by direct nitration of 5-chlorotetrahydroacridine. Reduction gave 5-*chloro*-9-*amino*-1 : 2 : 3 : 4-*tetrahydroacridine*, characterised by an *acetyl* derivative, and converted by alcoholic ammonia at 240° into the 5 : 9-*diamino*-compound. Reduction of the more soluble fractions from the nitration of 5-chlorotetrahydroacridine apparently gave a new homogeneous 5-*chloro-aminotetrahydroacridine*. This compound is probably a molecular addition complex of the 6- and 9-amino-5-chlorotetrahydroacridines. On acetylation followed by fractionation from glacial acetic acid, it gave *ca.* 30% of 5-chloro-9-acetamidotetrahydroacridine, hydrolysed by hydrochloric acid to the amino-compound. Crystallisation of the more soluble fractions from aqueous alcohol gave a product of indefinite m. p. (*ca.* 176°) admixed with some much higher-melting material. This observation suggested hydrolysis to the tetrahydroacridone during crystallisation from the aqueous alcohol. The more soluble fractions were therefore digested with 10% acetic acid for 8 hours, and finally submitted to fractionation, whereby 6-*acetamido*-1 : 2 : 3 : 4-*tetrahydroacridone* was obtained in 25% yield, smoothly hydrolysed by hydrochloric acid to the *amino*-derivative. The formulations assigned to the last two compounds rested on their non-identity with the known 7-, 8-, and 9-aminotetrahydroacridone analogues, previously described by Perkin and Sedgwick (*ibid.*, pp. 2444, 2445).

Experimental.

(M. p.'s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

12-*Amino*-2 : 3-*dihydro*-β-*quinindene* (II; R = H; R′ = NH_2).—9-Chlorodihydro-β-quinindene (5 g., Blount and Plant, *J.*, 1937, 377), saturated alcoholic ammonia (20 ml.), and a trace of copper acetate were heated in a sealed tube at 220—240° for 20 hours. The alcohol was removed, and the residue extracted several times (charcoal) with boiling water. The bulked filtrates were made alkaline with excess of 30% sodium hydroxide solution, and the precipitated solids crystallised from aqueous acetone 12-*Amino*-2 : 3-*dihydro*-β-*quinindene* formed silky needles, m. p. 183—183·5° (Found : C, 78·1; H, 6·5; N, 15·2. $C_{12}H_{12}N_2$ requires C, 78·3; H, 6·5; N, 15·2%). The *hydrochloride* formed octahedra from alcohol, m. p. >310° (Found : Cl, 16·1. $C_{12}H_{12}N_2$,HCl requires Cl, 16·1%). The *diacetyl* derivative, angular plates from aqueous methyl alcohol, m. p. 172—173° (Found : C, 72·0; H, 6·0; N, 11·2. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·5%), was obtained when the base (4 g.) was heated under reflux with acetic anhydride (30 ml.) and a little anhydrous sodium acetate for 30 minutes. 12-*Acetamido*-2 : 3-*dihydro*-β-*quinindene*, octahedra from aqueous methyl alcohol, m. p. 229·5—230·5° (decomp.) (Found : C, 74·3; H, 6·1; N, 12·3. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%), was obtained when the amino-compound (4 g.), acetic anhydride (4 ml.), and dry pyridine (8 ml.) were heated under reflux for 30 minutes, and the cooled product treated with excess of dilute ammonium hydroxide.

12-*Keto*-9-*methoxy*-2 : 3 : 5 : 12-*tetrahydro*-β-*quinindene* (I; R = OMe).—Ethyl *cyclo*pentanone-carboxylate (20 g.) and powdered *p*-anisidine (15 g.) were stirred at room temperature until solution was

complete. After a further 7 days the crystalline product was washed with a little ice-cold methyl alcohol, powdered, dried in a vacuum desiccator, and added to liquid paraffin at 280°. The mixture was vigorously stirred and kept at this temperature until reaction was complete with no further separation of crystalline material. After standing overnight, the solids were collected, thoroughly washed with hot benzene until free from liquid paraffin, and recrystallised from spirit (charcoal). 12-*Keto*-9-*methoxy*-2 : 3 : 5 : 12-*tetrahydro*-β-*quinindene* formed glistening white needles, m. p. >310° (Found : C, 72·2; H, 6·0; N, 6·5. $C_{13}H_{13}O_2N$ requires C, 72·6; H, 6·1; N, 6·5%).

12-*Chloro*-9-*methoxy*-2 : 3-*dihydro*-β-*quinindene* (II; R = OMe; R′ = Cl).—The foregoing compound (1 g.) was heated under reflux with phosphorus oxychloride (10 ml.) for 1½ hours. Excess of phosphorus halides was removed under reduced pressure on the water-bath, and the residue decomposed with ice–dilute ammonium hydroxide. The precipitated solids were collected and crystallised from aqueous methyl alcohol. 12-*Chloro*-9-*methoxy*-2 : 3-*dihydro*-β-*quinindene* formed glancing needles, m. p. 125—126° (Found : Cl, 15·3. $C_{13}H_{12}ONCl$ requires Cl, 15·2%); yield nearly quantitative.

12-*Phenoxy*-9-*methoxy*-2 : 3-*dihydro*-β-*quinindene* (II; R = OMe; R′ = OPh).—The foregoing chloro-compound (1 g.) in phenol at 180—190° was treated with a current of dry ammonia for 2 hours. The product was treated with excess of dilute sodium hydroxide solution, and the solids collected and crystallised from light petroleum. The 9-*methoxy*-compound formed large plates (1·4 g.), m. p. 133—134° (Found : C, 78·4; H, 5·8; N, 5·2. $C_{19}H_{17}O_2N$ requires C, 78·4; H, 5·8; N, 4·8%).

12-*Amino*-9-*methoxy*-2 : 3-*dihydro*-β-*quinindene* (II; R = OMe; R′ = NH_2) formed squat needles from aqueous acetone, m. p. 217·5° (with blackening) (Found : C, 72·8; H, 6·5; N, 13·5. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·5; N, 13·1%). The *hydrochloride* formed needles from aqueous-alcoholic hydrogen chloride, m. p. 308—309° (decomp.) (Found : Cl, 13·1. $C_{13}H_{14}ON_2,HCl,H_2O$ requires Cl, 13·2%).

9-*Chloro*-12-*keto*-2 : 3 : 5 : 12-*tetrahydro*-β-*quinindene* (I; R = Cl) was prepared from *p*-chloroaniline and formed sparingly soluble silky needles, from glacial acetic acid, m. p. >310° (Found : C, 65·6; H, 4·6; N, 6·4. $C_{12}H_{10}ONCl$ requires C, 65·6; H, 4·6; N, 6·4%). 9 : 12-*Dichloro*-2 : 3-*dihydro*-β-*quinindene* (II; R = R′ = Cl) formed squat rods from light petroleum, m. p. 115—116° (Found : Cl, 28·8. $C_{12}H_9NCl_2$ requires Cl, 28·8%). The 9-*chloro*-12-*amino*-analogue formed silky needles from aqueous acetone, m. p. 235·5—236° (with blackening) (Found : C, 65·9; H, 5·2; N, 12·9. $C_{12}H_{11}N_2Cl$ requires C, 65·9; H, 5·0; N, 12·8%); its *hydrochloride* formed silky needles from hydrochloric acid, m. p. 316° (decomp.) (Found : Cl, 27·8. $C_{12}H_{11}N_2Cl,HCl$ requires Cl, 27·9%).

9-*Dimethylamino*-12-*keto*-2 : 3 : 5 : 12-*tetrahydro*-β-*quinindene* (I; R = NMe_2) formed very sparingly soluble, pale yellow microcrystals, m. p. >310° (Found : N, 12·4. $C_{14}H_{16}ON_2$ requires N, 12·3%), showing an intense blue fluorescence in alcohol. 12-*Chloro*-9-*dimethylamino*-2 : 3-*dihydro*-β-*quinindene* (II; R = NMe_2; R′ = Cl) formed straw-coloured, silky needles from aqueous alcohol, m. p. 139·5—140·5° (Found : Cl, 14·5. $C_{14}H_{15}N_2Cl$ requires Cl, 14·4%). The 12-*amino*-derivative (II; R = NMe_2; R′ = NH_2) formed iridescent octahedra from aqueous alcohol, m. p. 256—257° (Found : C, 73·5; H, 7·3; N, 18·6. $C_{14}H_{1}{}_{1}N_3$ requires C, 74·0; H, 7·5; N, 18·5%); its *trihydrochloride* formed silky needles from hydrochloric acid, m. p. 296·5—297·5° (decomp.) (Found : Cl, 29·9. $C_{14}H_{17}N_3,3HCl,H_2O$ requires Cl, 30·1%).

5-*Aminotetrahydroacridine Derivatives*.—5-Aminotetrahydroacridine formed octahedra from very dilute alcohol, m. p. 183—184° (Found : C, 78·9; H, 7·0; N, 14·1. Calc. for $C_{13}H_{14}N_2$: C, 78·8; H, 7·1; N, 14·1%). The *hydrochloride* separated from concentrated hydrochloric acid in needles, m. p. 283—284° (efferv. at 110°) (Found : Cl, 14·5. $C_{13}H_{14}N_2,HCl,H_2O$ requires Cl, 14·4%). The *diacetyl* derivative, bright yellow octahedra from aqueous alcohol, m. p. 172·5—173·5° (Found : C, 72·4; H, 6·4; N, 10·3. $C_{17}H_{18}O_2N_2$ requires C, 72·4; H, 6·4; N, 9·9%), was obtained when the amino-compound (4 g.) was heated with acetic anhydride (30 ml.) for 30 minutes under reflux. 5-*Acetamidotetrahydroacridine*, white needles from aqueous methyl alcohol, m. p. 249—250° (decomp.) (Found : C, 74·9; H, 6·8; N, 11·7. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·7%), was obtained when the amino-compound (7·5 g.), dry pyridine (15 ml.), and acetic anhydride (7·5 g.) were heated under reflux for 30 minutes. The product was precipitated with dilute ammonium hydroxide, and the precipitated solids crystallised twice; yield, 5·5 g. The mother-liquors deposited the yellow diacetyl derivative on standing.

5-*Phenoxytetrahydrodroacridine*, irregular plates from light petroleum, m. p. 116—117° (Found : C, 83·1; H, 6·1; N, 5·5. $C_{19}H_{17}ON$ requires C, 82·9; H, 6·2; N, 5·1%), was obtained when 5-chlorotetrahydroacridine (5 g.) in phenol (15 g.) was treated with a current of ammonia at 170—180° for 45 minutes. The phenoxy-derivative was also obtained in somewhat better yield when the chloro-compound (10 g.) was heated with potassium hydroxide (2·8 g.) in phenol (20 g.) at 170° for 30 minutes.

5-*Chloro*-7-*amino*-1 : 2 : 3 : 4-*tetrahydroacridine*.—Powdered 5-chloro-7-nitrotetrahydroacridine (20 g.) (Magidson and Travin, *loc. cit.*), reduced iron (30 g.), water (28 ml.), spirit (72 ml.), and a drop of concentrated hydrochloric acid were heated under reflux for 1 hour. The filtrate and washings were taken to dryness, and the residue crystallised from absolute alcohol (charcoal). The required *compound* (12·7 g.) formed dimorphic straw-coloured octahedra, m. p. 167—168° and 185·5—186·5° (Found : N, 12·1; Cl, 15·2. $C_{13}H_{13}N_2Cl$ requires N, 12·0; Cl, 15·3%), showing an intense blue fluorescence in dilute alcoholic solution. The *monoacetyl* derivative, straw-coloured needles from acetone, m. p. 200—201° (Found : N, 9·8. $C_{15}H_{15}ON_2Cl$ requires N, 10·2%), was obtained when the base (1 g.) was heated with acetic anhydride (5 ml.) for 30 minutes under reflux on the water-bath.

5 : 7-*Diamino*-1 : 2 : 3 : 4-*tetrahydroacridine*, pale yellow crystals from aqueous alcohol, m. p. 182·5—183·5° (dried product) (Found : C, 73·2; H, 7·1; N, 19·7. $C_{13}H_{15}N_3$ requires C, 73·2; H, 7·1; N, 19·7%), was obtained when 5-chloro-7-aminotetrahydroacridine (6 g.) was heated with saturated alcoholic ammonia (20 ml.) and a trace of a copper salt at 220—240° for 10 hours. The *diacetyl* derivative, small needles from aqueous alcohol, m. p. >310° (Found : C, 68·6; H, 6·4; N, 14·0. $C_{17}H_{19}O_2N_3$ requires C, 68·7; H, 6·4; N, 14·1%), was obtained when the diamino-compound (1 g.) was heated under reflux with acetic anhydride (10 ml.) until solution was complete (*ca.* 1½ hours).

5-*Chloro*-8-*amino*-1 : 2 : 3 : 4-*tetrahydroacridine*, orange needles from alcohol, m. p. 217—218° (Found: N, 11·9; Cl, 15·3. $C_{13}H_{13}N_2Cl$ requires N, 12·0; Cl, 15·3%), was obtained by reduction of 5-chloro-8-

nitrotetrahydroacridine (Magidson and Travin, *loc. cit.*). The *acetyl* derivative formed angular orange crystals from aqueous methyl alcohol, m. p. 209—210° (Found : N, 10·1. $C_{15}H_{15}ON_2Cl$ requires N, 10·2%).

5-*Chloro*-9-*nitro*-1 : 2 : 3 : 4-*tetrahydroacridine*.—(a) A solution of 5-chlorotetrahydroacridine (60 g.) in concentrated sulphuric acid (200 ml.) was treated at 0° with nitric acid (25 g.; *d* 1·42), added dropwise with mechanical stirring. The product was poured on crushed ice, made alkaline with ammonia, and the precipitated solids crystallised six times from aqueous acetone (charcoal). The required *compound* formed squat pink needles (12 g.), m. p. 139·5—140·5° (Found : N, 10·8; Cl, 13·8. $C_{13}H_{11}O_2N_2Cl$ requires N, 10·7; Cl, 13·6%). (b) 9-Nitrotetrahydroacridone (18 g.) (Perkin and Sedgwick, *loc. cit.*), phosphorus pentachloride (16 g.), and phosphorus oxychloride (50 ml.) were heated under reflux on a water-bath for 30 minutes. The product was poured on crushed ice and decomposed with ammonia. The black tarry product was crystallised from aqueous acetone (charcoal), and gave 5-chloro-9-nitrotetrahydroacridine, m. p. 137—138° (Found : Cl, 13·8%), not depressed in admixture with the compound obtained by method (a); yield, 10%.

5-*Chloro*-9-*amino*-1 : 2 : 3 : 4-*tetrahydroacridine*, faintly coloured plates from aqueous alcohol, m. p. 92—93° (Found : N, 12·2; Cl, 15·7. $C_{13}H_{13}N_2Cl$ requires N, 12·0; Cl, 15·3%), was obtained by reduction of the foregoing nitro-compound. The *acetyl* derivative formed corn-coloured needles from alcohol, m. p. 178·5—179·5° (Found : N, 10·2. $C_{15}H_{15}ON_2Cl$ requires N, 10·2%). 5 : 9-*Diamino*-1 : 2 : 3 : 4-*tetrahydroacridine* formed pale yellow squat needles from alcohol–light petroleum, m. p. 180—181° (Found : C, 73·2; H, 7·1; N, 19·8. $C_{13}H_{15}N_3$ requires C, 73·2; H, 7·1; N, 19·7%).

6-*Amino*-1 : 2 : 3 : 4-*tetrahydroacridone*.—The more soluble fractions obtained in the nitration of 5-chlorotetrahydroacridine were freed from resinous material by washing with a little ice-cold acetone, and reduced with reduced iron in acidulated aqueous alcohol. The product was taken up in alcohol, saturated with hydrogen chloride, and the orange hydrochloride collected. The regenerated *base* (? addition complex) formed rhombic crystals from light petroleum, m. p. 114—115° (Found : N, 12·2; Cl, 15·3. $C_{13}H_{13}N_2Cl$ requires N, 12·0; Cl, 15·3%). In admixture with 5-chloro-9-aminotetrahydroacridine a definite depression of 3—4° was obtained. The base (8 g.) was heated under reflux with acetic anhydride (40 ml.) for 30 minutes on the water-bath. The product, isolated in the usual manner, was fractionally crystallised from glacial acetic acid, giving 5-chloro-9-acetamidotetrahydroacridine, m. p. 176°, not depressed in admixture with an authentic specimen, and hydrolysed by concentrated hydrochloric acid during 30 minutes at 100° to 5-chloro-9-aminotetrahydroacridine, m. p. 92—93°, alone or in admixture with an authentic specimen. The more soluble fractions were dissolved in 10% acetic acid and heated under reflux on the water-bath for 8 hours. The base was precipitated with ammonium hydroxide, and gave on crystallisation from aqueous alcohol and finally alcohol–ligroin, pale yellow needles of 6-*acetamidotetrahydroacridone*, m. p. 286—287° (Found : C, 70·4; H, 6·2; N, 10·6. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·2; N, 10·9%), hydrolysed by concentrated hydrochloric acid to 6-*amino*-1 : 2 : 3 : 4-*tetrahydroacridone*, pale yellow platelets from spirit, m. p. >300° (Found : C, 73·0; H, 6·3; N, 13·0. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·5; N, 13·1%).

The author thanks the Therapeutic Research Corporation of Great Britain Limited for grants and for certain facilities. This work was done while Queen Mary College was at Cambridge, and the author acknowledges with gratitude the laboratory facilities placed at his disposal by the University of Cambridge.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E.1. [*Received, August 13th*, 1946.]