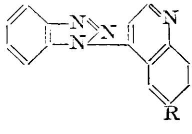
115. *Attempts to Find New Antimalarials. Part XXIX. The Synthesis of Various Derivatives of 2 : 3-Benz-γ-carboline.*

By William O. Kermack and (Mrs.) Nora E. Storey.

The Graebe–Ullmann method has been used to synthesise 2 : 3-benz-γ-carboline (II; R = H) and a number of its derivatives. Treatment of 2 : 3-benz-γ-carboline with 2-diethylaminoethyl chloride in nitrobenzene yields *4-2″-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline* (X), whilst in toluene in presence of sodamide the product of the reaction is *1-2″-diethylaminoethyl-2 : 3-benz-γ-carboline* (IX). The structure of (IX) has been confirmed by the synthesis of its dimethiodide (XII) from *4-methyl-2 : 3-benz-γ-*iso*carboline* (XI) and 2-diethylaminoethyl chloride, followed by treatment of the resulting 4-methyl-1-2″-diethylaminoethyl-2 : 3-benz-γ-carbolinium chloride, first with potassium iodide and then with methyl iodide. Two by-products isolated by Schofield and Simpson in the preparation of ethyl 4-hydroxyquinoline-3-carboxylate from aniline and ethyl ethoxymethylenemalonate have been identified.

A number of derivatives of 2 : 3-benz-γ-carboline containing a methyl group in position 5 have been synthesized by Kermack and Smith (*J.*, 1930, 1999). Clemo and Perkin (*ibid.*, 1924, **125**, 1608) treated the phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-4-quinolone with 20% sulphuric acid and instead of the expected 4 : 5-dihydro-2 : 3-benz-γ-carboline, $C_{15}H_{12}N_2$, isolated a compound, $C_{15}H_{10}N_2$, m.p. >320°, which they assumed to be 2 : 3-benz-γ-carboline (indolo-3′ : 2′-3 : 4-quinoline) itself. During investigations on the constitution of indigo-yellow, de Diesbach, de Bie, and Rubli (*Helv. Chim. Acta*, 1934, **17**, 113) isolated a degradation product, m. p. 332°, which they considered on the basis of oxidation experiments to be 2 : 3-benz-γ-carboline. It seemed desirable to synthesise this base by an unambiguous method and at the same time to prepare a number of derivatives carrying basic side chains in order that they might be subjected to biological tests.

The method employed was a modification of the Graebe–Ullmann carbazole synthesis used by Kermack and Smith in their synthesis of the 5-methyl derivatives of 2 : 3-benz-γ-carboline (*loc. cit.*). Thus 4-chloroquinoline was condensed with *o*-phenylenediamine, and the resulting *4-*o*-aminoanilinoquinoline* treated with nitrous acid to yield the *benztriazole* derivative (I; R = H). When heated in syrupy phosphoric acid this compound lost nitrogen and underwent the Graebe–Ullmann reaction to yield 2 : 3-benz-γ-carboline (II; R = H). Here it is assumed that cyclization occurs so as to involve position 3 of the quinoline nucleus, although it might occur at position 5 to yield the isomeric compound (III). The latter course is excluded not only by the properties of the product, but also by the experiments in the 5-methyl series (Kermack and Smith, *loc. cit.*).



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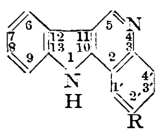

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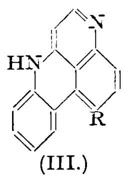

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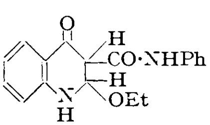

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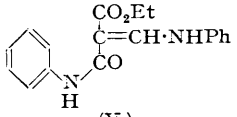

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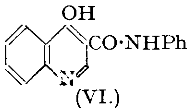

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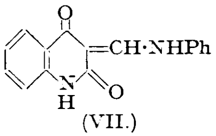


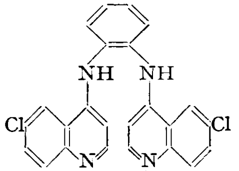
(VII.)

4-Chloroquinoline was prepared from aniline and ethyl ethoxymethylenemalonate (cf. Schofield and Simpson, *J.*, 1946, 1033, and Price and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 1204). When somewhat impure ethyl ethoxymethylenemalonate was employed cyclization of the crude intermediate ethyl anilinomethylenemalonate in liquid paraffin at 250° yielded three crystalline products. One of these was ethyl 4-hydroxyquinoline-3-carboxylate; the other two melted at 118° and 318° respectively and were evidently identical with Schofield and Simpson's by-products, $C_{18}H_{18}O_3N_2$ and $C_{16}H_{12}O_2N_2$ respectively (*loc. cit.*). Schofield and Simpson suggested for the lower-melting compound formula (IV) or (V) and for the higher-melting compound the formula (VI) or (VII), the last compound being formed from (V) by the loss of a molecule of ethanol. The following observations decide the constitution of these two products.

The compound, m. p. 118°, when heated in diphenyl was converted into the compound, m. p. 318°, with loss of ethanol. The compound, m. p. 318°, when boiled with acid yielded 4-hydroxyquinoline-3-carboxylic acid and also a diazotisable amine, presumably aniline. This strongly suggests that the compound is *4-hydroxyquinoline-3-carboxyanilide* (VI), which is confirmed by its synthesis from equimolecular amounts of ethyl 4-hydroxyquinoline-3-carboxylate and aniline. As (VI) is formed from the lower-melting compound with the loss of a molecule of alcohol, it appears very probable that the latter has the formula (V) and not (IV), which is confirmed by its synthesis from equimolecular amounts of ethyl anilinomethylenemalonate and aniline.

In contrast to Schofield and Simpson (whose product did not crystallise) and Price and Roberts (who obtained a product which set to a crystalline mass between −12° and −15°) we found that *p*-anisidine and ethyl ethoxymethylenemalonate, when heated on a steam-bath, yielded a crystalline compound, m. p. 38—40°; its analyses were in accord with its formulation as *ethyl* p-*anisidinomethylenemalonate* and it was converted into 4-chloro-6-methoxyquinoline by the series of reactions described by Price and Roberts.

From 4-chloro-6-methoxyquinoline and *o*-phenylenediamine, *4-*o*-aminoanilino-6-methoxyquinoline* was obtained, which with nitrous acid yielded the *benztriazole* derivative (I; R = OMe). This, when heated in syrupy phosphoric acid, afforded *2′-methoxy-2 : 3-benz-γ-carboline* (II; R = OMe). From 4 : 6-dichloroquinoline by an analogous series of reactions, there was obtained *2′-chloro-2 : 3-benz-γ-carboline* (II; R = Cl). On one occasion in the preparation of 2′-methoxy-2 : 3-benz-γ-carboline, *6-methoxy-4-(benztriazol-1-yl)quinoline*, when heated in syrupy phosphoric acid, yielded *4-anilino-6-methoxyquinoline*, the identity of which was confirmed by its synthesis from 4-chloro-6-methoxyquinoline and aniline. The special conditions responsible for the reaction taking this abnormal course were not ascertained; it would seem that some reducing agent must inadvertently have been present. A by-product isolated on one occasion from the reaction between 4 : 6-dichloroquinoline and *o*-phenylenediamine proved to be NN′-*di-(6-chloro-4-quinolyl)-*o*-phenylenediamine* (VIII), the structure of which was confirmed by its synthesis from *6-chloro-4-*o*-aminoanilinoquinoline* and 4 : 6-dichloroquinoline. (VIII) yielded a *dimethiodide* when boiled in nitrobenzene with excess of methyl sulphate and then treated with potassium iodide.



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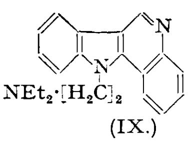

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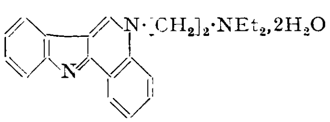

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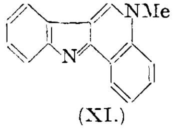

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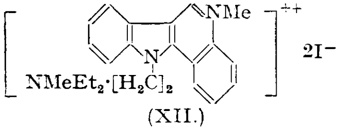

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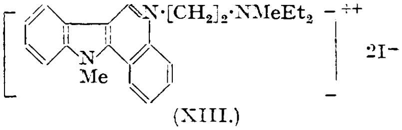

(XIII.)

2 : 3-Benz-γ-carboline was treated with 2-diethylaminoethyl chloride (*a*) in boiling toluene in presence of sodamide (cf. Dewar, *J.*, 1944, 619) and (*b*) in nitrobenzene at 100°. Two products were obtained: method (*a*) yielded a base, m. p. 103—104°, which was considered to be *1-2″-diethylaminoethyl-2 : 3-benz-γ-carboline* (IX), whilst the product, m. p. 84—86°, obtained by method (*b*) was probably *4-2″-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline dihydrate* (X). The latter compound, even after prolonged drying, contained a molecule of water, so that it may clearly be either the carbolinium hydroxide (in its ionic form or as the pseudo-base), or the monohydrate of the anhydronium base; it is relatively soluble in both benzene and light petroleum, and readily

forms a dimethiodide, one of the methyl groups of which is undoubtedly attached at $N_{(1)}$ (see below); it thus behaves as the anhydronium base rather than as the quaternary hydroxide, and this conclusion is confirmed by the fact that the analogous compound derived from 2′-chloro-2 : 3-benz-γ-carboline, when dried, forms first a compound of similar composition to that above, and then yields the anhydrous anhydronium base. However, the distinction between a hydrated anhydronium base and a quaternary hydroxide is not sharp, as the hydrated anhydronium base with a hydrogen atom co-ordinated at $N_{(1)}$ is scarcely distinguishable from the quaternary hydroxide.

When treated with excess of methyl iodide and nitrobenzene the bases (IX) and (X) yielded dimethiodides, m.p. 276—278° and 263—264° respectively. The dimethiodide, m. p. 276—278°, was also prepared as follows: from the *methiodide* of 2 : 3-benz-γ-carboline, the anhydronium base, 4-*methyl*-2 : 3-*benz*-γ-iso*carboline* (XI), was obtained by treatment with alkali; when this compound was warmed in nitrobenzene with 2-diethylaminoethyl chloride and the product treated with potassium iodide, a compound, m. p. 225°, was isolated which, on treatment with methyl iodide, yielded a compound, m. p. 276—278°, identical with the dimethiodide in question. In this second method of synthesis one methyl group is certainly located at $N_{(4)}$; it has been amply proved that, when alkyl*iso*carbolines are treated with alkyl halides, the second alkyl group becomes attached to $N_{(1)}$. It follows that the diethylaminoethyl group is here attached to $N_{(1)}$, so that the dimethiodide in question must have the structure (XII). This in turn proves that the product obtained by method (*a*) must have the constitution (IX), and the structure (X) of the product obtained by method (*b*) necessarily follows; the dimethiodide of (X) has presumably the structure (XIII).

Similarly, from 2′-chloro-2 : 3-benz-γ-carboline and 2-diethylaminoethyl chloride two compounds were obtained: under conditions (*a*) 2′-*chloro*-1-2″-*diethylaminoethyl*-2 : 3-*benz*-γ-*carboline*, and under conditions (*b*) 2′-*chloro*-4-2″-*diethylaminoethyl*-2 : 3-*benz*-γ-iso*carboline*. From 2′-*methoxy*-2 : 3-*benz*-γ-*carboline* conditions (*b*) afforded 2′-methoxy-4-2″-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline, isolated as the *dinitrobenzoate*, but it was not possible to isolate a crystalline compound from the products obtained under conditions (*a*). A by-product encountered in the experiments carried out under conditions (*b*) was 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride, formed by the interaction of two molecules of 2-diethylaminoethyl chloride. It was identified as its di-iodide, previously prepared by Gough and King (*J.*, 1928, 2436).

EXPERIMENTAL.

4-*Hydroxyquinoline*-3-*carboxyanilide*.—Ethyl 4-hydroxyquinoline-3-carboxylate (1 g.) was refluxed with aniline (1 g.) for 5 hours. On cooling the solution deposited shining white plates of the *anilide*, m. p. 316—318° (from acetic acid) (Found: C, 72·3; H, 4·6; N, 10·85. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·7; N, 10·6%).

Ethyl β-Anilino-α-phenylcarbamylacrylate.—Equimolecular amounts of ethyl anilinomethylenemalonate and aniline were heated together at 100° for 1 hour; the *product*, recrystallised from light petroleum, had m. p. 118° (Found: C, 69·4; H, 5·9; N, 9·3. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·8; N, 9·0%).

Conversion of Ethyl β-Anilino-α-phenylcarbamylacrylate into 4-*Hydroxyquinoline*-3-*carboxyanilide*.—Ethyl β-anilino-α-phenylcarbamylacrylate (0·5 g.) was heated in boiling diphenyl under reflux for 30 minutes. The diphenyl was extracted with ether to leave a solid residue, m. p. 315°. After crystallisation from glacial acetic acid, this product showed no depression in m. p. when mixed with a sample of 4-hydroxyquinoline-3-carboxyanilide.

4-o-*Aminoanilinoquinoline*.—4-Chloroquinoline (3·2 g.) (cf. Price and Roberts, *loc. cit.*) and *o*-phenylenediamine (2·1 g.) were heated together at 140° at 20—30 mm. After 10—20 minutes a brisk reaction occurred, and the solution set to a brittle resin. The solid was extracted with boiling N-hydrochloric acid and the solution filtered. The filtrate on cooling deposited the hydrochloride as greyish-white crystals, m. p. 285—290°. The *base* precipitated by alkali from an aqueous solution of this salt was recrystallised from a mixture of benzene and light petroleum (b. p. 40—60°) and formed buff-coloured prisms, m. p. 165—166° (3·5 g., 76%) (Found: C, 76·4; H, 5·4; N, 17·4. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·5; N, 17·8%).

4-(*Benztriazol*-1-*yl*)*quinoline*.—4-*o*-Aminoanilinoquinoline (3 g.), dissolved in N-hydrochloric acid (500 c.c.) and cooled to 5°, was treated with a solution of sodium nitrite (0·8 g.) in water (10 c.c.) until an excess of nitrite was present. The voluminous white precipitate was dissolved in boiling water, and 4-(*benztriazol*-1-*yl*)*quinoline*, precipitated by the addition of alkali, was recrystallised from ethanol; it formed slender white prisms, m. p. 132—133° (2·2 g., 70%) (Found: C, 73·0; H, 4·2; N, 23·0. $C_{15}H_{10}N_4$ requires C, 73·2; H, 4·1; N, 22·8%).

2 : 3-*Benz*-γ-*carboline*.—4-(Benztriazol-1-yl)quinoline (10 g.) was heated in syrupy phosphoric acid (15 c.c.) until the evolution of nitrogen ceased. The greyish-white precipitate which separated from the cool solution on dilution and basification was filtered off, washed, and recrystallised from aqueous methanol; it formed irregular colourless prisms, m. p. 342° with sublimation (7 g., 77%) (Found: C, 82·3; H, 4·9; N, 12·55. Calc. for $C_{15}H_{10}N_2$: C, 82·55; H, 4·6; N, 12·8%). This compound is insoluble in benzene or ether, sparingly soluble in ethanol, and more soluble in methanol or pyridine. It dissolves readily in hot dilute hydrochloric acid to give a clear solution which on cooling deposits white

crystals of the hydrochloride, and in hot concentrated nitric acid to yield a yellow nitrate (cf. Clemo and Perkin, and de Diesbach, de Bie, and Rubli, *locc. cit.*). The base exhibits a violet fluorescence under the arc light in most solvents, but not in concentrated sulphuric acid, though the crude product showed a marked fluorescence in the cold (cf. Clemo and Perkin, *loc. cit.*).

From 2 : 3-benz-γ-carboline and excess of methyl iodide in nitrobenzene, after 2 hours on the steam-bath, needle-shaped crystals of the *methiodide* separated. The product, recrystallised from methanol containing a trace of sodium thiosulphate, had m. p. 297° (0·2 g., 72%) (Found: C, 53·4; H, 3·4; N, 7·5. $C_{16}H_{13}N_2I$ requires C, 53·3; H, 3·6; N, 7·8%).

When a trace of iodine dissolved in ethanol is added to the alcoholic solution of this methiodide, a dark red colour immediately develops. The crystals of the methiodide prepared in the absence of thiosulphate also tend to develop a reddish colour which deepens to black on storage. This colour which may be discharged by sodium thiosulphate is apparently due to the action of traces of iodine in the salt or in the crystals [cf. Kermack, Smith, and Spragg, *Proc. Roy. Soc.* (*Edin.*), 1929—1930, **50**, 243].

4-*Methyl*-2 : 3-*benz*-γ-iso*carboline*.—An aqueous solution of the above methiodide was rendered alkaline with aqueous ammonia, and the yellow solid which separated was recrystallised from dry benzene, giving yellow prisms of the *monohydrate*, m. p. 195° (Found : C, 76·75; H, 5·5. $C_{16}H_{12}N_2,H_2O$ requires C, 76·8; H, 5·6%). The anhydrous *base*, obtained by drying the monohydrate *in vacuo* at 80° over phosphoric oxide for 4 hours, had m. p. 195° (Found : C, 82·8; H, 5·0; N, 11·7. $C_{16}H_{12}N_2$ requires C, 82·75; H, 5·2; N, 12·1%).

4-2′′-*Diethylaminoethyl*-2 : 3-*benz*-γ-iso*carboline*.—2 : 3-Benz-γ-carboline (0·54 g.) and 2-diethylaminoethyl chloride (0·5 g.) in nitrobenzene (100 c.c.) were heated at 100° under reflux for 9 hours and set aside at room temperature overnight. The solution was filtered from some 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride and diluted with light petroleum (b. p. 100—120°) to yield a brown precipitate which was filtered off. The aqueous solution of the product was basified with aqueous ammonia to give a yellow precipitate which, recrystallised from aqueous ethanol, had m. p. 84—86°. When dried in a vacuum over calcium chloride, the yellow needles changed to a highly viscous liquid. When an analytical specimen of the crystals was dried over phosphoric oxide at 80° in a vacuum, the loss of weight was 5·07%. The resulting viscous liquid gave the following analytical values : Found : C, 74·3; H, 7·35; N, 12·2% ($C_{21}H_{23}N_3,1\frac{1}{4}H_2O$ requires C, 74·2; H, 7·5; N, 12·4%). It thus appears that the liquid is the monohydrate of the expected base and that the crystals, m. p. 84—86°, are a *dihydrate* (Required : $C_{21}H_{23}N_3,2H_2O \longrightarrow C_{21}H_{23}N_3,H_2O$, loss 5·09%).

Dimethiodide of 4-2′′-*Diethylaminoethyl*-2 : 3-*benz*-γ-iso*carboline*.—From 4-2′′-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline dihydrate (0·53 g.) and methyl iodide (0·24 g.) in nitrobenzene (10 c.c.), heated under reflux at 60° (for 30 minutes), needle-shaped crystals of a *dimethiodide* separated almost immediately. These were filtered off, washed with ether, and crystallised from boiling water, forming white feathery needles, m. p. 263—264° (Found : C, 45·75; H, 4·65; N, 6·6. $C_{21}H_{23}N_3,2CH_3I$ requires C, 45·9; H, 4·8; N, 6·9%). An aqueous solution of the salt gives no precipitate with aqueous ammonia or sodium hydroxide, indicating that an anhydronium base is not formed.

1-2′′-*Diethylaminoethyl*-2 : 3-*benz*-γ-*carboline*.—2 : 3-Benz-γ-carboline (1·09 g.), 2-diethylaminoethyl chloride (1·01 g.), finely powdered sodamide (1·95 g.), and toluene (10 c.c.) were heated on an oil-bath at 70° for 30 minutes and then at 115° for 30 minutes, and finally refluxed at 110° for 4 hours. To the cold mixture, water was added and a small amount of insoluble 2 : 3-benz-γ-carboline removed by filtration. The toluene layer was separated and extracted with dilute acetic acid (5%). The acid extracts were basified with aqueous ammonia, and the resulting oily precipitate extracted with ether. After drying (K_2CO_3) and reduction of volume, fine crystals of the 1-2′′-*diethylaminoethyl* derivative separated; recrystallised from aqueous ethanol, this had m. p. 103—104° (0·96 g., 60%) (Found : C, 79·6; H, 7·1; N, 13·2. $C_{21}H_{23}N_3$ requires C, 79·5; H, 7·25; N, 13·25%).

Dimethiodide of 1-2′′-*Diethylaminoethyl*-2 : 3-*benz*-γ-*carboline*.—The preceding base (0·5 g.), methyl iodide (0·3 g.), and nitrobenzene (10 c.c.) were heated together at 60° for 30 minutes; the white solid was washed with ether and recrystallised from methanol; this *dimethiodide* formed prisms, m. p. 276—278° (Found : C, 45·6; H, 5·1; N, 6·4. $C_{21}H_{23}N_3,2CH_3I$ requires C, 45·9; H, 4·8; N, 6·9%). Addition of aqueous ammonia or sodium hydroxide to its aqueous solution gave no precipitate.

Dimethiodide of 1-2′′-*Diethylaminoethyl*-2 : 3-*benz*-γ-*carboline from* 4-*Methyl*-2 : 3-*benz*-γ-iso*carboline*.—4-Methyl-2 : 3-benz-γ-*iso*carboline (0·5 g.) and excess of 2-diethylaminoethyl chloride were heated in nitrobenzene (20 c.c.) for 6 hours under reflux and set aside at room temperature overnight. The cooled solution was filtered to remove some 1 : 1 : 4 : 4-tetraethylpiperazinium dichloride and then diluted with light petroleum (b. p. 80—100°). The crystalline material which separated was washed with ether and dissolved in the minimum amount of water. This aqueous solution, treated with a saturated solution of potassium iodide, yielded a white precipitate which, recrystallised from ethanol, had m. p. 225°. This compound 4-methyl-1-2′′-diethylaminoethyl-2 : 3-benz-γ-carbolinium iodide was treated with methyl iodide in nitrobenzene at 100°, and yielded 1-2′′-diethylaminoethyl-2 : 3-benz-γ-carboline dimethiodide (m. p. 276—278°), identical (mixed m. p.) with the compound prepared by the previous method.

Ethyl p-*Anisidinomethylenemalonate*.—The oil obtained by heating *p*-anisidine (31 g.) and ethyl ethoxymethylenemalonate (54 g.) for 45 minutes on the steam-bath was freed from alcohol and triturated with light petroleum. On long storage the oil solidified and, although difficult to purify, eventually recrystallised from light petroleum (b. p. 80—100°) in large irregular prisms, m. p. 38—40° (Found : C, 61·1; H, 6·2; N, 4·9. $C_{15}H_{19}O_5N$ requires C, 61·4; H, 6·5; N, 4·8%).

4-o-*Aminoanilino*-6-*methoxyquinoline*.—When 4-chloro-6-methoxyquinoline (cf. Price and Roberts, *loc. cit.*) (3·9 g.) and *o*-phenylenediamine (2·16 g.) were heated together at 140° under reduced pressure a brisk reaction took place and the mixture solidified. The solid was extracted with boiling water; the hot solution was filtered and basified with aqueous ammonia; recrystallised from benzene, the *compound* formed colourless rectangular plates, m. p. 192° (Found : C, 72·3; H, 5·5; N, 15·7. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·85%).

6-*Methoxy*-4-(*benztriazol*-1-*yl*)*quinoline*.—To a solution of the preceding base (3·5 g.) in N-hydrochloric acid (100 c.c.), a solution of sodium nitrite (1·15 g. in 5 c.c. of water) was added until a slight excess was present. The solution was set aside for 2 hours at room temperature, after which the precipitate of hydrochloride was filtered off. The *base* was precipitated from the hot aqueous solution of the hydrochloride by aqueous ammonia and, recrystallised from light petroleum (b. p. 80—100°), had m. p. 129—130° (Found : C, 70·2; H, 4·2; N, 20·5. $C_{16}H_{12}ON_4$ requires C, 69·6; H, 4·3; N, 20·3%).

2′-Methoxy-2 : 3-benz-γ-carboline.—6-Methoxy-4-(benztriazol-1-yl)quinoline (5 g.) was heated in syrupy phosphoric acid until the evolution of nitrogen ceased. The resulting reddish-brown solution was poured into a large volume of water, and aqueous ammonia added to precipitate a yellow gelatinous solid which was dried and purified through its *dihydrochloride*, m. p. 310° (Found : C, 57·5; H, 4·8; $C_{16}H_{12}ON_2,2HCl,0·75H_2O$ requires C, 57·4; H, 4·65%). The *base*, regenerated from its hydrochloride and recrystallised from pyridine, had m. p. 315° (Found : C, 77·0; H, 4·8; N, 11·1. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%).

In one experiment the product of this reaction proved to be *4-anilino-6-methoxyquinoline* (Found : C, 76·4; H, 5·8. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6%), which did not depress the m. p. of a specimen prepared as described below.

4-Anilino-6-methoxyquinoline.—Aniline (0·5 g.) and 4-chloro-6-methoxyquinoline (1 g.) were heated together at 100° in the presence of a trace of copper bronze for 3 hours. After cooling, the melt was dissolved in dilute hydrochloric acid from which 4-anilino-6-methoxyquinoline was precipitated by aqueous ammonia. Recrystallised from ethanol, it formed pale yellow prisms, m. p. 220° (Found : C, 76·5; H, 5·4; N, 10·9. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

2′-Methoxy-4-2″-diethylaminoethyl-2 : 3-benz-γ-isocarboline.—2′-Methoxy-2 : 3-benz-γ-carboline (0·5 g.) and 2-diethylaminoethyl chloride in nitrobenzene were heated at 100° for 6 hours. The precipitate obtained on dilution of the cold solution with light petroleum was dissolved in water and basified with aqueous sodium hydroxide, and the resulting yellow oil extracted with ether. The ethereal extract was dried (Na_2SO_4), and the solvent removed, leaving a yellow oil which did not crystallise. The *bis-3 : 5-dinitrobenzoate* of the compound, recrystallised from ethanol, formed white prisms, m. p. 268° (Found : C, 55·7; H, 4·0; N, 12·3. $C_{22}H_{25}ON_3,2C_7H_4O_6N_2$ requires C, 56·0; H, 4·3; N, 12·7%).

6-Chloro-4-o-aminoanilinoquinoline.—4 : 6-Dichloroquinoline (9·9 g.) and *o*-phenylenediamine (5·4 g.) were heated under the conditions used for the methoxy-derivative. No reaction took place, but in the presence of a trace of copper bronze reaction occurred. The product was worked up as described for the 6-methoxy-compound; the *base*, recrystallised from light petroleum, formed irregular plates, m. p. 186—187° (Found : C, 66·8; H, 4·35; N, 15·3. $C_{15}H_{12}N_3Cl$ requires C, 66·8; H, 4·45; N, 15·6%).

NN′-Di-(6-chloro-4-quinolyl)-o-phenylenediamine.—6-Chloro-4-*o*-aminophenylaminoquinoline (0·54 g.) and 4 : 6-dichloroquinoline (0·4 g.) were heated together under reduced pressure at 140° for 30 minutes in the presence of copper. The product was extracted with dilute hydrochloric acid (5%), and the solution basified, to yield a white precipitate of *NN′-di-(6-chloro-4-quinolyl)-o-phenylenediamine*; recrystallised from nitrobenzene, this formed white needles, m. p. 342—344° (Found : C, 67·2; H, 3·5; N, 12·75. $C_{24}H_{16}N_4Cl_2$ requires C, 66·8; H, 3·7; N, 13·0%). The compound was also occasionally obtained as a by-product (highly insoluble in ethanol) in the preparation of 6-chloro-4-*o*-aminoanilinoquinoline.

A solution of this pentacyclic compound (0·55 g.) in nitrobenzene was treated with methyl sulphate (1 g.) at 130° for 2 hours under reflux. When the product was set aside at room temperature a dark red oil separated which was extracted several times with water; the combined aqueous extracts were concentrated to small volume. Addition of a saturated solution of potassium iodide yielded a yellow precipitate of the *dimethiodide*, m. p. 330—332° (from water) (Found : C, 41·4; H, 3·2. $C_{24}H_{16}N_4Cl_2,2CH_3I,2H_2O$ requires C, 41·6; H, 3·5%). The aqueous solution, basified with concentrated sodium hydroxide solution, gave an orange precipitate.

6-Chloro-4-(benztriazol-1-yl)quinoline.—A solution of 6-chloro-4-*o*-aminoanilinoquinoline (6·7 g.) in N-hydrochloric acid at 100° was treated with sodium nitrite as for the methoxy-analogue. After 2 hours' storage at room temperature, the white gelatinous precipitate of the hydrochloride was filtered off, and the *base* regenerated and recrystallised from ethanol; it yielded long white needles, m. p. 185—186° (Found : C, 64·1; H, 2·9; N, 19·7. $C_{15}H_9N_4Cl$ requires C, 64·2; H, 3·2; N, 19·9%).

2′-Chloro-2 : 3-benz-γ-carboline.—6-Chloro-4-(benztriazol-1-yl)quinoline (2 g.) was heated in boiling syrupy phosphoric acid (10 c.c.) until evolution of nitrogen ceased. *2′-Chloro-2 : 3-benz-γ-carboline*, obtained by basification of the diluted solution with aqueous ammonia, crystallised from pyridine in small white needles, subliming, without melting, at >360° (Found : C, 71·4; H, 3·4; N, 10·9. $C_{15}H_9N_2Cl$ requires C, 71·3; H, 3·6; N, 11·1%).

2′-Chloro-4-methyl-2 : 3-benz-γ-isocarboline.—From 2′-chloro-2 : 3-benz-γ-carboline (0·5 g.) and an excess of methyl iodide in nitrobenzene at 100°, a crystalline methiodide separated which, recrystallised from water, melted at 225°. An aqueous solution of this methiodide was basified with sodium hydroxide, to yield a yellow base which after being washed and dried was recrystallised from benzene. Dried in a vacuum at 80° for 4 hours over P_2O_5, *15-chloro-4-methyl-2 : 3-benz-γ-isocarboline* melted at 245° (Found : C, 67·3; H, 4·3. $C_{16}H_{11}N_2Cl,H_2O$ requires C, 67·5; H, 4·55%).

2′-Chloro-4-2″-diethylaminoethyl-2 : 3-benz-γ-isocarboline.—A solution of 2′-chloro-2 : 3-benz-γ-carboline (0·25 g.) in nitrobenzene (50 c.c.) was heated with 2-diethylaminoethyl chloride (0·2 g.) for 9 hours. The precipitate which formed on cooling and storage overnight at room temperature was separated, dissolved in water, and treated with aqueous ammonia hydroxide. The *base*, thus formed, was a yellow solid, which, when recrystallised from ethanol, softened at 40° and melted at 69—71°. After drying in a vacuum over potassium hydroxide and recrystallisation from dry light petroleum (b. p. 60—80°) the product melted at 125—126° (Found : C, 71·4; H, 5·9; N, 11·8. $C_{21}H_{22}N_3Cl$ requires C, 71·7; H, 6·3; N, 11·95%).

2′-Chloro-1-2″-diethylaminoethyl-2 : 3-benz-γ-carboline.—2-Diethylaminoethyl chloride (0·14 g.), 2′-chloro-2 : 3-benz-γ-carboline (0·25 g.), and finely ground sodamide (0·03 g.) in toluene (10 c.c.) were heated at 70° for 30 minutes and then at 115° for a further 30 minutes, and refluxed at 110° for 4 hours. After the mixture had been cooled water was added, the insoluble material removed by filtration, and the toluene layer separated and extracted with 5% acetic acid, from which the base was precipitated by aqueous ammonia. The ethereal solution of the *base* was dried (K_2CO_3) and the solvent removed; the residue, recrystallised from aqueous ethanol, had m. p. 114—115° (Found : C, 71·3; H, 5·95; N, 11·6. $C_{21}H_{22}N_3Cl$ requires C, 71·7; H, 6·3; N, 11·95%). This base is a white crystalline solid and depresses the m. p. of 2′-chloro-4-2″-diethylaminoethyl-2 : 3-benz-γ-*iso*carboline (m. p. 125—126°) described above.

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