64. *Attempts to find New Antimalarials. Part XVI. Synthesis of Some Derivatives of 4-Carboline and 5 : 6-Benz-4-carboline.*

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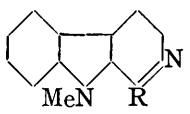
Various carboline derivatives have been prepared in order that they might be tested for possible antimalarial activity. The condensation of 3-chloro-1-methyl-4-carboline, or preferably of its *methosulphate*, with diethylaminoalkylamines has been effected with the formation of the corresponding diethylaminoalkylamino-derivatives. Analogous compounds have been prepared in the 5 : 6-benz-4-carboline series. Replacement of nuclear hydrogen by chlorine has been observed when certain carboline and benzcarboline derivatives are treated with an excess of phosphorus pentachloride.

THE object of the present work was to prepare derivatives of 4-carboline carrying a basic side chain similar to that present in the synthetic antimalarials atebrin and plasmoquine. To this end 3-chloro-1-methyl-4-carboline (I; R = Cl) (Kermack, Perkin, and Robinson, J., 1922, **121**, 1884) was heated with β-diethylaminoethylamine under various conditions, but condensation proceeded only with great difficulty. In one experiment a small quantity of a crystalline hydrobromide was isolated; this appeared to be the dihydrobromide of 3-β-*diethylaminoethylamino*-1-*methyl*-4-*carboline* (I; R = NH·$[CH_2]_2$·NEt_2) (Found: C, 43·3; H, 6·7. $C_{18}H_{24}N_2$,2HBr,2H_2O requires C, 43·7; H, 6·1%), but the amount available was insufficient for purification. In order to raise the activity of the chlorine atom, the *methosulphate* of 3-chloro-1-methyl-4-carboline was prepared (II; R = Cl, X = $MeSO_4$). When this was heated with β-diethylaminoethylamine, condensation took place with the formation of the 3-β-diethylaminoethylamino-1 : 4-dimethylcarbolinium base (II; R = NH·$[CH_2]_2$·NEt_2, X = OH), isolated as the *disalicylate*. The analysis of this salt agrees with its formulation as $(C_{19}H_{27}N_4)^+(C_7H_5O_3)^-$,$C_7H_6O_3$,2$H_2O$, one molecule of salicylic acid being united to the side chain in ordinary salt formation and the other being combined with the quaternary carbolinium carbon atom. Similarly, from the condensation of 1 : 4-dimethylcarboliniummethyl sulphate and γ-diethylaminopropylamine, was isolated 3-γ-*diethylaminopropylamino*-1 : 4-*dimethylcarbolinium disalicylate* (II; R = NH·$[CH_2]_3$·NEt_2).

Analogous reactions have also been carried out in the benzcarboline series. When 3-keto-3 : 4-dihydro-5 : 6-benz-4-carboline (Kermack and Slater, J., 1928, 32) was heated at 110° with phosphorus oxychloride and one molecule of phosphorus pentachloride, 3-*chloro*-5 : 6-*benz*-4-*carboline* (III; R = H, R′ = Cl) was obtained. This condensed with β-diethylaminoethylamine to yield 3-β-diethylaminoethylamino-5 : 6-benz-4-carboline (III; R = H, R′ = NH·$[CH_2]_2$·NEt_2). In a similar way 3-keto-1-methyl-3 : 4-dihydro-

5 : 6-benz-4-carboline (Kermack and Slater, *loc. cit.*) was converted into 3-*chloro*-1-*methyl*-5 : 6-*benz*-4-*carboline* (III; R = CH_3, R′ = Cl), and this compound condensed with β-diethylaminoethylamine to yield 3-β-diethylaminoethylamino-1-methyl-5 : 6-benz-4-carboline (III; R = CH_3, R′ = $NH{\cdot}[CH_2]_2{\cdot}NEt_2$), isolated as the *dihydrochloride*.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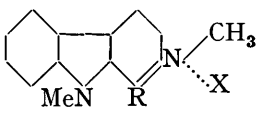
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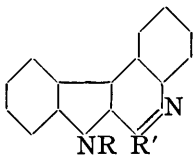
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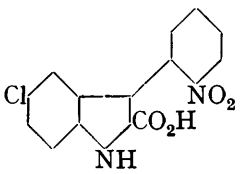
The conversion of 3-keto-1-methyl-3 : 4-dihydro-4-carboline into 3-chloro-1-methyl-4-carboline by the action of phosphorus oxychloride and phosphorus pentachloride proceeds only under strictly defined conditions (Kermack, Perkin, and Robinson, J., 1922, **121**, 1884). It has now been found that, when 3-keto-3 : 4-dihydro-5 : 6-benz-4-carboline is treated with phosphorus oxychloride and more than one molecule of phosphorus pentachloride, a dichlorobenzcarboline is formed. The fact that the second chlorine atom is in position 10 of the carboline ring was shown by its alternative synthesis as follows: *p*-Chlorophenylhydrazine was condensed with *o*-nitrophenylpyruvic acid, and the resulting hydrazone cyclised to 5-*chloro*-3-*o*-*nitrophenylindole*-2-*carboxylic acid* (IV). The reduction product, 5-chloro-3-*o*-aminophenylindole-2-carboxylic acid, at once cyclised to yield 10-*chloro*-3-*keto*-3 : 4-*dihydro*-5 : 6-*benz*-4-*carboline* (V), which on treatment with phosphorus oxychloride and one molecule of phosphorus pentachloride gave 3 : 10-*dichloro*-5 : 6-*benz*-4-*carboline* (VI) identical with the dichlorobenzcarboline already obtained. This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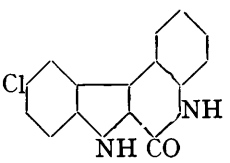
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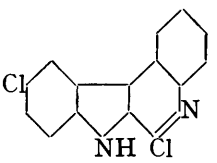
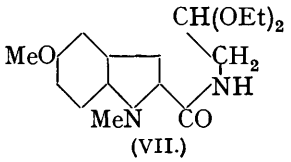

(VI.)

chlorinating action of phosphorus pentachloride is analogous to that observed when, for example, an excess of phosphorus pentachloride in chlorobenzene acts on certain diphenylaminecarboxylic acids (cf. Goodall and Kermack, J., 1936, 1163).

A similar action was also observed in the preparation of 3-*chloro*-10-*methoxy*-1-*methyl*-4-*carboline*. This compound was prepared as follows: The product of the condensation of *as*-*p*-methoxyphenylmethylhydrazine and pyruvic acid was cyclised by treatment with a warm acid into 5-*methoxy*-1-*methylindole*-2-*carboxylic acid*. Following the method of Kermack, Perkin, and Robinson (J., 1921, **119**, 1637), this was converted into the acid chloride and condensed with aminoacetal. On treatment with alcoholic hydrogen chloride, the 5-*methoxy*-1-*methylindole*-2-*carboxydiethylacetalylamide* (VII) so formed was converted into 3-*keto*-10-*methoxy*-1-*methyl*-3 : 4-*dihydro*-4-*carboline* (VIII). When this was treated under specified conditions with phosphorus oxychloride and one molecule of phosphorus pentachloride, it yielded 3-chloro-10-methoxy-1-methyl-4-carboline (IX). When, however, an excess of phosphorus pentachloride was present, the product was a mixture, from which was isolated a *trichloro*-derivative of 3-keto-10-methoxy-1-methyl-3 : 4-dihydro-4-carboline. One of the chlorine atoms is of course in position 3, and though the positions of the other two are not certain, analogy would suggest that they are in positions 9 and 11.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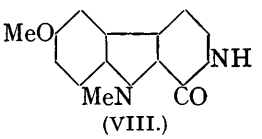
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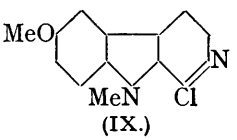
(IX.)

Experimental.

3-Chloro-1-methyl-4-carboline Methosulphate.—A solution of 3-chloro-1-methyl-4-carboline (0·2 g.) in warm benzene (2 c.c.) was heated with dry methyl sulphate (0·1 c.c.) on the water-bath for 1 hour. The yellow precipitate was filtered off, washed with benzene, and dried at 100° (yield, 0·2 g.). It crystallised from alcohol in yellow needles, m. p. 180°. As the methosulphate was very hygroscopic, it was dried in a vacuum at 80° before analysis (Found: C, 48·7; H, 4·5. $C_{14}H_{15}O_4N_2ClS$ requires C, 49·0; H, 4·4%). *3-Chloro-1-methyl-4-carboline methosulphate* is easily soluble in water, moderately easily soluble in alcohol, and insoluble in benzene, ether and acetone. Dilute alcoholic solutions containing a trace of ammonia exhibit a distinct blue-violet fluorescence. This is not shown by aqueous solutions whether alkaline or acid. Addition of sodium hydroxide to aqueous solutions precipitates the base as a colourless crystalline compound. The methosulphate tastes markedly bitter.

3-β-Diethylaminoethylamino-1 : 4-dimethylcarbolinium Disalicylate.—3-Chloro-1-methyl-4-carboline methosulphate (0·25 g.), dissolved in molten phenol (1·2 g.), was heated with β-diethylaminoethylamine (0·1 c.c.) for 1 hour on the water-bath (cf. B.P. 450,254). The product was poured into 2N-sodium hydroxide (5 c.c.). The yellow semi-liquid base was extracted with ether, and the ethereal solution freed from phenol by repeated extractions with 2N-sodium hydroxide and water. The base was extracted from the ethereal solution with 10% acetic acid (6 c.c.), precipitated from the latter with 2N-sodium hydroxide, and finally extracted with ether several times. From the dried ethereal solution the product was isolated as the salicylate (yield, 0·1 g.). This crystallised from absolute alcohol or ethyl acetate in colourless silky needles, m. p. 189° (Found: C, 64·4; H, 6·5; N, 8·9. $C_{33}H_{38}O_6N_4,2H_2O$ requires C, 63·9; H, 6·7; N, 9·0%). *3-β-Diethylaminoethylamino-1 : 4-dimethylcarbolinium disalicylate* is a very hygroscopic compound containing 2 molecules of water of crystallisation. It is moderately easily soluble in alcohol and ethyl acetate and insoluble in ether, acetone and benzene. Its aqueous solution containing a trace of mineral acid exhibits a strong blue fluorescence with a greenish tinge. Addition of sodium hydroxide precipitates the base.

3-γ-Diethylaminopropylamino-1 : 4-dimethylcarbolinium disalicylate (0·2 g.), prepared from 3-chloro-1 : 4-dimethylcarbolinium methosulphate (0·25 g.) and γ-diethylaminopropylamine (0·25 c.c.) by the method described above, crystallised from ethyl acetate in colourless needles, m. p. 152° (Found: C, 66·5; H, 6·8; N, 9·4. $C_{34}H_{40}O_6N_4,H_2O$ requires C, 66·0; H, 6·8; N, 9·1%). It closely resembles the diethylaminoethylamino-compound in its properties.

3-Chloro-5 : 6-benz-4-carboline.—A suspension of 3-keto-3 : 4-dihydro-5 : 6-benz-4-carboline (0·9 g.) in phosphorus oxychloride (9 c.c.) was heated with phosphorus pentachloride (0·9 g.) in a sealed tube at 100—110° for 6 hours. After removal of the excess of phosphorus oxychloride under reduced pressure, the residue was poured on ice, and the yellow hydrochloride (0·8 g.) filtered off. Treatment with dilute aqueous ammonia gave the colourless *base*. This was dissolved in a small quantity of hot benzene to separate it from an insoluble residue, recovered, and crystallised from ligroin containing a little benzene, forming colourless needles, m. p. 182° (Found: N, 10·7. $C_{15}H_9N_2Cl$ requires N, 11·0%), moderately easily soluble in alcohol, easily soluble in ether, acetone and benzene, and insoluble in water and ligroin. Under the carbon arc, but not in ordinary day-light, very dilute alcoholic solutions show a blue-violet fluorescence.

3-β-Diethylaminoethylamino-5 : 6-benz-4-carboline.—3-Chloro-5 : 6-benz-4-carboline (0·5 g.) was heated with β-diethylaminoethylamine (0·4 c.c.) at 150° for 6 hours with exclusion of moisture. On cooling, the product solidified to a brown glassy material, which was dissolved by prolonged boiling in the minimum quantity of alcohol. The base was isolated as the hydrobromide by careful addition of saturated alcoholic hydrogen bromide. The light yellow, crystalline precipitate was filtered off, washed with acetone, and dried in a vacuum desiccator (yield, 0·7 g.). It crystallised from alcohol in colourless silky needles, m. p. 270°. For analysis it was dried at 100° in a vacuum (Found: N, 11·3; Br, 32·7. $C_{21}H_{24}N_4,2HBr$ requires N, 11·3; Br, 32·8%). *3-β-Diethylaminoethylamino-5 : 6-benz-4-carboline dihydrobromide* is soluble in water, moderately easily soluble in alcohol, and insoluble in ether, acetone and benzene. Very dilute aqueous solutions show a blue-violet fluorescence, which is destroyed by acid. The compound has a marked bitter taste. On addition of sodium carbonate to an aqueous solution of the dihydrobromide, the base separates as a semi-solid product.

3-Chloro-1-methyl-5 : 6-benz-4-carboline. — 3-Keto-1-methyl-3 : 4-dihydro-5 : 6-benz-4-carboline (0·4 g.) was heated with freshly distilled phosphorus oxychloride (0·4 g.) in a sealed tube at 100—110° for 24 hours. The product was treated as in the case of 3-chloro-5 : 6-benz-4-carboline, and the base (0·4 g.) recrystallised from ligroin containing a little benzene (Found:

N, 10·2. $C_{16}H_{11}N_2Cl$ requires N, 10·5%). 3-*Chloro*-1-*methyl*-5 : 6-*benz*-4-*carboline*, m. p. 145°, closely resembles 3-chloro-5 : 6-benz-4-carboline in its properties.

3-β-*Diethylaminoethylamino*-1-*methyl*-5 : 6-*benz*-4-*carboline*. — 3-Chloro-1-methyl-5 : 6-benz-4-carboline (0·3 g.) was heated with β-diethylaminoethylamine (0·3 c.c.) at 145° for 6 hours, as in the case of 3-β-diethylaminoethylamino-5 : 6-benz-4-carboline. The viscous product was dissolved in dilute hydrochloric acid. On addition of ammonia an emulsion was formed, from which the base was extracted with ether. Addition of alcoholic hydrochloric acid to the dried ethereal solution produced a pale yellow precipitate, which was washed with acetone. The compound crystallised from alcohol in cream-coloured silky needles (0·3 g.), m. p. 261°. For analysis it was dried in a vacuum at 100° (Found : C, 60·0; H, 7·3; N, 13·3; Cl, 16·5. $C_{22}H_{26}N_4,2HCl,H_2O$ requires C, 60·3; H, 6·9; N, 12·9; Cl, 16·2%). 3-β-*Diethylaminoethylamino*-1-*methyl*-5 : 6-*benz*-4-*carboline dihydrochloride* is easily soluble in water, moderately easily soluble in alcohol, and insoluble in acetone, ether and benzene. Dilute alcoholic solutions show a blue-violet fluorescence and dilute aqueous solutions exhibit a blue-greenish fluorescence. Small traces have a marked bitter taste and produce considerable anæsthesia of the tongue.

3 : 10-*Dichloro*-5 : 6-*benz*-4-*carboline*.—(1) 3-Keto-5 : 6-benz-4-carboline (1 g.) was heated with phosphorus oxychloride (10 c.c.) and phosphorus pentachloride (2 g.) in a sealed tube at 120° for 24 hours. The excess of phosphorus oxychloride was sucked off, and the residue poured on ice. The yellow product, after being washed, was converted by treatment with dilute aqueous ammonia into the colourless base, which was dissolved in hot benzene. On cooling, a crystalline fraction (0·5 g.) separated, repeated crystallisation of which from benzene or benzene–ligroin yielded 3 : 10-*dichloro*-5 : 6-*benz*-4-*carboline* in fine needles arranged in rosettes, m. p. 250° (Found : N, 9·4; Cl, 24·1. $C_{15}H_8N_2Cl_2$ requires N, 9·7; Cl, 24·7%), easily soluble in alcohol, acetone and ether, moderately easily soluble in benzene and glacial acetic acid, and insoluble in ligroin. Under the carbon arc dilute neutral alcoholic solutions show a distinct blue-violet fluorescence.

(2) *p*-Chlorophenylhydrazine (4 g.) (Willgerodt and Böhm, *J. pr. Chem.*, 1891, **43**, 842) was refluxed with *o*-nitrophenylpyruvic acid (7 g.) in alcohol (50 c.c.) for 30 minutes (cf. Kermack and Slater, J., 1928, 37). The solution was then cooled slightly and saturated with hydrogen chloride. Boiling was continued for another 30 minutes, and the solution again saturated with hydrogen chloride. After cooling, it was poured into water (150 c.c.), the dark oil which separated extracted with ether several times, and the extract dried over anhydrous sodium sulphate. The oil obtained on removal of the ether was boiled with 10% alcoholic potassium hydroxide (30 c.c.) for 30 minutes on the water-bath. On cooling, red-brown hexagonal plates of potassium 6-chloro-3-*o*-nitrophenylindole-2-carboxylate separated, which were filtered off and washed with alcohol. From an aqueous solution of the salt, 6-*chloro*-3-*o*-*nitrophenylindole*-2-*carboxylic acid* was precipitated with hydrochloric acid; the yellow compound crystallised from alcohol in stout prisms, m. p. 303° (decomp.) (Found : N, 8·8. $C_{15}H_9O_4N_2Cl$ requires N, 8·8%), insoluble in water, sparingly soluble in benzene, moderately in alcohol, but easily soluble in acetone and ether.

Zinc dust (10 g.) was gradually added to a solution of the preceding acid (3 g.) in boiling 80% acetic acid (75 c.c.), and the whole refluxed for 30 minutes. The solution was filtered hot, and the zinc dust washed twice with boiling acetic acid. When the filtrate was poured into much water, 10-*chloro*-3-*keto*-3 : 4-*dihydro*-5 : 6-*benz*-4-*carboline* was precipitated as a pink compound, which was filtered off, washed with water, and dried at 100° (yield, 1·2 g.); it crystallised from pyridine in colourless needles, m. p. 337° (Found : N, 10·6. $C_{15}H_9ON_2Cl$ requires N, 10·4%), very sparingly soluble in most solvents, but moderately easily soluble in pyridine. A dilute acetic acid solution showed a very slight blue-violet fluorescence under the arc.

10-Chloro-3-keto-3 : 4-dihydro-5 : 6-benz-4-carboline (0·5 g.) was heated with phosphorus oxychloride (5 c.c.) and phosphorus pentachloride (0·5 g.) in a sealed tube at 125° for 24 hours. The excess of phosphorus oxychloride was removed under reduced pressure, and the residue poured on ice. The yellow hydrochloride was filtered off and washed with dilute aqueous ammonia to convert it into 3 : 10-dichloro-5 : 6-benz-4-carboline (0·4 g.), which crystallised from benzene in colourless needles, m. p. 251°, which did not lower the m. p. of the product obtained in (1).

5-*Methoxy*-1-*methylindole*-2-*carboxylic Acid*.—*p*-Methoxyphenylmethylhydrazine (10 g.) (Späth and Brunner, *Ber*, 1925, **58**, 522) was dissolved in 15% acetic acid (100 c.c.) and warmed with pyruvic acid (10 c.c.) for 5—10 minutes at 50—60°. To the hydrazone, which had separated as a yellow oil, concentrated hydrochloric acid (30 c.c.) was added after 2 minutes, and the dark solution warmed in water at 50° for 5 minutes. The expected *carboxylic acid* separated in brown crystals, which were quickly filtered off, washed with water, dried (yield, 4·3 g.), and

recrystallised from alcohol. The very pale brown prisms obtained, m. p. 216° (Found : N, 6·8. $C_{11}H_{11}O_3N$ requires N, 6·8%), were easily soluble in ether and acetone, moderately easily soluble in alcohol, and insoluble in water and benzene. With *p*-dimethylaminobenzaldehyde the acid developed a purple colour after some heating on the water-bath, and addition of sodium nitrite increased the intensity of the colour.

5-Methoxy-1-methylindole-2-carboxydiethylacetalylamide.—Phosphorus pentachloride (1 g.) was added to a cooled suspension of finely divided 5-methoxy-1-methylindole-2-carboxylic acid (1 g.) in acetyl chloride (10 c.c.), and the mixture hand-warmed until the acid dissolved. After standing at room temperature for 4 hours, the excess of acetyl chloride and the phosphorus oxychloride formed were completely removed in a vacuum at 50° (any trace left interferes with the subsequent reaction). The dark-coloured crystalline acid chloride was dissolved in warm dry chloroform (10 c.c.) and rapidly filtered from a little impurity. To the cooled solution was added a chloroform solution of aminoacetal (1·5 g.), prepared from bromodiethylacetal (Freundler and Ledru, *Bull. Soc. chim.*, 1907, **1**, 71) by the method of Hartung and Adkins (*J. Amer. Chem. Soc.*, 1927, **49**, 2521). After 1 hour the chloroform was distilled in a vacuum. On being rubbed with water, the semi-solid residue solidified to a light brown product, which was washed with water and dried at 37° (yield, 1·4 g.). *5-Methoxy-1-methylindole-2-carboxydiethylacetalylamide* crystallised from benzene–ligroin in colourless needles, m. p. 104° (Found : N, 8·7. $C_{17}H_{24}O_4N_2$ requires N, 8·7%), readily soluble in alcohol, chloroform, ether and benzene, moderately easily soluble in dilute mineral acids, very sparingly soluble in ligroin, and insoluble in water. With *p*-dimethylaminobenzaldehyde it gave a purple colour in the cold, which changed to dark red on addition of sodium nitrite.

3-Keto-10-methoxy-1-methyl-3 : 4-dihydro-4-carboline.—The preceding compound (3·4 g.) was dissolved in alcoholic hydrogen chloride (30 c.c.) and warmed at 50° for 15 minutes. After some time the crystalline hydrochloride which had separated from the dark purple solution was filtered off, pressed on a porous plate, and dissolved in much hot alcohol, from which, on cooling *3-keto-10-methoxy-1-methyl-3 : 4-dihydro-4-carboline* separated in feather-like clusters (2 g.); it crystallised from alcohol in long colourless needles, m. p. 263° (Found : N, 12·3. $C_{13}H_{12}O_2N_2$ requires N, 12·3%), insoluble in water, acetone, ether and benzene. It was sparingly soluble in hot alcohol, and, like 3-keto-1-methyl-3 : 4-dihydro-4-carboline (Kermack, Perkin, and Robinson, J., 1922, **121**, 1884), exists in two crystalline modifications. If the alcohol contains some water, the compound crystallises in short rectangular prisms instead of in long needles. Dilute alcoholic solutions containing a trace of mineral acid exhibit a marked blue-violet fluorescence.

3-Chloro-10-methoxy-1-methyl-4-carboline.—The preceding dihydro-compound (0·5 g.) was heated with phosphorus oxychloride (5 c.c.) and phosphorus pentachloride (0·5 g.) in a sealed tube at 105—110° for 6 hours. The crystalline *3-chloro-10-methoxy-1-methyl-4-carboline hydrochloride* was filtered off, washed with acetone, and dried on the water-bath (yield, 0·35 g.). It separated from hot acetone in yellow needles, m. p. 185° (Found : N, 9·8. $C_{13}H_{11}ON_2Cl,HCl$ requires N, 9·9%), soluble in water, ether and benzene, moderately easily soluble in acetone and easily soluble in alcohol. Under the arc dilute alcoholic solutions showed a blue-violet fluorescence. On treatment with aqueous ammonia the hydrochloride was converted into the grey base, which, however, could not be obtained crystalline.

Trichloro-10-methoxy-1-methyl-4-carboline. — 3-Keto-10-methoxy-1-methyl-3 : 4-dihydro-4-carboline (1 g.) was heated with phosphorus oxychloride (10 c.c.) and phosphorus pentachloride (2 g.) in a sealed tube at 110° for 6 hours. The yellow product was poured on ice, and the hydrochloride separated and washed with dilute aqueous ammonia to convert it into the base. Recrystallised from ligroin–benzene, *3 : (9 : 11) ?-trichloro-10-methoxy-1-methyl-4-carboline* separated in pale yellow needles, m. p. 214° (Found : C, 49·5; H, 3·0; N, 8·6; Cl, 33·0. $C_{13}H_9ON_2Cl_3$ requires C, 49·5; H, 2·9; N, 8·9; Cl, 33·7%), soluble in alcohol, acetone, ether and benzene and insoluble in ligroin. It showed a blue-violet fluorescence in dilute alcoholic solutions.

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