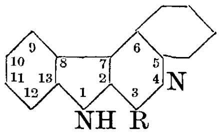
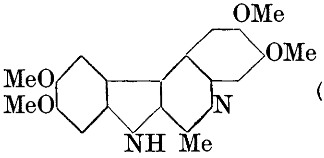
IV.—*Syntheses in the Indole Series. Part II.* 5 : 6-*Benz*-4-*carboline and its Derivatives.*

By William Ogilvy Kermack and Robert Henry Slater.

It has of recent years been shown that certain naturally occurring alkaloids are derivatives of 4-carboline. Methods for the synthesis of the analogous 5:6-*benz*-4-*carboline* (I; R = H) and its derivatives are now described. One derivative (II) of this base has been prepared by Lawson, Perkin, and Robinson (J., 1924, **125**, 629) as a step in the synthesis of *apo*harmine, but their method is not generally applicable. The methods to be described render 5 : 6-benz-4-carboline and its homologues comparatively readily accessible and the detailed examination of the reactions and physiological properties of synthetic polynuclear bases of this type has thus become feasible.

(I.)





(II.)

Two schemes were investigated for the synthesis of benzcarboline derivatives. In the first, an attempt was made by condensing *o*-nitrobenzyl chloride with ethyl acetoacetate, to obtain ethyl *o*-nitrobenzylacetoacetate, which it was thought might yield 3-methyl-5 : 6-benz-4-carboline (benzharman) (I; R = Me) by a similar method to that used by Manske, Perkin, and Robinson (J., 1927, 2) for the synthesis of harmaline. Under various conditions, however, the products of the condensation were the compound (m. p. 103°) formulated by Reissert (*Ber.*, 1896, **29**, 637) as $CH_3\cdot CO\cdot C(CO_2Et)(CH_2\cdot C_6H_4\cdot NO_2)_2$, and an *isomeride*, m. p. 183°, which was insoluble in aqueous sodium carbonate but soluble in sodium hydroxide solution. It is difficult to formulate the latter otherwise than as

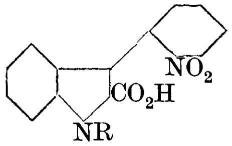
$$NO_2\cdot C_6H_4\cdot CH_2\cdot CH(C_6H_4\cdot NO_2)\cdot CH(CO_2Et)\cdot CO\cdot CH_3.$$

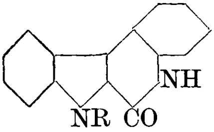
For the second scheme *o*-nitrophenylpyruvic acid was required in large quantities. The original method of preparation described by

Reissert (*Ber.*, 1897, **30**, 1036) gave yields of less than 50% and the procedure necessary to obtain the pure crystalline acid was very laborious and sometimes uncertain. We have found that, when special precautions are taken, Blaikie and Perkin's method (J., 1924, **125**, 310), in which certain methoxy-derivatives of *o*-nitrotoluene are condensed with ethyl oxalate in ethereal solution in the presence of potassium ethoxide, can be utilised for the preparation of *o*-nitrophenylpyruvic acid in excellent yield and in a state of high purity.

The phenylhydrazone of *o*-nitrophenylpyruvic acid (Reissert, *Ber.*, 1897, **30**, 1038) readily underwent the Fischer indole condensation when its boiling alcoholic solution was saturated with dry hydrogen chloride. The resulting *ethyl* 3-o-*nitrophenylindole-2-carboxylate* was converted through the *potassium* salt into the *acid* (III; R = H), which was readily obtained in a pure condition. The alkaline mother-liquor from the preparation of the potassium salt contained 3-o-*nitrophenylindole,* formed, apparently, during the indole cyclisation by loss of carbon dioxide : the amount formed varied with the duration of boiling during the saturation with hydrogen chloride; in some experiments a large yield was obtained accompanied by very little acid. Attempts to increase the yield of the acid by carrying out the saturation at 50° did not lead to the desired result, since the potassium salt isolated after boiling with alcoholic potassium hydroxide consisted mainly of that of the unchanged phenylhydrazone.

(III.)





(IV.)

When 3-*o*-nitrophenylindole-2-carboxylic acid or its calcium salt was heated, some 3-*o*-nitrophenylindole was produced; the ammonium salt, however, decomposed smoothly at 270—280°, and 3-*o*-nitrophenylindole was obtained in very good yield.

3-*o*-Nitrophenylindole-2-carboxylic acid was reduced by zinc dust in acetic acid solution; ring closure also occurred, the product being 3-*keto*-3 : 4-*dihydro*-5 : 6-*benz*-4-*carboline* (IV; R = H). The facility with which ring closure takes place, even in an alkaline solution, is shown by the fact that, in an experiment in which the reduction was carried out by means of ferrous sulphate and ammonium hydroxide so that the solution remained alkaline, no product of the reduction could be detected in the filtrate from the ferric oxide, but the product was obtained as the carboline derivative after dissolution of the ferric oxide in dilute hydrochloric acid.

The conversion of 3-keto-3 : 4-dihydro-5 : 6-benz-4-carboline (IV; R = H) into 5 : 6-benz-4-carboline (I; R = H) presented difficulties and only when it was reduced with zinc dust in a current of hydrogen could a small amount of the base be obtained. This and other carboline bases, however, can be obtained, as described below, from 3-*o*-nitrophenylindole.

The reduction of 3-*o*-nitrophenylindole to the corresponding amino-compound proceeds satisfactorily only under special conditions. When it was reduced in acetic acid solution with zinc dust, a non-basic substance, m. p. about 265°, was obtained, the constitution of which has not yet been elucidated. Owing, apparently, to the insolubility of the nitrophenylindole in water, reduction with tin and hydrochloric acid or with stannous chloride solution did not take place. When a solution of the compound in boiling alcohol containing hydrochloric acid was treated with tin, reduction occurred, but very little or none of the aminophenylindole could be isolated from the reaction product. It appeared that this difficulty was due to the fact that the base forms very sparingly soluble compounds both with stannic salts and with hydrochloric acid and that the former are not readily decomposed by alkali. Ultimately it was found that 3-o-*aminophenylindole* could be readily obtained in good yield by reduction of the nitro-compound in alcoholic solution with iron and hydrochloric acid (compare West, J., 1925, **127**, 494).

When 3-*o*-aminophenylindole was refluxed with anhydrous formic acid 3-o-*formamidophenylindole* was obtained mixed with a small quantity of 5 : 6-benz-4-carboline (I; R = H). The crude formyl derivative itself, on treatment in boiling toluene with phosphoryl chloride, was converted into this base.

Various homologues of 5 : 6-benz-4-carboline were prepared in a similar manner, *e.g.*, 3-*methyl*-5 : 6-*benz*-4-*carboline* (I; R = Me) from 3-o-*acetamidophenylindole*, which was obtained in excellent yield from 3-*o*-aminophenylindole in boiling acetic anhydride. When 3-*o*-acetamidophenylindole was boiled for a long time with acetic anhydride, with or without the addition of zinc chloride, the extent of ring closure, as manifested by the appearance of a fluorescence, was so small that none of the benzcarboline could be isolated. Saturation of a solution of the acetyl derivative in alcohol with hydrogen chloride, and addition of phosphorus pentoxide to a solution in boiling benzene, were even less effective, as in neither case was there even a development of the fluorescence.

3-Methyl-5 : 6-benz-4-carboline has many points of resemblance to harman : it gives none of the usual indole reactions, but exhibits a marked blue fluorescence in acid solutions. It appears to be a much weaker base than harman and it shows no tendency to absorb carbon dioxide from the atmosphere (compare diveratroharmyrine [II], which is so strongly basic that special precautions had to be taken to exclude carbon dioxide during its preparation). When precipitated from cold solutions it exhibits no tendency to form a gelatinous mass like that characteristic of the tetramethoxy-compound; this property of the latter compound, therefore, does not depend merely on the nuclear structure.

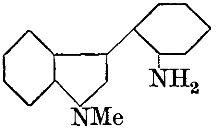
3-*o*-Propionamidophenylindole was converted by the phosphoryl chloride method into 3-*ethyl*-5 : 6-*benz*-4-*carboline* (I; R = Et). Apart from a tendency to combine with and retain solvents, this compound closely resembles 5 : 6-benz-4-carboline and the methyl derivative in its properties.

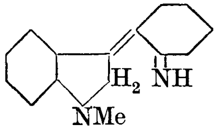
Unlike *o*-nitrophenylpyruvic acid phenylhydrazone, *o*-nitrophenylpyruvic acid phenylmethylhydrazone,

$$NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}C(CO_2H){:}N{\cdot}NPhMe,$$

underwent the Fischer indole condensation when acted upon with dilute hydrochloric acid. This result is in accord with the general experience that hydrazones prepared from phenylmethylhydrazine undergo indole cyclisation with much greater ease that the corresponding ones obtained from phenylhydrazine. The product of the reaction was 3-o-*nitrophenyl*-1-*methylindole*-2-*carboxylic acid* (III; R = Me), which is very similar in its properties to 3-*o*-nitrophenylindole-2-carboxylic acid; *e.g.*, it was converted by zinc dust and acetic acid into 3-*keto*-1-*methyl*-3 : 4-*dihydro*-5 : 6-*benz*-4-*carboline* (IV; R = Me), and when heated to 250° it decomposed with evolution of carbon dioxide and formation of 3-o-*nitrophenyl*-1-*methylindole.* This was reduced in alcoholic solution to the corresponding amino-compound by means of iron filings and hydrochloric acid. 3-o-*Aminophenyl*-1-*methylindole* is peculiar in that it has an old-gold colour and is only sparingly soluble in alcohol and ether, whereas 3-*o*-aminophenylindole itself is colourless and is readily soluble in these solvents. Further, the *N*-methyl derivative melts 47° higher than the parent base; in all other cases the melting point of the methyl derivative is lower than that of the compound from which it is derived. These facts suggest that this compound may have a quinonoid structure and that its formula may be (VI) rather than (V).

(V.)

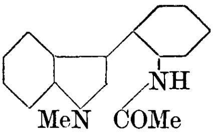


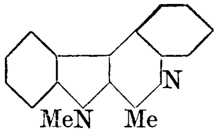


(VI.)

3-o-*Acetamidophenyl*-1-*methylindole* (VII) was obtained in excellent yield by acetylation of 3-*o*-aminophenyl-1-methylindole, and was readily converted into 1 : 3-*dimethyl*-5 : 6-*benz*-4-*carboline* (VIII) by boiling in toluene solution with phosphoryl chloride. This carboline derivative closely resembles 3-methyl-5 : 6-benz-4-carboline, and fluoresces strongly in acid solutions.

(VII.)





(VIII.)

These compounds are being studied from the point of view of the theory of anhydronium base formation in carboline derivatives, and it is hoped to submit the results in a future communication.

A consideration of the formula of 3-*o*-nitrophenylindole-2-carboxylic acid (III; R = H) suggests the possibility that the free rotation of the *o*-nitrophenyl group might be inhibited by the carboxyl group on the one hand and the projecting apex of the benzenoid ring on the other. It appears probable that the optical activity of certain diphenyl derivatives is occasioned by the absence of free rotation due to steric hindrance (compare Christie and Kenner, J., 1922, **121**, 614, *et seq.*), and it was therefore desirable to ascertain whether 3-*o*-nitrophenylindole-2-carboxylic acid could be resolved. The *brucine* salt was prepared, and this well-defined compound was recrystallised from alcohol but no sign of resolution was observed. The acid, when liberated carefully in the cold from its brucine salt, proved to be inactive. It seems, therefore, that the projecting apex of the benzenoid ring adjacent to the point of attachment of the *o*-nitrophenyl group is, in this case at least, insufficient to prevent free rotation.

EXPERIMENTAL.

Condensation of o-*Nitrobenzyl Chloride and Ethyl Acetoacetate.*—Ethyl acetoacetate (13 g.) was added to absolute ethyl alcohol (200 c.c.) in which sodium (2·3 g.) had been dissolved. To this mixture, cooled to 0°, was added *o*-nitrobenzyl chloride (8·6 g.) dissolved in the minimum quantity of alcohol, and the whole was allowed gradually to attain room temperature; sodium chloride then slowly separated. After 12 hours, the mixture was slightly acidified with 5% hydrochloric acid and steam-distilled, the residue was extracted with ether, and the combined ethereal extracts were shaken with 1% sodium hydroxide solution. The ethereal solution gradually deposited crystals of the compound, m. p. 103°, described by Reissert (*loc. cit.*). From the combined alkaline extracts, carbon dioxide precipitated a *substance* which, after several recrystallisations from alcohol, was obtained in brownish-yellow, microscopic needles, m. p. 183° (decomp.) (Found : C, 60·0 ; H, 4·8 ; N, 6·6 ; *M*, ebullioscopic in alcohol, 371. $C_{20}H_{20}O_7N_2$ requires C, 60·0 ; H, 5·0 ; N, 7·0% ; *M*, 400). It is very sparingly soluble in most of the usual organic solvents except boiling ethyl alcohol, in which it dissolves to the extent of about 2 parts in 100 ; the solution has an intense reddish-brown colour.

o-*Nitrophenylpyruvic Acid.*—In the preparation of this acid by the method described by Blaikie and Perkin (*loc. cit.*) it was found particularly important to cool the solution of potassium ethoxide (prepared from potassium, 19·6 g., and absolute alcohol, 24 g.) and ethyl oxalate (73 g.) in ether (500 c.c.) very efficiently before adding *o*-nitrotoluene (68·5 g.) in order to obtain satisfactory results. The total yield obtained from carefully dried reactants was 96 g. The acid crystallised from benzene in large, pale yellow, octagonal plates, m. p. 121° (compare Reissert, *Ber.*, 1897, **30**, 1037 ; Blaikie and Perkin, *loc. cit.*, p. 332), but a much purer product, m. p. 130°, decomposing at 140°, was obtained from alcohol.

o-Nitrophenylpyruvic acid phenylhydrazone was prepared by heating a mixture of the acid (8·4 g.) and phenylhydrazine (4·8 g.) in 50% acetic acid (70 c.c.) for 30 minutes on the steam-bath ; the viscid oil that separated, after solidifying, crystallised from benzene in pale yellow, well-shaped prismatic needles (yield 10·2 g.), m. p. 153·5° (decomp.) (Reissert, *Ber.*, 1897, **30**, 1038, gives m. p. 148—149°).

The phenylhydrazone is readily soluble in alcohol or glacial acetic acid, moderately easily soluble in ether or boiling benzene, and almost insoluble in cold benzene or light petroleum. It is only slightly soluble in cold dilute sodium hydroxide or sodium carbonate solution, but dissolves slowly on warming, giving in the latter case a yellow solution from which the original material is deposited on cooling, and in the former case ultimately a blood-red solution which smells of phenylhydrazine and probably contains sodium *o*-nitrophenylpyruvate. The phenylhydrazone is insoluble in concentrated hydrochloric acid even on warming and no indication of the formation, by this treatment, of any indole derivative could be obtained.

3-o-*Nitrophenylindole-2-carboxylic Acid* (III ; R = H).—A boiling alcoholic solution of the preceding phenylhydrazone was saturated with dry hydrogen chloride, ammonium chloride separating, and after hydrolysis of the oil which was precipitated on dilution with water 3-*o*-nitrophenylindole-2-carboxylic acid was isolated in the form of the sparingly soluble potassium salt.

The following method is more convenient in practice : A mixture of *o*-

nitrophenylpyruvic acid (80 g.), absolute ethyl alcohol (500 c.c.), and phenylhydrazine (50 g.) was boiled for 30 minutes and then cooled somewhat, and dry hydrogen chloride passed in; ammonium chloride and sometimes a brown solid separated, but the latter redissolved. The saturated mixture was boiled for 30 minutes, again saturated with dry hydrogen chloride, kept for a few hours, and then diluted with water (1000 c.c.). The oil that separated was isolated by means of ether and boiled for 30 minutes with a solution of potassium hydroxide (30 g.) in absolute alcohol (300 c.c.). After 12 hours, the reddish-orange crystals which had separated were collected, washed with absolute alcohol, and dried in the steam-oven (55 g.). The acid, liberated from this potassium salt, crystallised from benzene–absolute alcohol in pale yellow, rectangular, prismatic needles, m. p. 276° (decomp.) (Found: C, 64·1; H, 3·9; N, 9·8. $C_{15}H_{10}O_4N_2$ requires C, 63·8; H, 3·6; N, 9·9%).

3-o-*Nitrophenylindole-2-carboxylic acid* is insoluble in water, sparingly soluble in benzene or boiling chloroform, but is much more free soluble in alcohol. It dissolves readily in hot glacial acetic acid and crystallises, on cooling, in pale greenish-yellow rhombic plates. From a solution in cold dilute aqueous sodium or ammonium hydroxide, excess of the alkali precipitates the sodium or ammonium salt. The acid gives with *p*-dimethylaminobenzaldehyde and hydrochloric acid in alcoholic solution (Ehrlich's reagent) an orange coloration which is unchanged on prolonged boiling with excess of hydrochloric acid: no change is observed on addition of sodium nitrite to the cooled solution. The vanillin and the pine-shaving reaction are negative.

The *calcium* and the *barium* salt separate from water in sheaves of fine, long, golden-yellow needles and in large, yellow, well-shaped, rhombic plates respectively, and the bright yellow, crystalline *magnesium* salt in feathery rosettes. The amorphous, yellow *lead* and *zinc* salts are insoluble in hot water. The *brucine* salt separates readily when alcoholic solutions of the acid and of brucine are mixed and crystallises from alcohol in fine, bright yellow, rectangular, prismatic needles, m. p. 230° (Found: N, 8·4. $C_{15}H_{10}O_4N_2,C_{23}H_{26}O_4N_2$ requires N, 8·3%). $[\alpha]_D^{16^\circ} = -50{\cdot}5^\circ$ in 1% chloroform solution.

When the alcoholic mother-liquor from which potassium 3-*o*-nitrophenylindole-2-carboxylate had separated was diluted with much water an orange-red substance (39 g.) was precipitated. (The filtrate gives no precipitate on the addition of hydrochloric acid, thus showing that the above method of separating 3-*o*-nitrophenylindole-2-carboxylic acid as its potassium salt is quantitative.) This was freed from a tarry impurity by solution in ether, and recrystallised from light petroleum (b. p. 60—80°), containing a little benzene, 3-o-*nitrophenylindole* being thus obtained in long, bright orange, prismatic needles, m. p. 119° (Found: C, 71·0; H, 4·6; N, 11·5. $C_{14}H_{10}O_2N_2$ requires C, 70·6; H, 4·2; N, 11·8%).

3-*Keto*-3 : 4-*dihydro*-5 : 6-*benz*-4-*carboline* (IV; R = H).—Zinc dust (20 g.) was added gradually to a solution of 3-*o*-nitrophenylindole-2-carboxylic acid (6 g.) in boiling acetic acid (150 c.c. of 80%) and the whole refluxed during 30 minutes. The mixture was filtered while hot, and the residue extracted thrice with small quantities of boiling acetic acid. The combined filtrates were poured into an excess of water; the pale pink solid which separated (4·5 g.) crystallised from pyridine in snow-white, microscopic, rectangular, prismatic needles which showed no tendency to melt at 316° (Found: C, 76·4; H, 4·6. $C_{15}H_{10}ON_2$ requires C, 76·9; H, 4·3%).

The same substance was formed when a mixture of 3-*o*-nitrophenylindole-2-carboxylic acid (2·8 g.), ammonium hydroxide (14 c.c.; *d* 0·880), ferrous sulphate (18 g.), and water (40 c.c.) was boiled for 2 hours, and remained undissolved (1·2 g.) when the washed precipitate of iron oxide was dissolved in dilute hydrochloric acid.

3-*Keto*-3 : 4-*dihydro*-5 : 6-*benz*-4-*carboline* is practically insoluble in benzene, alcohol, and light petroleum even on boiling, but it is moderately easily soluble in hot glacial acetic acid and in pyridine. It is best recrystallised from the latter solvent, since its solution in acetic acid tends to develop a pink coloration when exposed to the atmosphere and the crystals deposited from such a solution are coloured. A fine blue fluorescence develops in an acetic acid solution and also when the compound is boiled with water containing a trace of hydrochloric acid.

This benzcarboline is in many respects similar to 3-keto-4-methyl-3 : 4-dihydro-4-carboline and other derivatives previously described (Kermack, Perkin, and Robinson, J., 1922, **121**, 1886; Blaikie and Perkin, *loc. cit.*, p. 319). With Ehrlich's reagent it gives no reaction in the cold, but a very faint green coloration develops on prolonged boiling with excess of concentrated hydrochloric acid; the colour fades on cooling and no further change is observed on addition of aqueous sodium nitrite. A faint green coloration, which does not change on prolonged boiling, is observed when this compound is treated with vanillin and hydrochloric acid. The pine-shaving test is negative.

3-o-*Nitrophenylindole*.—This compound, which was first obtained as described above, was also prepared by heating 3-*o*-nitrophenylindole-2-carboxylic acid in quantities of 2 g. at 275—280°, carbon dioxide being evolved; when the decomposition appeared to be complete, the temperature was raised to 285—290°. Owing to resinification, the yield was very poor. Attempts to increase it by heating the acid with glycerol or quinoline, and by heating its calcium or potassium salt under atmospheric pressure or in a vacuum were unsuccessful. When, however, the ammonium salt was heated, in quantities of 2 g., at 270—280°, decomposition took place smoothly with evolution of carbon dioxide and ammonia. The product, after cooling, was dissolved in ether, and the ethereal solution shaken with small volumes of aqueous sodium carbonate (5%) to free it from unchanged acid. The subsequent purification of the nitrophenylindole was effected as described on p. 39 (yield, 87%).

3-o-*Nitrophenylindole* has a slight indole odour, especially when heated, and is readily soluble in alcohol and benzene but much less soluble in light petroleum. With Ehrlich's reagent it develops, after prolonged boiling with excess of concentrated hydrochloric acid, a faint pink colour, which fades on cooling. With vanillin and hydrochloric acid it gives a pink coloration on warming. The pine-shaving test is negative.

3-o-*Aminophenylindole.*—Iron filings (20 g.) were added in small portions during 30 minutes to a boiling solution of 3-*o*-nitrophenylindole (23·8 g.) in 90% alcohol (200 c.c.) containing concentrated hydrochloric acid (10 c.c.; *d* 1·19). Boiling was continued for 3 hours, sodium ethoxide (4 g. of sodium in 100 c.c. of alcohol) then added, and the liquid refluxed for a few minutes. The mixture of iron and ferric oxide was filtered off and extracted thrice with small quantities of boiling alcohol. The combined filtrate and extracts were submitted to steam-distillation to remove the alcohol; the aminophenylindole then separated as a brown oil which solidified on cooling. The crude base (17 g.) was freed from any unchanged nitro-compound by saturation of its ethereal solution with dry hydrogen chloride; the hydrochloride thus quantitatively precipitated was washed with a little alcohol, and the base was set free by the action of warm aqueous sodium hydroxide and isolated by means of ether as a yellow oil which solidified. Great difficulty was experienced in its further purification. It dissolved on warming in most organic solvents, but separated on cooling as an uncrystallisable oil. It decomposed below the b. p. when attempts were made to distil it under diminished pressure, pungent indole vapours being evolved. Ultimately, crystallisation was effected by dissolving the base in light petroleum (b. p. 80—100°) containing a little benzene, a few chips of potassium hydroxide being added to prevent the formation of the carbonate of the base. The base separated partly as a yellow oil which slowly solidified and partly in fine, long, colourless, rectangular needles, m. p. 82°; on further recrystallisation the melting point fell to 75°. The analytical results indicate that the compound was still not quite pure (Found: C, 79·5; H, 6·1. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8%).

3-o-*Aminophenylindole* has a slight aniline odour. It is readily soluble in alcohol and benzene, but much less soluble in light petroleum. The *hydrochloride* forms pear-shaped plates, m. p. 288° (Found: Cl, 14·5. $C_{14}H_{12}N_2,HCl$ requires Cl, 14·5%), and is sparingly soluble in water; the solution has a very faint blue fluorescence. The *picrate*, prepared from the base and picric acid in benzene, crystallises from benzene in long, orange needles, m. p. 190°, decomp. 200° (Found: N, 15·8. $C_{14}H_{12}N_2,C_6H_3O_7N_3$ requires N, 16·0%). When 3-*o*-aminophenylindole is heated with chloroform and alcoholic potassium hydroxide no carbylamine odour is produced; acidification of the mixture does not give rise to a fluorescent solution. Ehrlich's reagent gives with this indole compound, on prolonged boiling in presence of concentrated hydrochloric acid, a faint pink coloration, which disappears on cooling. The addition of sodium nitrite to the cooled solution effects no change. Vanillin and hydrochloric acid give with this base a faint pink coloration in the cold, which changes to green on warming and fades on dilution. The pine-shaving test is negative. 3-*o*-Aminophenylindole hydrochloride is diazotised only very slowly and the diazotised solution gives a yellow precipitate with an alkaline solution of β-naphthol.

5 : 6-*Benz*-4-*carboline* (I; R = H).—3-*o*-Aminophenylindole (2·3 g.) was formylated by boiling under reflux with an excess of formic acid (98—99%) for 15 minutes. When the reaction mixture was poured into excess of water, the latter exhibited a brilliant bluish-green fluorescence due to the formation of a trace of 5 : 6-benz-4-carboline by the dehydrating action of the formic acid; this trace was precipitated on addition of excess of aqueous ammonia. The crude formyl derivative separated as an oil which solidified slowly (2 g.). It was boiled under reflux with perfectly dry toluene (8 c.c.) and freshly distilled phosphoryl chloride (5 c.c.) for 2 hours, hydrogen chloride being slowly evolved; as the reaction neared completion, a dark, viscid oil separated, which solidified on cooling. The liquor was decanted, the solid washed several times with light petroleum (b. p. 60—80°) and dissolved in an excess of alcoholic potassium hydroxide (20%), and the filtered solution poured into an excess of water; the resulting emulsion slowly deposited yellow, needle-shaped crystals of the benzcarboline (1·4 g.). This was dissolved in boiling dilute hydrochloric acid, reprecipitated by ammonia, and crystallised from benzene containing a little solid potassium hydroxide, 5 : 6-*benz*-4-*carboline*

being obtained in pale yellow, microscopic needles, m. p. 245° (Found : C, 82·9 ; H, 4·8. $C_{15}H_{10}N_2$ requires C, 82·6 ; H, 4·6%). The base gives none of the usual indole reactions, and in acid solutions it exhibits a beautiful bluish-green fluorescence.

5 : 6-Benz-4-carboline was also obtained when 3-keto-3 : 4-dihydro-5 : 6-benz-4-carboline (2·5 g.) was distilled over a large excess of zinc dust in a current of hydrogen. The small quantity of light brown oil that condensed in the unheated portions of the tube and slowly solidified crystallised from benzene in fine, needle-shaped crystals; it then melted at 243°, and at 244° in admixture with 5 : 6-benz-4-carboline prepared as described above.

3-*Methyl*-5 : 6-*benz*-4-*carboline* (I ; R = Me).—A solution of 3-*o*-aminophenylindole (16 g.) in freshly distilled acetic anhydride (40 c.c.) was boiled under reflux for 30 minutes and then poured into much water ; this acquired a fine blue fluorescence and 0·6 g. of the carboline was isolated from it. The aqueous mixture was warmed on the water-bath ; the oil which separated solidified slowly after cooling (18·5 g.) and was then crystallised from aqueous alcohol, 3-o-*acetamidophenylindole* being obtained in colourless, rhombic plates, m. p. about 158°. It is readily soluble in alcohol and benzene, but only sparingly soluble in light petroleum.

3-*Methyl*-5 : 6-*benz*-4-*carboline* was produced by the phosphoryl chloride method (see p. 41) (3-*o*-acetamidophenylindole, 7 g. ; dry toluene, 30 c.c. ; phosphoryl chloride, 15 c.c.). It was isolated (6 g.) in the same way as the lower homologue and crystallised from benzene–light petroleum (b. p. 60—80°) containing potassium hydroxide, separating in stellate clusters of pale yellow, prismatic needles, m. p. 204—205° (Found : C, 83·1 ; H, 5·5 ; N, 12·0. $C_{16}H_{12}N_2$ requires C, 82·8 ; H, 5·2 ; N, 12·1%).

3-Methyl-5 : 6-benz-4-carboline is readily soluble in alcohol, benzene, and chloroform, but much less soluble in light petroleum ; the solutions exhibit a brilliant blue fluorescence. The *hydrochloride* crystallises in bright yellow needles and is sparingly soluble in water ; the saturated solution exhibits a vivid green fluorescence, which becomes blue on dilution, and is considerably reduced in intensity on addition of sodium chloride. Picric acid and chloroplatinic acid precipitate from the hydrochloride solution the *picrate* in bright yellow, hexagonal plates and the *chloroplatinate* in flat, sharp-pointed, yellow plates.

3-*Ethyl*-5 : 6-*benz*-4-*carboline* (I ; R = Et).—3-*o*-Aminophenylindole (20 g.) was boiled under reflux with an excess of propionic anhydride (or propionyl chloride and an excess of pyridine) for 30 minutes, and the crude dried propionyl derivative, obtained in the usual way, was refluxed in dry toluene (80 c.c.) for 2 hours with phosphoryl chloride (40 c.c.). The product was worked up in the same way as the two lower homologues and recrystallised from benzene or ethyl acetate, 3-*ethyl*-5 : 6-*benz*-4-*carboline* (14·5 g.) being obtained in large, pale yellow, rectangular plates radially arranged, m. p. 158° with frothing. This frothing appears to be due to the loss of a small quantity of solvent of crystallisation and was observed even after prolonged heating of the crystals at 100° (Found : C, 82·0; H, 6·1. $10C_{17}H_{14}N_2,CH_3\cdot CO_2Et$ requires C, 82·0; H, 5·8%). 3-Ethyl-5 : 6-benz-4-carboline has an intense bluish-green fluorescence in acid solutions. It does not give the ordinary indole reactions.

3-o-*Nitrophenyl*-1-*methylindole*-2-*carboxylic Acid* (III; R = Me).—A solution of *o*-nitrophenylpyruvic acid (42 g.) in warm glacial acetic acid (150 c.c.) was diluted with an equal volume of boiling water, warmed for a few minutes with phenylmethylhydrazine (25 g.), treated with hydrochloric acid (200 c.c.; *d* 1·19), and heated on a boiling water-bath for 30 minutes. The yellow oil thus produced solidified (43 g.), and crystallised from a small volume of hot alcohol in bright yellow, rectangular, prismatic needles, m. p. 234° (decomp.) (Found : C, 65·1; H, 3·9. $C_{16}H_{12}O_4N_2$ requires C, 64·9; H, 4·1%).

3-o-*Nitrophenyl*-1-*methylindole*-2-*carboxylic acid* is insoluble in water, sparingly soluble in benzene, and moderately easily soluble in alcohol. When it is boiled with aqueous sodium or ammonium hydroxide, a small quantity dissolves and the remainder is converted into a reddish-orange compound—apparently the sodium or ammonium salt. The *calcium* salt crystallises from water in fine, bright yellow needles, and the *barium* salt in long, yellow, prismatic needles. The amorphous *lead* and *zinc* salts are insoluble in boiling water. The *magnesium* salt separates from a hot concentrated solution in orange, well-shaped, hexagonal plates. With Ehrlich's reagent the acid develops, on prolonged boiling with excess of concentrated hydrochloric acid, a faint pink coloration which disappears on cooling and no further change is observed on addition of sodium nitrite. With vanillin and hydrochloric acid a deep green coloration develops on warming, which persists on cooling but changes to yellow on dilution. The pine-shaving test is negative.

3-*Keto*-1-*methyl*-3 : 4-*dihydro*-5 : 6-*benz*-4-*carboline* (IV; R = Me).—Small quantities of zinc dust were added to a boiling solution of 3-*o*-nitrophenyl-1-methylindole-2-carboxylic acid (2·5 g.) in acetic acid (100 c.c.) until the colour was almost discharged. The mixture was refluxed for 10 minutes and filtered, the residual zinc dust repeatedly extracted with acetic acid until a test portion of the filtered extract, on dilution with water, showed hardly any opalescence, and the combined filtrate and washings, which showed a marked fluorescence, were diluted with water (4 vols.); the pink precipitate thus produced crystallised from pyridine in fine, white, felted needles, m. p. 302° (Found : N, 11·2. $C_{16}H_{12}ON_2$ requires N, 11·3%).

3-*Keto*-1-*methyl*-3 : 4-*dihydro*-5 : 6-*benz*-4-*carboline* is almost insoluble in water, alcohol, or benzene, but is slightly soluble in boiling glacial acetic acid, from which it separates in small needles on cooling. It is more soluble in hot pyridine; the solution exhibits a very slight blue fluorescence. Fluorescence is more marked in acetic acid and is also observed when a trace of the compound is boiled with water containing a little hydrochloric acid. The carboline gives none of the usual indole colour reactions.

3-o-*Nitrophenyl*-1-*methylindole.*—3-*o*-Nitrophenyl-1-methylindole-2-carboxylic acid decomposed at 250° with loss of carbon dioxide. The product was freed from unchanged acid by repeated extractions with boiling 5% sodium carbonate solution, dried (yield, 80%), and recrystallised from light petroleum (b. p. 80—100°) or alcohol, 3-o-*nitrophenyl*-1-*methylindole* separating in large, orange octahedra, m. p. 98° (Found : C, 71·4; H, 4·8; N, 11·2. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%).

This compound is readily soluble in benzene, chloroform, and glacial acetic acid, moderately easily soluble in alcohol, but only sparingly soluble in light petroleum. It gives a faint pink coloration with Ehrlich's reagent in the cold; the colour is intensified slightly on prolonged boiling with hydrochloric acid, but fades on cooling; the cooled solution gives an orange coloration with sodium nitrite. When the compound is treated with vanillin and hydrochloric acid a pink colour develops in the cold; on warming, this changes to a purple colour which persists on cooling but disappears on dilution. The pine-shaving test is negative.

3-o-*Aminophenyl*-1-*methylindole* (V and VI).—Iron filings (20 g.) were added in small quantities to a boiling solution of 3-*o*-nitrophenyl-1-methylindole (17 g.) in alcohol (400 c.c.) containing hydrochloric acid (10 c.c.). Boiling was continued for 3 hours and the reduction product was worked up as described in the case of 3-*o*-aminophenylindole, except that the hydrochloride was precipitated from benzene instead of ether, in which the base is rather sparingly soluble. The dried base (14·5 g.) crystallised from hot alcohol, containing a little aqueous ammonia, in large, old-gold, rectangular, prismatic needles, m. p. 129° (Found : C, 81·5; H, 6·3. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·3%).

3-o-*Aminophenyl*-1-*methylindole* is only slightly soluble in alcohol, light petroleum, and ether, but is readily soluble in benzene. The *hydrochloride* forms long, sharp-pointed, colourless plates, m. p. 246° (decomp.), slightly soluble in water, ether, and benzene but readily soluble in alcohol. The *picrate* separates from alcohol in bright orange, hexagonal prisms, m. p. 196°, decomp. 205° (Found: N, 15·3. $C_{15}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·5%). The base gives with Ehrlich's reagent in the cold a faint pink coloration which is intensified slightly on boiling and fades on cooling; addition of sodium nitrite does not alter the colour. With vanillin and hydrochloric acid the base gives a pink coloration which is intensified on warming and fades on dilution. The pine-shaving test is negative. The hydrochloride of the base diazotises only very slowly and the diazotised solution gives an orange precipitate when treated with an alkaline solution of β-naphthol.

3-o-*Acetamidophenyl*-1-*methylindole* (VII).—3-*o*-Aminophenyl-1-methylindole (7·3 g.) was refluxed with an excess of acetic anhydride for 30 minutes, and the product isolated in the usual way; the water used acquired a fine green fluorescence due to the presence of a small quantity of carboline. The *acetyl* derivative (7 g.) crystallised from alcohol in long, pale yellow, hexagonal prisms, m. p. 159°. It is only sparingly soluble in alcohol, ether, and light petroleum, but readily soluble in benzene, chloroform, and glacial acetic acid. With Ehrlich's reagent a pale green colour develops on prolonged boiling with excess of concentrated hydrochloric acid; the colour fades on cooling and addition of sodium nitrite produces no further change. With vanillin and hydrochloric acid the acetyl derivative gives a faint purple coloration on warming, which persists on cooking. The pine-shaving test is negative.

1 : 3-*Dimethyl*-5 : 6-*benz*-4-*carboline* (VIII).—3-*o*-Acetamidophenyl-1-methylindole (4·5 g.), dissolved in dry toluene (40 c.c.), was refluxed for 2 hours with phosphoryl chloride (9 c.c.), and the *carboline* produced was worked up in the same way as the other homologues (yield, 2·9 g.). It crystallised from hot alcohol, containing a little aqueous ammonia, in long, pale yellow, rectangular plates, m. p. 154° (Found: C, 83·0; H, 5·7. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7%). It exhibits a beautiful green fluorescence in acid solutions, and gives none of the usual indole reactions.

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