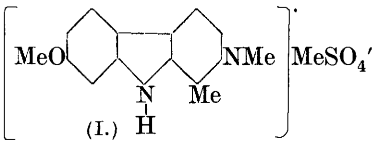
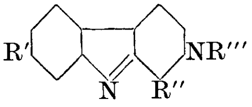
CVII.—*Syntheses in the Indole Series. Part III. The Theory of Anhydronium Base Formation and the Constitution of Methosulphates, with some Observations on the Fluorescence of 5 : 6-Benz-4-carboline and its Derivatives.*

By William Ogilvy Kermack and Robert Henry Slater.

In support of the view that the anhydronium base formed from harmine methosulphate (I) by the action of alkali has the constitution II ($R' = OMe$; $R'' = Me$; $R''' = Me$) and is a derivative of 4-ψ-carboline (II : $R' = R'' = R''' = H$), it has been shown by



(I.)



(II.)

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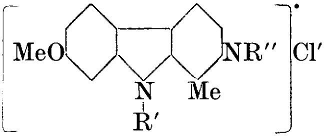
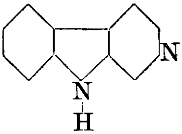
* The author has been informed in a private communication from Professor G. G. Henderson that the results he has obtained in the fractional distillation of large quantities of caryophyllene are very similar indeed to those recorded in this paper. The two main fractions into which he separated caryophyllene both yielded the dihydrochloride and the alcohol.

Kermack, Perkin, and Robinson (J., 1922, **121**, 1877) that the propochloride of methylharmine (III : R′ = Pr; R″ = Me) is not identical with the methochloride of propylharmine (III : R′ = Me; R″ = Pr). This evidence is not quite conclusive, inasmuch as it is conceivable that the addition of the alkyl salt to the anhydronium base might take place in such a way that the alkyl group did not attach itself to either nitrogen atom. This possibility, although rather unlikely, must be considered and therefore direct evidence as to the constitution of the anhydronium bases in the carboline series appears desirable. Definite evidence upon this point would obviously be of importance with reference to the general problem of the structure of heterocyclic polynuclear bases.

(III.)

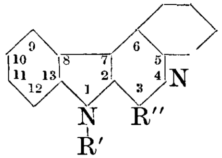


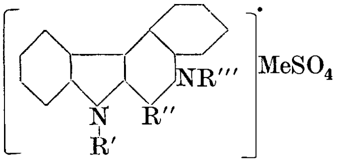


(IV.)

Closely related to 4-carboline (IV), of which harmine and all the above compounds are derivatives, is the somewhat more complex 5 : 6-benz-4-carboline (V : R′ = R″ = H). The syntheses of this compound and of some of its derivatives have been described (Kermack and Slater, this vol., p. 32), and it is the comparative ease with which members of the benzcarboline series can be prepared that makes them particularly suitable for the further investigation of the theory of anhydronium base formation. They are compounds very similar to 4-carboline in their properties, and so there seems little doubt that a rigorous proof of the constitution of the anhydronium bases and their metho-salts in this series would imply that a similar constitution holds in the carboline and other related series also. By the method previously described (Kermack and Slater, *loc. cit.*, p. 41), 5 : 6-benz-4-carboline (V : R′ = R″ = H) and 1-methyl-5 : 6-benz-4-carboline (V : R′ = Me; R″ = H) can be prepared in a way that leaves no doubt as to their constitution.

(V.)



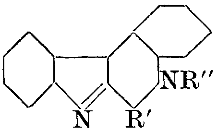


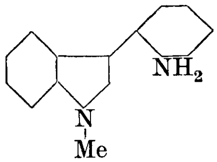
(VI.)

Now according to the above theory the anhydronium base formed from 5 : 6-benz-4-carboline methosulphate (VI : R′ = R″ = H; R‴ = Me) should be a derivative of 4-ψ-carboline (II : R′ = R″ = R‴ = H) and should possess the constitution VII (R′ = H; R″ =

Me), and so the methosulphate of this anhydronium base ought to be identical with 1-methyl-5 : 6-benz-4-carboline methosulphate, which must have the constitution VI (R′ = R‴ = Me; R″ = H). This is so, as is shown below, and the identity of these two methosulphates, prepared quite independently, proves definitely that methyl sulphate adds itself on to the pyrrole nitrogen atom of the anhydronium base, and that the theory described above is correct.

(VII.)

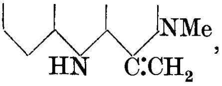




(VIII.)

When heated in benzene suspension with methyl sulphate, 5 : 6-benz-4-carboline yields a bright yellow *methosulphate* (VI : R′ = R″ = H; R‴ = Me), m. p. 235°, from an aqueous solution of which sodium or ammonium hydroxide readily precipitates an orange *anhydronium base* (VII : R′ = H; R″ = Me), m. p. 205°. When dissolved in benzene and treated with methyl sulphate, this base gives a *methosulphate* (VI : R′ = R‴ = Me; R″ = H), m. p. 300°.

1-*Methyl*-5 : 6-*benz*-4-*carboline* (V : R′ = Me; R″ = H), m. p. 142°, prepared from the formyl derivative of 3-*o*-aminophenyl-1-methylindole (VIII) (Kermack and Slater, *loc. cit.*, p. 44) by the phosphoryl chloride method, is converted by methyl sulphate in benzene solution into a compound, m. p. 300°, which is identical with the methosulphate (VI : R′ = R‴ = Me; R″ = H) of the anhydronium base described above. This anhydronium base and its methosulphate are therefore properly named 4-*methyl*-5 : 6-*benz*-4-*ψ-carboline* and 1 : 4-*dimethyl*-5 : 6-*benz*-4-*carbolinium methyl sulphate* respectively.

In order to confirm the conclusions just discussed, the work was repeated with 3-methyl-5 : 6-benz-4-carboline (V : R′ = H; R″ = Me) and 1 : 3-dimethyl-5 : 6-benz-4-carboline (V : R′ = R″ = Me) (Kermack and Slater, *loc. cit.*, pp. 42, 45). 3-*Methyl*-5 : 6-*benz*-4-*carboline methosulphate* (VI : R′ = H; R″ = R‴ = Me), m. p. 270°, prepared in the usual way, was converted into 3 : 4-*dimethyl*-5 : 6-*benz*-4-*ψ-carboline* (VII : R′ = R″ = Me), m. p. 225°, and this anhydronium base reacted readily with methyl sulphate to form 1 : 3 : 4-*trimethyl*-5 : 6-*benz*-4-*carbolinium methyl sulphate* (VI : R′ = R″ = R‴ = Me), m. p. 292°, which was identical with the methosulphate obtained from 1 : 3-dimethyl-5 : 6-benz-4-carboline. The methyl sulphate and the benzene used in the preparation of these methosulphates must be perfectly dry and neutral to litmus; in the earlier experiments, in which this precaution was not taken, the product obtained from 1 : 3-dimethyl-5 : 6-benz-4-carboline melted at 296° and proved to be essentially 1 : 3-*dimethyl*-5 : 6-*benz*-4-*carbolinium methyl sulphate* (VI : R′ = R″ = Me; R‴ = H) (which could not readily be distinguished by analysis from 1 : 3 : 4-trimethyl-5 : 6-benz-4-carbolinium methyl sulphate), its formation being apparently due to water or methyl hydrogen sulphate in the methyl sulphate used. Before the nature of this product had been ascertained, the possibility (which was considered improbable) suggested itself that the anhydronium base (VII : R′ = R″ = Me) might have reacted in the ethylenic form, 

, with methyl sulphate, with the formation of 3-ethyl-5:6-benz-4-carboline methosulphate (VI: R′ = H; R″ = Et; R‴ = Me). This possibility was disproved by preparing this *methosulphate* from 3-ethyl-5 : 6-benz-4-carboline (Kermack and Slater, *loc. cit.*, p. 42); it melted at 250° and was clearly not identical with the substance of m. p. 292°.

Since the quaternary ammonium base is precipitated from an aqueous solution of 1 : 3 : 4-trimethyl-5 : 6-benz-4-carbolinium methyl sulphate (VI : R′ = R″ = R‴ = Me), both by sodium hydroxide and by ammonium hydroxide, this base appears to be weaker than the quaternary ammonium base of 1 : 4-dimethyl-5 : 6-benz-4-carbolinium methyl sulphate, which is precipitated by sodium hydroxide only (see p. 795). From 4-methylharmine methosulphate, even sodium hydroxide fails to precipitate the quaternary base in the cold (Perkin and Robinson, J., 1919, **115**, 949); the present authors have observed, however, that a very large excess of sodium hydroxide does effect precipitation. The extra benzene ring present in the benzcarboline series therefore appears considerably to diminish the basic nature of the nitrogen atom.

As a number of closely related fluorescent compounds were available, they were examined with the object of ascertaining whether any relation exists between the constitution of a compound and the colour of its fluorescence. Solutions of the compounds were prepared by adding 0·1 c.c. of an *N*/100-solution of the compound in water to 9·8 c.c. of alcohol and 0·1 c.c. of *N*-hydrochloric acid or of ammonium hydroxide (*d* 0·880). The acid and the alkaline alcoholic solutions obtained, each containing a compound at a concentration of *N*/10,000, were arranged by several independent observers according to the colour of their fluorescences, which varied from blue to greenish-yellow. The tubes were illuminated by means of a carbon arc, which provided a constant source of light and excited a very strong fluorescence. The results are in Table I, 4-methyl-

TABLE I.

Compound.	Acid or alkali added.	Colour of fluorescence.	Highest dilution showing fluorescence.
1 : 3-Dimethyl-5 : 6-benz-4-carboline hydrochloride	NH_4OH	Blue	$N/10^6$
1-Methyl-5 : 6-benz-4-carboline hydrochloride....................	,,	,,	$N/2.10^6$
4-Methylharmine methosulphate	HCl	,,	$N/10^7$
3-Ethyl-5 : 6-benz-4-carboline hydrochloride....................	NH_4OH	,,	$N/4.10^5$
5 : 6-Benz-4-carboline hydrochloride	,,	,,	$N/10^6$
3-Methyl-5 : 6-benz-4-carboline hydrochloride....................	,,	,,	$N/4.10^5$
4-Methylharmine methosulphate	,,	,,	$N/10^7$
3-Ethyl-5 : 6-benz-4-carboline hydrochloride....................	HCl	Blue with greenish tinge	$N/2.10^7$
3-Methyl-5 : 6-benz-4-carboline hydrochloride....................	,,	,, ,,	$N/10^7$
Quinine hydrochloride	,,	,, ,,	$N/10^7$
3 : 4-Dimethyl-5 : 6-benz-4-ψ-carboline hydrochloride	,,	Greenish-blue	$N/2.10^7$
3-Methyl-5 : 6-benz-4-carboline methosulphate	,,	,,	$N/2.10^7$
3-Ethyl-5 : 6-benz-4-carboline methosulphate	,,	,,	$N/10^7$
1 : 3-Dimethyl-5 : 6-benz-4-carboline hydrochloride	,,	Bluish-green	$N/2.10^7$
5 : 6-Benz-4-carboline hydrochloride	,,	,,	$N/10^7$
3 : 4-Dimethyl-5 : 6-benz-4-ψ-carboline hydrochloride	NH_4OH	Green	$N/10^7$
3-Methyl-5 : 6-benz-4-carboline methosulphate	,,	,,	$N/10^7$
3-Ethyl-5 : 6-benz-4-carboline methosulphate	,,	,,	$N/10^7$
4-Methyl-5 : 6-benz-4-ψ-carboline hydrochloride	HCl	,,	$N/2.10^7$
5 : 6-Benz-4-carboline methosulphate	,,	,,	$N/2.10^7$
1-Methyl-5 : 6-benz-4-carboline hydrochloride....................	,,	,,	$N/10^7$
1 : 3 : 4-Trimethyl-5 : 6-benz-4-carbolinium methyl sulphate	,,	,,	$N/10^7$
4-Methyl-5 : 6-benz-4-ψ-carboline hydrochloride	NH_4OH	Yellowish-green	$N/4.10^6$
5 : 6-Benz-4-carboline methosulphate	,,	,,	$N/4.10^6$
1 : 3 : 4-Trimethyl-5 : 6-benz-4-carbolinium methyl sulphate	,,	,,	$N/4.10^6$
1 : 4-Dimethyl-5 : 6-benz-4-carbolinium methyl sulphate	,,	Greenish-yellow	$N/10^7$
1 : 4-Dimethyl-5 : 6-benz-4-carbolinium methyl sulphate	HCl	,,	$N/10^7$
Quinine hydrochloride	NH_4OH	None at $N/10^4$	Less than $N/10^4$

harmine methosulphate and quinine hydrochloride being included for comparison. *N*/10,000-Solutions of these compounds in water and in *N*/100-hydrochloric acid were also examined: the order for these was the same as that for the hydrochloric acid–alcohol solutions. Addition of alkali to the aqueous solutions precipitated the bases in many cases and so destroyed the fluorescence. Alcoholic solutions containing sodium hydroxide (0·1 c.c. of *N*/100-carboline solution, 9·7 c.c. of alcohol, 0·2 c.c. of 5*N*-sodium hydroxide) exhibited fluorescences identical with those of solutions containing ammonium hydroxide.

The chief deductions to be drawn from the table are as follows. A methyl (or ethyl) group attached to the carbon atom in position 3 (see formula V) invariably renders the fluorescence more blue. With the introduction of a methyl group attached to either nitrogen atom, the fluorescence in acid solution becomes more yellow, the effect being greater when the methyl group is in position 1 than when it is in position 4. In acid solution the effect of a methyl group in position 3 is almost balanced by that of a methyl group in position 4. In alkaline solution a methyl group in position 1 renders the fluorescence more blue, whereas in position 4 it makes the fluorescence more green. In alkaline solution a methyl group in the 4-position is much more powerful in making the fluorescence more green than one in the 3-position is in making it blue. 1-Methyl-5 : 6-benz-4-carboline fluoresces bluer in alkaline solution than in acid solution, whereas 4-methyl-5 : 6-benz-4-ψ-carboline fluoresces yellower in alkaline solution than in acid solution. It seems a probable assumption that the yellowish-green colour of 4-methyl-5 : 6-benz-4-ψ-carboline in alkaline solution is due to the existence of the ψ-carboline structure.

The compounds which contain a methyl group in the 4-position (that is, those compounds whose bases cannot possess a normal structure in alkaline solution) fluoresce more yellow in alkaline than in acid solution, whereas those compounds not possessing a methyl group in this position are bluer in alkaline than in acid solution. Hence derivatives of the normal base (5 : 6-benz-4-carboline) fluoresce very blue, particularly in alkaline solution, and 5 : 6-benz-4-carboline and 3-methyl-5 : 6-benz-4-carboline exist essentially in the normal form.

The figures in the fourth column in Table I represent the concentrations at which the fluorescences are just visible. They are only approximate, but it is clear that the fluorescence of these compounds is usually considerably stronger in acid than in alkaline solution. In respect to colour and intensity of fluorescence, pairs of compounds such as 5 : 6-benz-4-carboline methosulphate and 4-methyl-5 : 6-

benz-4-ψ-carboline hydrochloride, which contain the same organic kation, are identical.

EXPERIMENTAL.

5 : 6-*Benz*-4-*carboline Methosulphate* (VI : R′ = R″ = H; R‴ = Me).—The method here described is of general application for the preparation of 5 : 6-benz-4-carboline methosulphates. They are best recrystallised from methyl alcohol. The absence of by-product such as VI (R′ = R″ = Me; R‴ = H) is readily indicated by the non-production of a precipitate when a few drops of concentrated hydrochloric acid are added to an aqueous solution of the methosulphate.

Finely powdered 5 : 6-benz-4-carboline (3 g.), dry benzene (10 c.c.), and methyl sulphate (2·5 g.) were heated together on the steam-bath for 30 minutes. The product that separated was recrystallised from a small quantity of boiling methyl alcohol, 5 : 6-*benz*-4-*carboline methosulphate* being obtained in thick, bright yellow, prismatic needles which exhibited a greenish fluorescence, m. p. 235° (Found: C, 58·3; H, 5·3. $2C_{17}H_{16}O_4N_2S,CH_3{\cdot}OH$ requires C, 58·1; H, 5·0%). The salt is readily soluble in water and in methyl and ethyl alcohol, the solutions exhibiting a green fluorescence. Its solution in concentrated sulphuric acid also exhibits a green fluorescence, which changes to deep greenish-blue on warming.

4-*Methyl*-5 : 6-*benz*-4-ψ-*carboline* (VII : R′ = H; R″ = Me) was obtained in a hydrated form as an orange precipitate when an aqueous solution of 5 : 6-benz-4-carboline methosulphate was treated with an excess of ammonium hydroxide in the cold (it is also precipitated by sodium hydroxide). It crystallised from boiling water, in which it was only sparingly soluble, in fine, orange, prismatic needles which, after being heated at 100° for 6 hours, darkened at 190° and melted at 205° (Found: C, 82·6; H, 5·2. $C_{16}H_{12}N_2$ requires C, 82·8; H, 5·2%). It is readily soluble in alcohol and moderately easily soluble in benzene, the solutions exhibiting a brilliant green fluorescence.

1 : 4-*Dimethyl*-5 : 6-*benz*-4-*carbolinium methyl sulphate* (VI : R′ = R‴ = Me; R″ = H), prepared both from 4-methyl-5 : 6-benz-4-ψ-carboline and from 1-methyl-5 : 6-benz-4-carboline, forms long, chrome-yellow, rectangular prismatic needles which exhibit a greenish fluorescence; m. p. 300° (Found: C, 59·8; H, 5·2. $C_{18}H_{18}O_4N_2S$ requires C, 60·3; H, 5·0%). Its solutions in water, boiling methyl alcohol, and concentrated sulphuric acid exhibit a greenish-yellow fluorescence, the last becoming greenish-blue on warming. The addition of sodium hydroxide, but not ammonium hydroxide, to the aqueous solution precipitates the hydrated

quaternary ammonium hydroxide as a voluminous, buff, amorphous compound.

1-*Methyl*-5 : 6-*benz*-4-*carboline* (V : R′ = Me; R″ = H).—This was prepared from 3-*o*-aminophenyl-1-methylindole (5 g.) by a method almost exactly identical with that described for the preparation of 5 : 6-benz-4-carboline (Kermack and Slater, *loc. cit.*, p. 41), the only differences being the extraction of the crude formyl derivative with ether, its drying over anhydrous sodium sulphate, and the use of 30 c.c. of toluene and 12 c.c. of phosphoryl chloride. The *benzcarboline* crystallised from ligroin, containing a little solid potassium hydroxide, in long, pale pink, feathery needles exhibiting radial formation; m. p. 142° (Found : C, 83·3; H, 5·4. $C_{16}H_{12}N_2$ requires C, 82·8; H, 5·2%). It is readily soluble in alcohol, benzene, and chloroform, but much less soluble in ligroin and light petroleum; these solutions exhibit a brilliant green fluorescence. The hydrochloride is only sparingly soluble in water and gives none of the usual indole reactions.

3-*Methyl*-5 : 6-*benz*-4-*carboline methosulphate* (VI : R′ = H; R″ = R‴ = Me) forms stout, bright yellow, prismatic needles, m. p. 270° (Found : C, 60·4; H, 5·2; N, 7·9. $C_{18}H_{18}O_4N_2S$ requires C, 60·3; H, 5·0; N, 7·8%). Its solutions in water, boiling methyl alcohol, and concentrated sulphuric acid exhibit a vivid greenish-blue fluorescence, the last becoming brilliant blue on warming and bluish-green on dilution.

3 : 4-*Dimethyl*-5 : 6-*benz*-4-*ψ*-*carboline* (VII : R′ = R″ = Me).—To an aqueous solution of 3-methyl-5 : 6-benz-4-carboline methosulphate, ammonium hydroxide was added until precipitation of the hydrated quaternary ammonium hydroxide was complete. (This is also precipitated by sodium hydroxide.) The *base* crystallised from boiling water in long, yellow, felted needles which, after being heated for 6 hours at 100°, darkened slightly at 200° and melted at 225° (Found: C, 82·6; H, 5·8; N, 11·2. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7; N, 11·4%). It is readily soluble in alcohol and benzene, the solutions exhibiting a brilliant greenish-blue fluorescence.

1 : 3 : 4-*Trimethyl*-5 : 6-*benz*-4-*carbolinium methyl sulphate* (VI : R′ = R″ = R‴ = Me), prepared both from 3 : 4-dimethyl-5 : 6-benz-4-ψ-carboline and from 1 : 3-dimethyl-5 : 6-benz-4-carboline, forms long, chrome-yellow, rectangular prismatic needles which exhibit a bright green fluorescence; m. p. 292° (Found : C, 61·2; H, 5·4; N, 7·3. $C_{19}H_{20}O_4N_2S$ requires C, 61·3; H, 5·4; N, 7·5%). Its solutions in water, hot methyl alcohol, and concentrated sulphuric acid exhibit a vivid green fluorescence, the last becoming brilliant blue on warming and greenish-blue on dilution. The addition of sodium hydroxide or ammonium hydroxide to the

aqueous solution precipitates the quaternary ammonium hydroxide as a fine emulsion, from which yellow crystals slowly separate.

3-*Ethyl*-5 : 6-*benz*-4-*carboline methosulphate* (VI : R′ = H ; R″ = Et ; R‴ = Me) forms pale yellow, tetragonal plates, m. p. 250° (Found : C, 61·6 ; H, 5·6. $C_{19}H_{20}O_4N_2S$ requires C, 61·3 ; H, 5·4%). Its solutions in water, boiling methyl alcohol, and concentrated sulphuric acid exhibit a greenish-blue fluorescence, the last becoming brilliant blue on warming. The addition of sodium hydroxide or ammonium hydroxide to the aqueous solution gives at once a voluminous, bright yellow, crystalline precipitate of the hydrated quaternary ammonium hydroxide.

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