611. *A Synthesis of Substituted 2 : 3-Benzpyrrocolines.*

By Sir Robert Robinson and J. E. Saxton.

During synthetical studies in the strychnine field it has been found that the condensation of acetonylacetone with indole and its simple derivatives, in the presence of hydrogen chloride, follows different paths mainly dependent on the substitution-type of the indole. Skatole is attacked in the 1- and 2-positions, yielding a base, $C_{15}H_{15}N$, which is considered to be 1 : 5 : 8-trimethyl-2 : 3-benzpyrrocoline; 3-ethylindole behaves similarly.

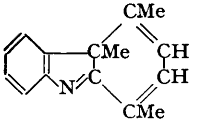
2-Methylindole gave no characteristic product under the conditions employed, and indole, which we thought should yield a dimethyltetrahydrocarbazole, was actually converted into a substance in which the 2-position remains free. The condensation of skatole with lævulic acid leads to the formation of a neutral product derived from two molecules of the indole derivative and one molecule of the keto-acid by loss of two molecules of water; a possible structure is suggested. Precedent researches are reviewed and a new interpretation of the course of the self-condensation of 2 : 4-dimethylpyrrole is advanced.

Construction of the strychnine skeleton would be facilitated by a knowledge of the circumstances that allow the attack of carbonyl groups on a 3-substituted indole at the 3-position so as to produce indolenines. For that reason we attempted the condensation of skatole with acetonylacetone in the presence of hydrogen chloride. The reaction could have proceeded with formation of a carbazolenine (I) and a base, $C_{15}H_{15}N$, was indeed obtained. Its properties showed, however, that the constitution (I) is inapplicable and the substance is almost certainly 1 : 5 : 8-trimethyl-2 : 3-benzpyrrocoline (II), the first representative of a tricyclic aromatic system of considerable stability. A substance possessing the structure (I) should yield a *sec.*-basic hexahydro-derivative (III), whereas (II) would give a tetrahydro-derivative (IV) in which the nitrogen is tertiary. The base, $C_{15}H_{15}N$, takes up four or twelve hydrogen atoms on catalytic hydrogenation, and the properties of the tetrahydro-product show that it is an aromatic indole substituted in positions 1, 2, and 3. Reduction of trimethylbenzpyrrocoline by means of zinc dust and boiling hydrochloric acid gives a solution that exhibits a typical strychnidine ferric reaction and must contain a hexahydro-derivative. The decision in favour of (IV), and hence of (II) for the original base, was confirmed by examination of ultra-violet absorption spectra and comparison with suitable models (see Fig.). It can be seen, for example, that the light absorption by tetrahydro-trimethylbenzpyrrocoline closely resembles that by 9-ethyl-1 : 2 : 3 : 4-tetrahydrocarbazole. A related carbazolenine and a substituted hexahydrocarbazole (not figured but available in connexion with other studies) gave quite different results.

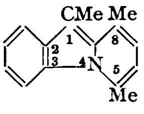
The 2 : 3-benzpyrrocoline skeleton has formal similarity to that of the indolediazines (Kermack, Perkin, and Robinson, *J.*, 1921, **119**, 1602; 1922, **121**, 1872) and occurs in strychnine and brucine derivatives, as well as in a number of synthetic compounds (Openshaw and Robinson, *J.*, 1937, 941), in reduced and oxidised–reduced forms.

During experiments in the strychnine group over a long period it has been recurrently observed that degradation products are obtained which exhibit a yellow colour and an intense apple-green fluorescence. It was suggested (Bailey and Robinson, *Nature*, 1948, **161**, 433) that the partial structure (V) is contained in these fluorescent by-products and this was rendered probable by the circumstances in which they were formed.

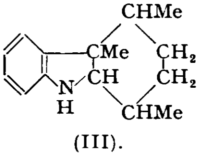
The expression (V) denotes a hydroxy-2 : 3-benzpyrrocoline and hence it is of interest that the base (II) is yellow and exhibits a striking green fluorescence in organic solvents. A simple model for the strychnine derivatives would be the substance (VI) which we hoped to obtain from lævulic acid and skatole. The condensation with the help of hydrogen chloride results under some conditions in the formation of small quantities of a yellow substance that fluoresces green in alcoholic alkali, but the main product under the conditions described below is a colourless compound, $C_{23}H_{22}ON_2$, which we consider to be (VII).



(I.)

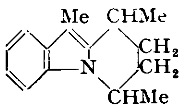


(II.)

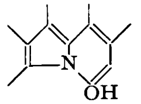


(III).

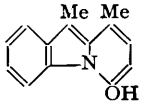
Condensation of indole with acetonylacetone in alcoholic hydrogen chloride gives a crystalline product which does not appear to be homogeneous and of which the analytical figures are not decisive. The results suggest the formula, $C_{14}H_{15}ON$, and contamination by a compound less rich in oxygen (possibly with none) to an extent equivalent to loss of $0{\cdot}1H_2O$ from the said molecule. Provisionally the main product may be represented as (VIII) because its Ehrlich reaction discloses a free 2-position in the indole nucleus.



(IV.)

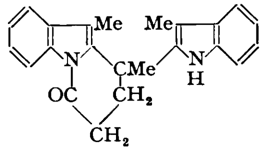


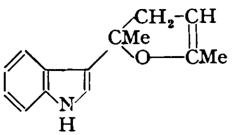
(V.)



(VI.)

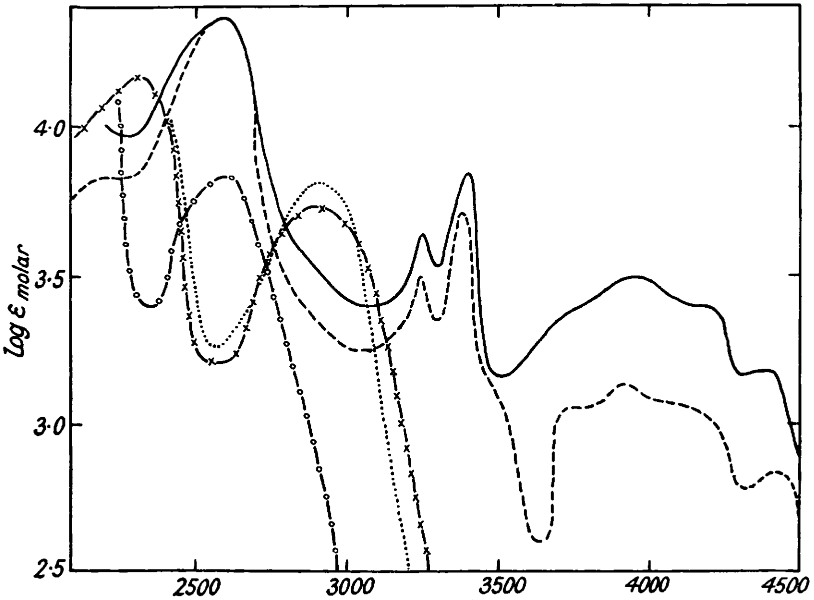
(VII.)





(VIII.)

Ultra-violet absorption spectra.



———— 1 : 5 : 8-*Trimethyl*-2 : 3-*benzpyrrocoline.*
- - - - - - - - 5 : 8-*Dimethyl*-1-*ethyl*-2 : 3-*benzpyrrocoline.*
—x—x—x— 1 : 5 : 8-*Trimethyl*-5 : 6 : 7 : 8-*tetrahydro*-2 : 3-*benzpyrrocoline.*
. . . . 9-*Ethyl*-1 : 2 : 3 : 4-*tetrahydrocarbazole.**
—o—o—o— 11-*Methyl*-1 : 2 : 3 : 4-*tetrahydrocarbazolenine.**

When indole was found to give an unexpected product we decided to attempt the use of ethyl indole-3-carboxylate but this investigation was delayed and postponed by the erroneous claims of Mentzer (*Compt. rend.*, 1946, **222**, 1176) which have been refuted by G. F. Smith (*J.*, 1950, 1637). (We read this communication on the day of writing the manuscript of the present paper.) Our observations on the condensation of ethyl formylchloroacetate and *p*-toluidine confirm in all particulars the findings of Smith.

The new method of formation of benzpyrrocolines may well be of interest in the synthetical approach to the strychnine skeleton. Thus condensation of *N*-acetyltryptamine and acetonylacetone furnishes a good yield of 1-2′-acetamidoethyl-5 : 8-dimethyl-2 : 3-benzpyrrocoline (IX), the properties of which are closely similar to those of (II).

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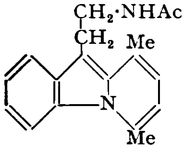
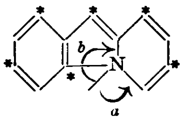
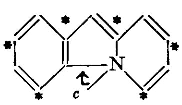
* From Grammaticakis, *Compt. rend.*, 1940, **210**, 569.

The benzpyrrocoline salts are quite colourless (visible region) and non-fluorescent, and hence the yellow colour and green fluorescence of the bases are probably the result of some activity of the unshared electrons of the nitrogen atom. Electronic displacements which include an increased sharing of covalency electrons between the nitrogen and adjacent carbon atoms could distribute some unshared electron value over all the ring-carbon atoms of the system. In (II) and (IX) the displacements (*a*), (*b*), and (*c*) can be included in hetero-enoid conjugations (X) which may bring an unshared electron value to the positions marked with an asterisk.



(IX.)





(X.)

On current theories of light absorption and fluorescence this implication of the structure is consistent with the optical properties of the substance. The probability of finding a potential bonding electron at any one position in the rings at any instant must, however, be of a low order because the benzpyrrocolines exhibit no significant reactivity such as is characteristic of dialkylanilines, pyrrole, and indole. It appears that the unshared electron value is well distributed (statically or dynamically) over one, or both, of the groups of positions shown in (X) and for this reason the reaction-initiating level of electron availability is not reached.

The relation of trimethylbenzpyrrocoline to its salts is of a very unusual kind. It can be seen from the preceding discussion that the cation formed by union of a proton with the nitrogen will possess stability factors independent of those in the base. HB^+ can, for example, be a true benzene and this nucleus is conjugated with a hexatriene. It is therefore conceivable that the benzpyrrocolines can form stable salts as the result of a transformation of the whole system and in spite of the fact that there is a low unshared electron value at the nitrogen atom of the base.

The benzpyrrocolines are in fact *pseudo*-bases in the sense that union with a proton brings about profound changes in the valency-electron systems of the rest of the molecule. The benzpyrrocolines are very weak bases which yield the salts of moderately strong bases. When the latter are liberated, electronic displacements very rapidly re-establish the original position.

Perhaps the term " pseudomeric " may suitably describe this type of base in which the electronic constitution of B is different from that of HB^+.

It should be pointed out that the phenomenon is widespread in the hetero-enoid bases; for example, aniline is pseudomeric, as shown by a comparison of chemical reactivity and absorption spectra of the base and its salts. But in the benzpyrrocolines the pseudomeric character can be recognised by means of simple experiments (see below) made possible by the optical properties of the bases, and probably by the manifestation of the valency isomerism in B to an extreme degree.

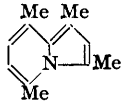
The amide group in (IX) proved very resistant to acid hydrolysis and we have not yet obtained the corresponding amine in substance. Solutions probably containing it are yellow at a lower pH than are those of (IX), the turning point of which is between pH 5 and pH 5·5. This was to be expected on account of the enfeebled strength of the weaker centre in a di-acid base.

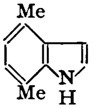
Condensation of Pyrroles with Acetonylacetone.—An attempted reduction of 2 : 5-dimethylpyrrole with zinc and acetic acid led to the formation of a base, $C_{12}H_{17}N$ (Zanetti and Cimatti, *Ber.*, 1897, **30**, 1588). This was confirmed by Plancher (*Ber.*, 1902, **35**, 2606; Plancher and Ciusa, *Atti R. Accad. Lincei*, 1902, [v], **11**, ii, 210; *idem, ibid.*, 1906, [v], **15**, ii, 453) who postulated hydrolysis to acetonylacetone followed by condensation with another molecule of the dimethylpyrrole, and lastly reduction (2H) of the product. The Italian chemists regard this base as *xx*-dihydrotetramethylindolenine, but a dihydrotetramethylpyrrocoline structure is also possible. However, Allen, Young, and Gilbert (*J. Org. Chem.*, 1937, **2**, 235) have shown, for some cases at least, that indole formation from pyrroles does not proceed by preliminary hydrolysis and later condensation, but rather by dimerisation and later loss of ammonia.

The constitution of the above-mentioned base, $C_{12}H_{17}N$, and similar substances from other pyrroles, is obscure from more than one point of view.

Nevertheless, in the case of the condensation of 2 : 4-dimethylpyrrole with acetonylacetone (cf. Plancher and Ciusa, *loc. cit.*), the close formal analogy with the skatole reaction persuades us that the product cannot be represented by any of the formulæ hitherto considered, but is 1 : 3 : 5 : 8-tetramethylpyrrocoline (XI).

(XI.)





(XII.)

It should be noted that pyrrole and acetonylacetone condense with formation of 4 : 7-dimethylindole (XII) (Plancher, 1902, *loc. cit.*; Plancher and Caravaggi, *Atti R. Accad. Lincei*, 1905, [v], **14**, i, 157). When the 3-position is free this is the natural result although it is conceivable that a pyrrocoline could be first produced and then rearranged. The contrast with the behaviour of indole is evidently due to the well known facts that pyrrole is attacked first in the 2-position, and indole first in the 3-position.

EXPERIMENTAL.

1 : 5 : 8-*Trimethyl*-2 : 3-*benzpyrrocoline* (II).—A solution of skatole (1 g.) and acetonylacetone (2 g.) in alcohol (20 c.c.) was saturated with hydrogen chloride, with cooling, and kept for 12 hours. In later experiments it was found that the reaction was completed in the time needed for saturation of the solutions. No precipitation occurred on dilution of the mixture with water and the solution was basified with sodium hydroxide. The solid was collected and washed with cold alcohol (3 × 5 c.c.).

1 : 5 : 8-*Trimethyl*-2 : 3-*benzpyrrocoline* crystallised from methanol or light petroleum (b. p. 60—80°) as yellow prisms, m. p. 134° (0·5 g.) (Found : C, 85·6; H, 7·2%). As this analysis was not very satisfactory the substance was adsorbed on alumina from light petroleum solution and eluted with the same solvent (b. p. 60—80°). After crytallisation from methanol the m. p. was still 134° [Found : C, 85·7; H, 7·2%; *M* (cryoscopic in camphor), 194. $C_{15}H_{15}N$ requires C, 86·1; H, 7·2%; *M*, 209]. In the later experiments a 47% yield was obtained after one crystallisation from ethanol and another from light petroleum. When a small quantity is heated in a test-tube a sublimate and distillate of unchanged substance are obtained and there is only a trace of brown non-volatile residue. When kept in the air for a long period the crystals become green.

The solutions of this substance in neutral organic solvents are yellow and exhibit a fine, slightly blue-tinged, green fluorescence. There is a striking resemblance to the colour and fluorescence shown by 4-ketotetrahydroquinoline and similar cyclic amino-ketones (tetramethyleneindoxyl, *iso*quinamine, etc.) in alcoholic solution. Since the common factors are the benzene ring and the nitrogen atom it must be concluded that these elements of the structure are in a like condition in the two series. However, the benzpyrrocolines exhibit their colour and fluorescence in benzene and in ethereal solution, whereas the colourless solutions of the keto-imines in benzene fluoresce violet.

Trimethylbenzpyrrocoline does not dissolve in cold 1% hydrochloric acid but slowly does so when heated, and the solution is quite colourless and remains so on cooling or on dilution. Addition of dilute hydrochloric acid to an alcoholic solution produces immediate decolorisation and salt-formation. On the other hand 1% hydrochloric acid does not extract the base from an ethereal solution, and ether does not extract the base from its solution in 1% hydrochloric acid. Thus according to the way in which the mixture is prepared we can achieve two entirely different results. In the one case the base is in the ethereal and in the other it is in the aqueous layer. A cold solution in glacial acetic acid is yellow and fluorescent but it becomes colourless and non-fluorescent on the addition of water.

This trimethylbenzpyrrocoline shows no indole reactions (*e.g.*, negative Ehrlich test) and does not couple with diazobenzenesulphonic acid. With *p*-nitrobenzenediazonium acetate in aqueous alcohol it slowly yields a yellow-brown solution which becomes blood-red on the addition of sodium hydroxide.

The *perchlorate* crystallised from methanol in dense, colourless rhombs, m. p. 196—197° (Found : C, 58·1; H, 5·1. $C_{15}H_{15}N,HClO_4$ requires C, 58·1; H, 5·2%).

5 : 6 : 7 : 8-*Tetrahydro*-1 : 5 : 8-*trimethyl*-2 : 3-*benzpyrrocoline* (IV).—Trimethylbenzpyrrocoline (0·8 g.) was hydrogenated in methanolic solution in the presence of palladised strontium carbonate (0·1 g. of 2½%) (an equal amount of Raney nickel was also used and with the same result). The reduction was slow at the room temperature and pressure, and took about 24 hours. The product was isolated by distillation, and 5 : 6 : 7 : 8-*tetrahydro*-1 : 5 : 8-*trimethyl*-2 : 3-*benzpyrrocoline* obtained as a colourless oil (0·5 g.), from a bath at 120°/0·08 mm. This solidified on trituration with methanol and crystallised from methanol as colourless prisms, m. p. 76—80° (Found : C, 84·4; H, 9·0; N, 6·3, 6·7. $C_{15}H_{19}N$ requires C, 84·5; H, 8·9; N, 6·6%). The m. p. indicates that this specimen may be contaminated by a stereoisomeride.

In all respects this substance exhibits the behaviour of a 2 : 3-disubstituted (or 1 : 2 : 3-trisubstituted) indole. It is a very weak base, precipitated from its solution in acetic acid on the addition of water, insoluble in dilute hydrochloric acid, soluble in cold concentrated hydrochloric acid or 60% perchloric acid. It forms a red picrate. No reaction with Ehrlich's reagent is observed in the cold; when heated the solution becomes green, then yellow on cooling, and the alternation can be often repeated. The ferric reaction is negative and no coupling with diazobenzenesulphonic acid was observed. When the substance is heated with vanillin and concentrated hydrochloric acid a weak red colour is developed.

*Dodecahydro-*1 : 5 : 8-*trimethyl-*2 : 3-*benzpyrrocoline.*—Trimethylbenzpyrrocoline (10 g.) in acetic acid (20 c.c.) was hydrogenated at the room temperature and pressure after the addition of platinum oxide (0·1 g.); the slow process was completed in 48 hours. The filtered solution was evaporated under diminished pressure and the residue mixed with aqueous sodium hydroxide. The oily base was taken up in ether, and the solution dried ($MgSO_4$) and distilled. *Dodecahydro-*1 : 5 : 8-*trimethyl-*2 : 3-*benzpyrrocoline* was collected as a colourless oil (0·6 g.), b. p. 116°/0·65 mm. (Found : C, 81·7; H, 12·5. $C_{15}H_{27}N$ requires C, 81·5; H, 12·2%). This is certainly a mixture of stereoisomerides (6 asymmetric carbon atoms). These are strong bases readily soluble in dilute acids and behaving as *tert.*-bases towards nitrous acid and acetic anhydride. No colour reactions with ferric salts, diazobenzenesulphonic acid, or Ehrlich's reagent could be observed.

The *picrate*(*s*) crystallised from methanol as yellow rhombs, m. p. 161—166° (Found : C, 56·0; H, 6·8; N, 12·4. $C_{21}H_{30}O_7N_4$ requires C, 56·0; H, 6·7; N, 12·4%).

The production of *tert.*-bases on perhydrogenation is important evidence of the benzpyrrocoline constitution of the starting product.

1-*Ethyl-*5 : 8-*dimethyl-*2 : 3-*benzpyrrocoline.*—The crude product from 3-ethylindole and acetonylacetone, after basification, was triturated with methanol and the yellow solid was crystallised twice from aqueous ethanol, and then from methanol. 1-*Ethyl-*5 : 8-*dimethyl-*2 : 3-*benzpyrrocoline* crystallised in golden flakes, m. p. 74° (Found : C, 85·8, 86·2; H, 7·7, 7·8; N, 6·4. $C_{16}H_{17}N$ requires C, 86·1; H, 7·6; N, 6·3%). The crystals became brown when kept in air, and all the properties of the substance closely resembled those of the lower homologue. The *perchlorate* crystallised from methanol in colourless prisms, decomp. 205–215° (Found : C, 59·4; H, 5·4. $C_{16}H_{17}N,HClO_4$ requires C, 59·4; H, 5·6%).

1-2′-*Acetamidoethyl-*5 : 8-*dimethyl-*2 : 3-*benzpyrrocoline* (IX).—A cooled solution of *N*-acetyltryptamine (10 g.) and acetonylacetone (2·0 g.) in alcohol (10 c.c.) was saturated with hydrogen chloride and kept for 15 minutes. The solution was diluted with water (10 c.c.) and basified with 2N-sodium hydroxide, and, after an hour at 0°, the product was collected. 1-2′-*Acetamidoethyl-*5 : 8-*dimethyl-*2 : 3-*benzpyrrocoline* (1·1 g.) was obtained as clusters of slender yellow needles, m. p. 190—191° (Found : C, 76·9; H, 7·4; N, 9·8. $C_{18}H_{20}ON_2$ requires C, 77·1; H, 7·1; N, 10·0%). The yellow colour and green fluorescence, as well as the behaviour towards acids, of this substance are like those of trimethylbenzpyrrocoline. The colourless solution in concentrated hydrochloric acid was kept for several days and the unchanged base was recovered. Hydrolysis occurs very slowly on boiling. The *perchlorate*, long, colourless prisms from methanol, had m. p. 202° (decomp.) (Found: C, 56·4; H, 5·7; N, 7·9. $C_{18}H_{20}ON_2,HClO_4$ requires C, 56·8; H, 5·5; N, 7·4%).

Condensation of Indole with Acetonylacetone.—(*a*) A mixture of indole (1 g.), acetonylacetone (2 g.), zinc acetate (4 g.), and acetic acid (50 c.c.; 90%) was refluxed for 44 hours. The product was eventually twice crystallised from light petroleum (b. p. 80—100°) and obtained as colourless prisms, m. p. 80—86° (0·5 g.) (Found : C, 79·7; H, 7·3; N, 5·1%). The last crystallisation did not alter the m. p.

(*b*) A mixture of indole (1 g.), acetonylacetone (2 g.), alcohol (2 c.c.), and concentrated hydrochloric acid (1·5 c.c.) was heated on the steam-bath for 15 minutes. On cooling, long colourless, prisms separated and the substance was recrystallised from light petroleum (b. p. 60—80°) and obtained as colourless prisms, m. p. 85—90° (Found : C, 80·8; H, 7·0; N, 5·9%). Fractional crystallisation gave materials of m. p. 76—84° and m. p. 88—90° of which the Ehrlich reactions were somewhat different. The former was purple in the cold and magenta when hot; the latter was blue-violet in the cold and violet when hot. A possible interpretation of the analytical results has been mentioned in the Introduction.

Under conditions similar to (*b*), skatole gave no isolable products with acetylacetone or heptane-2 : 6-dione, nor could 2-methylindole be condensed with acetonylacetone to a definite product.

Condensation of Skatole with Lævulic Acid.—When skatole was condensed with an excess of lævulic acid in the presence of hydrogen chloride products were obtained which exhibited a yellow colour and green fluorescence in alcoholic potassium hydroxide solution. A cooled solution of skatole (1 g.) and lævulic acid (1 g.) in alcohol (20 c.c.) was saturated with hydrogen chloride, kept for 12 hours, and then diluted and neutralised with sodium hydroxide. A benzene–light petroleum solution of the oily product was passed through an alumina column which was washed until the product was eluted. The substance crystallised from ethanol as dense, colourless, hexagonal prisms, m. p. 220° (0·2 g.) [Found: C, 80·6, 80·4; H, 6·7, 6·5; N, 7·9, 8·4; active H, 0·64%; *M* (cryoscopic in camphor), 288. $C_{23}H_{22}ON_2$ requires C, 80·7; H, 6·5; N, 8·2; 2H, 0·59%; *M*, 342]. The substance does not exhibit indole colour reactions and is probably 5-*keto-*8-(3-*methyl-*2-*indolyl*)-1 : 8-*dimethyl-*5 : 6 : 7 : 8-*tetrahydro-*2 : 3-*benzpyrrocoline* (VII).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

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