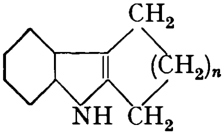
224. *Addition Reactions of the Indole Nucleus.*

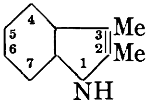
By S. G. P. Plant and (Miss) M. L. Tomlinson.

Earlier investigations (Perkin and Plant, J., 1923, **123**, 676, 3242; Plant, J., 1929, 2493; Plant and Tomlinson, J., 1931, 3324; this vol., p. 298) have shown that the indole nucleus contained in derivatives of tetrahydrocarbazole (I; $n = 2$) and dihydropentindole (I; $n = 1$) is capable of undergoing several interesting addition reactions. By the action of nitric acid, OH and NO_2, or in some cases 2OH, can be attached to the double linkage shown in (I), while bromine and chlorine readily combine additively at the same point to give substances which easily undergo various secondary transformations. It has been demonstrated, however, that the tendency to form these addition compounds is enormously diminished when the indole nucleus is contained in more complex polycyclic systems containing four rings fused together (Oakeshott and Plant, J., 1928, 1840; Bryant and Plant, J., 1931, 93; Plant and Tomlinson, J., 1932, 2192), and the present work was undertaken in order to discover how far the processes can be realised in the simple indoles. To avoid complications caused by substitution in the 3-position, 2 : 3-dimethylindole (II) and its 1-*acetyl*- and 1-*benzoyl*-derivatives were selected for the purpose.

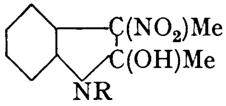
Nothing crystalline was obtained during attempts to nitrate 2 : 3-dimethylindole in acetic acid, but in concentrated sulphuric acid 5-*nitro*-2 : 3-*dimethylindole* was formed. The constitution of the latter was established by its synthesis from the *p*-nitrophenylhydrazone of methyl ethyl ketone by the Fischer reaction. The only substance isolated from the interaction of nitric acid and 1-acetyl-2 : 3-dimethylindole in acetic acid was a simple substitution *product*. This compound was hydrolysed to the corresponding 4(or 6)-*nitro*-2 : 3-*dimethylindole*, which was also obtained by application of Fischer's reaction to the *m*-nitrophenylhydrazone of methyl ethyl ketone, although the latter process could yield three other isomeric products.



(I.)



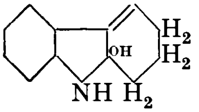
(II.)



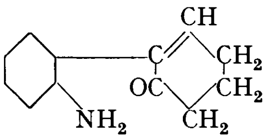
(III.)

The nitration of 1-benzoyl-2 : 3-dimethylindole, however, was found readily to result in the formation of an addition *compound* (III ; R = Bz) analogous to those obtained in the tetrahydrocarbazole and dihydropentindole series ; on treatment with aqueous alkali this yielded (III ; R = H).

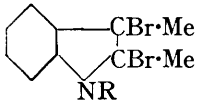
Bromination of tetrahydrocarbazole in acetic acid and subsequent treatment with an excess of aqueous ammonia leads to a hydroxy-compound (IV), which, from the fact that it can be diazotised, must react as (V) in acid solution (this vol., p. 298). Similar treatment of 2 : 3-dimethylindole yields a compound, $C_{10}H_{11}ON$, undoubtedly formed by the primary addition of bromine, the loss of a molecule of hydrogen bromide from the resulting 2 : 3-dibromide (VI ; R = H), and the ultimate replacement of the remaining bromine by hydroxyl.



(IV.)

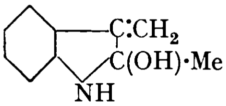


(V.)

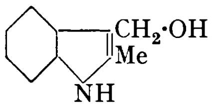


(VI.)

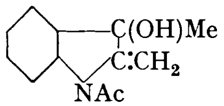
In view of the basic nature of (VI ; R = H) the bromine in the 3-position will be the more readily eliminated, and the hydroxy-compound would be expected to possess the structure (VII), analogous to (IV). Unlike (IV), however, this substance is insoluble in aqueous acids and cannot be diazotised ; it is extremely probable, therefore, that it is 3-*hydroxymethyl*-2-*methylindole* (VIII), the hydroxyl group in (VII) having migrated with the restoration of the indole nucleus.



(VII.)

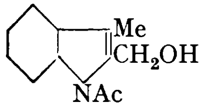


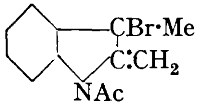
(VIII.)

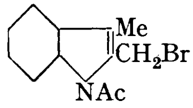


(IX.)

The bromination of 1-acetyl-2 : 3-dimethylindole by a similar procedure also gave a monohydroxy-compound, but this yielded, on hydrolysis, a substance isomeric with (VIII). These results are readily explained by the fact that the primary dibromide (VI ; R = Ac) is not in this case basic, so that the bromine in the 2-position is eliminated, while the replacement of the second bromine by hydroxyl leads to the compound (IX). It is extremely probable, however, that the substance actually isolated is 1-*acetyl*-2-*hydroxymethyl*-3-*methylindole* (X), formed by the ultimate migration of the hydroxyl group as before. The course of this reaction recalls the bromination of 9-benzoyl- and 9-cinnamoyl-tetrahydrocarbazole (J., 1931, 3324). When 1-acetyl-2 : 3-dimethylindole was treated with bromine in a very small amount of acetic acid, a compound, $C_{12}H_{12}ONBr$, separated. It is evident that this is represented by one of the formulæ (XI) and (XII) and is an intermediate product, derived as mentioned above, in the formation of (X). This view was confirmed by the facile conversion of the compound into (X) on replacement of its bromine by hydroxyl. Attempts to obtain crystalline products from the bromination of 1-benzoyl-2 : 3-dimethylindole


(X.)


(XI.)


(XII.)

have been unsuccessful, but the results described above are sufficient to demonstrate the ability of the simple indole nucleus to exhibit the addition reactions observed in the more complex derivatives.

The reaction between nitric acid and certain 1-acyl-2 : 3-diphenylindoles has previously been shown to be too complex for the purpose of examining the addition reactions of the simple indole nucleus (Fennell and Plant, J., 1932, 2872). The interesting observation has now been made that the bromination of 1-acetyl-, 1-benzoyl-, 1-carbethoxy-, and 1-cinnamoyl-2 : 3-diphenylindole leads in every case to a simple bromo-derivative in good yield. The position of the bromine was established by applying Fischer's reaction to the *m*-bromophenylhydrazone of phenyl benzyl ketone, two isomeric bromo-compounds being obtained. In accordance with the procedure adopted in analogous cases, these have been named 4(or 6)-bromo- and 6(or 4)-bromo-2 : 3-diphenylindole, and the former, on acylation, has been converted into a series of compounds which proved to be identical with the substitution products mentioned above. It is therefore obvious that the bromine in these products has entered a position which is *meta* with respect to the >N-acyl group. The bromination of 2 : 3-diphenylindole itself yielded a product which, although it was not crystallised, consisted essentially of 4(or 6)-bromo-2 : 3-diphenylindole, since it was converted by the action of ethyl chloroformate and alkali into the 1-carbethoxy-derivative of the latter. The interesting fact emerges that, while the bromination of 2 : 3-dimethylindole and its acetyl derivative has yielded exclusively substances which have resulted from the primary addition of bromine at the 2 : 3-position, no evidence of the formation of analogous addition products has been obtained in the case of the corresponding 2 : 3-diphenyl compounds. This enormous reduction in the reactivity of the double linkage in 2 : 3-diphenylindole could be explained by the steric effect of the phenyl radicals, but it is very much more probable that it is due to conjugation of the double linkage with the two phenyl groups.

In view of the above results an obvious interest attaches to the reactions of 2-phenyl-3-methylindole. Bromination of this substance in acetic acid leads to the immediate separation of a primary product which soon goes into solution, from which 4(or 6)-*bromo*-2-*phenyl*-3-*methylindole* ultimately separates. The intermediate substance liberated iodine from aqueous potassium iodide and was evidently a loose addition compound of the type frequently met in the bromination of, for example, certain carbonyl compounds; its behaviour was incompatible with its formulation as a dibromide analogous to (VI). The constitution of the bromo-derivative was established by its synthesis from the *m*-bromophenylhydrazone of propiophenone; of the two products theoretically possible in the latter process only one, named the 4(or 6)-bromo-compound, has been isolated. The failure of attempts to acylate 2-phenyl-3-methylindole has prevented a further extension of this investigation, but it is already obvious that the reactivity of the double linkage in the 2 : 3-position is again diminished.

EXPERIMENTAL.

Nitration of 2 : 3-*Dimethylindole*.—When pulverised potassium nitrate (1·21 g.) was added gradually to a solution of this compound (2 g.) in concentrated sulphuric acid (14 c.c.), the temperature being kept below − 3°, and the whole then poured on ice, 5-*nitro*-2 : 3-*dimethylindole*, orange prisms, m. p. 188°, from alcohol, was precipitated (Found : N, 14·9. $C_{10}H_{10}O_2N_2$ requires N, 14·7%).

The *p*-nitrophenylhydrazone of methyl ethyl ketone was refluxed for 8 hours with acetic acid–concentrated hydrochloric acid (equal volumes), the whole was poured into water, and the precipitate extracted with boiling petroleum (b. p. 100—120°). The solid which separated from the latter on cooling was recrystallised from alcohol, and, on standing, 5-nitro-2 : 3-dimethylindole, orange prisms, m. p. 188—189°, identical (mixed m. p.) with the above product, was obtained. This nitro-compound, on rapid crystallisation from alcohol, can be obtained in yellow needles which gradually change to orange prisms.

Nitration of 1-*Acetyl*-2 : 3-*dimethylindole*.—When a solution of 2 : 3-dimethylindole in acetic anhydride containing a trace of *d*-camphorsulphonic acid was refluxed for 7 hours and then distilled under reduced pressure, 1-*acetyl*-2 : 3-*dimethylindole*, colourless needles, m. p. 74°, from alcohol, was collected at 185—210°/13 mm. (Found : N, 7·9. $C_{12}H_{13}ON$ requires N, 7·5%). After a solution of the latter (4 g.) in a little acetic acid had been treated gradually with nitric acid (1·8 g., *d* 1·4) and left for several hours, 4(or 6)-*nitro*-1-*acetyl*-2 : 3-*dimethylindole*, pale yellow needles, m. p. 170°, from alcohol, separated (Found : C, 62·4; H, 5·1. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2%). 4(or 6)-*Nitro*-2 : 3-*dimethylindole*, orange prisms, m. p. 142°, from alcohol, was obtained when a solution of the latter in aqueous-alcoholic potash was refluxed for ½ hour and then diluted with water (Found : N, 14·9%).

The *m*-nitrophenylhydrazone of methyl ethyl ketone (prepared by heating a mixture of equivalent quantities of the hydrazine and ketone on the steam-bath), red needles, m. p. 98°, from alcohol, was refluxed for 5 hours with concentrated hydrochloric acid–acetic acid (equal volumes), and the whole was then poured into water. When the solid which separated was crystallised from petroleum (b. p. 100—120°), a mixture of products was obtained. This was recrystallised from benzene, and the substance remaining in the mother-liquor was then further recrystallised from petroleum and aqueous alcohol; 4(or 6)-nitro-2 : 3-dimethylindole, orange prisms, m. p. 142°, identical (mixed m. p.) with the product described above, was isolated.

Nitration of 1-*Benzoyl*-2 : 3-*dimethylindole*.—A solution of magnesium (2·5 g.) in dry ether containing methyl iodide (15 g.) was treated gradually with 2 : 3-dimethylindole (10 g.), and, after the addition of benzoyl chloride (10 g.) with shaking and standing, the whole was diluted with ice and dilute hydrochloric acid. When the ethereal layer had been dried (calcium chloride) and evaporated, the residue, on distillation, yielded 1-*benzoyl*-2 : 3-*dimethylindole*, yellow prisms, m. p. 98°, from alcohol, at 280—310°/11 mm. (Found : N, 5·8. $C_{17}H_{15}ON$ requires N, 5·6%).

3-*Nitro*-2-*hydroxy*-1-*benzoyl*-2 : 3-*dimethyl*-2 : 3-*dihydroindole*, colourless prisms, m. p. 125° (decomp.), from petroleum (b. p. 100—120°), gradually separated when nitric acid (1·36 g., *d* 1·4) was added to the benzoyl compound (4 g.) in acetic acid (Found : C, 65·6; H, 5·3. $C_{17}H_{16}O_4N_2$ requires C, 65·4; H, 5·1%). This product was found to dissolve in cold potassium hydroxide solution (15%); the solution was acidified with acetic acid after 2 mins., and ether then extracted 3-*nitro*-2-*hydroxy*-2 : 3-*dimethyl*-2 : 3-*dihydroindole*, colourless prisms, m. p. 103°, from benzene–petroleum (Found : C, 57·6; H, 5·8. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8%). The latter dissolved in sodium hydroxide, but was insoluble in dilute hydrochloric acid and could not be diazotised.

Bromination of 2 : 3-*Dimethylindole*.—This compound, in small quantities, was treated in acetic acid with an equimolecular amount of bromine, and the whole was immediately diluted with water. After the addition of ice, the mixture was made alkaline with ammonia, and the product extracted with ether. The ethereal solution was dried (sodium sulphate) and evaporated, and, after the residue had been purified by crystallisation from benzene, benzene–petroleum, and aqueous-alcoholic potash, 3-*hydroxymethyl*-2-*methylindole*, colourless plates, m. p. 225°, from aqueous alcohol, was obtained (Found : C, 74·5; H, 6·8. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8%). It was unchanged by boiling aqueous-alcoholic potash and was insoluble in dilute hydrochloric acid. A product, m. p. 196°, described by Sanna (*Gazzetta*, **1931**, **61**, 68) may be a less pure form of this substance, which is particularly difficult to purify.

Bromination of 1-*Acetyl*-2 : 3-*dimethylindole*.—When the acetyl compound was brominated by a procedure similar to that used for 2 : 3-dimethylindole, a sticky product separated from the alkaline solution. On crystallisation from petroleum (b. p. 40—60°), this yielded 1-*acetyl*-2-*hydroxymethyl*-3-*methylindole* in colourless needles, m. p. 90—91° (Found : C, 70·7; H, 6·4. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4%). When the latter was refluxed with aqueous-alcoholic potash for ½ hour, 2-*hydroxymethyl*-3-*methylindole*, colourless needles, m. p. 122°, from benzene, was obtained; it separated slowly on dilution with water and the subsequent addition of acetic acid till just acid (Found : C, 74·3; H, 7·0%).

When 1-acetyl-2 : 3-dimethylindole was treated with an equimolecular amount of bromine in the minimum quantity of acetic acid, the solution developed a deep purple colour, but, on rubbing, 1-*acetyl*-2-*bromomethyl*-3-*methylindole*, colourless prisms, m. p. 92—94°, from petroleum (b. p. 60—80°), separated (Found : C, 53·3; H, 4·6; Br, 29·2. $C_{12}H_{12}ONBr$ requires C, 54·1;

H, 4·5; Br, 30·1%). Nothing crystalline could be isolated from the product obtained by boiling this substance with aqueous-alcoholic or dilute aqueous potassium hydroxide, but when its solution in ether was shaken with water and an excess of freshly precipitated silver oxide, and then evaporated, 1-acetyl-2-hydroxymethyl-3-methylindole, identical (mixed m. p.) with the substance described above, remained; it was purified by crystallisation from petroleum (b. p. 60—80°). The same transformation was effected by dissolving the bromo-compound in acetic acid, diluting with water, and making alkaline with ammonia.

Bromination of 2 : 3-*Diphenylindole.*—The 2 : 3-diphenylindole and its various 1-acyl derivatives used in these experiments were prepared by the methods of Fennell and Plant (*loc. cit.*). 2 : 3-Diphenylindole in acetic acid was treated with an equimolecular amount of bromine and the solvent was removed by evaporation under reduced pressure. The residue, which could not be crystallised, was shaken in acetone with potassium hydroxide solution (66%) and ethyl chloroformate, and the product, isolated by dilution with water, yielded ethyl 4(or 6)-bromo-2 : 3-diphenylindole-1-carboxylate, m. p. 110° (identified by mixed m. p. with the synthetical compound described below), on being thrice recrystallised from alcohol.

4(or 6)-*Bromo*-1-*acetyl*-2 : 3-*diphenylindole* separated slowly after bromine (in equimolecular amount) had been added to 1-acetyl-2 : 3-diphenylindole in acetic acid; it crystallised from methyl alcohol as a mixture of colourless needles and prisms, but, on keeping, the latter, m. p. 141—142°, alone remained (Found, after heating for some time at 100° : C, 67·7; H, 4·1. $C_{22}H_{16}ONBr$ requires C, 67·7; H, 4·1%). The same product was obtained by the bromination of 1-acetyl-2 : 3-diphenylindole in carbon disulphide; it was isolated by evaporation of the solvent, and purified by crystallisation from alcohol.

Phenyl benzyl ketone (4·8 g.) and *m*-bromophenylhydrazine (4·2 g.) were heated together at 140° for 15 mins., and the resulting hydrazone, yellow needles, m. p. 102°, from alcohol, was boiled for 15 mins. with alcoholic hydrogen chloride. The product, which was precipitated with water and extracted with ether, did not crystallise and was therefore shaken in acetone with aqueous potassium hydroxide (66%) and acetyl chloride. When the precipitate obtained by the addition of water was crystallised from much alcohol, 6(or 4)-*bromo*-1-*acetyl*-2 : 3-*diphenylindole*, colourless needles, m. p. 223—225°, after further crystallisation from acetic acid, separated (Found : N, 3·4. $C_{22}H_{16}ONBr$ requires N, 3·6%). The alcoholic mother-liquor yielded, on being concentrated to small bulk, 4(or 6)-bromo-1-acetyl-2 : 3-diphenylindole, colourless prisms, m. p. 141° (after recrystallisation from methyl alcohol), identical (mixed m. p.) with the substance described above. 4(or 6)-Bromo-2 : 3-diphenylindole, colourless needles, m. p. 116—117°, from petroleum (b. p. 40—60°), was obtained when its acetyl derivative was boiled for ½ hour with aqueous-alcoholic potash; it was isolated by dilution with water.

4(or 6)-*Bromo*-1-*benzoyl*-2 : 3-*diphenylindole*, colourless needles, m. p. 174—176°, from acetic acid (Found : N, 3·0. $C_{27}H_{18}ONBr$ requires N, 3·1%), separated slowly when 1-benzoyl-2 : 3-diphenylindole was brominated in acetic acid. The same compound (mixed m. p.) was obtained when 4(or 6)-bromo-2 : 3-diphenylindole was shaken in acetone with aqueous potassium hydroxide (66%) and benzoyl chloride; it was isolated by dilution with water.

Ethyl 4(or 6)-*bromo*-2 : 3-*diphenylindole*-1-*carboxylate*, colourless needles, m. p. 110°, from alcohol (Found : N, 3·2. $C_{23}H_{18}O_2NBr$ requires N, 3·3%), and 4(or 6)-*bromo*-1-*cinnamoyl*-2 : 3-*diphenylindole*, yellow plates, m. p. 176°, from alcohol (Found : N, 2·9. $C_{29}H_{20}ONBr$ requires N, 2·9%), were obtained by processes similar to both those used for the above benzoyl derivative.

The *p*-bromophenylhydrazone of phenyl benzyl ketone, colourless needles, m. p. 136°, from alcohol (compare Bodforss, *Ber.*, 1925, **58**, 775), was prepared like the *m*-compound, and, when boiled with alcoholic hydrogen chloride as before, gave 5-bromo-2 : 3-diphenylindole, pale brown plates, m. p. 148°, from acetic acid. The latter was converted into 5-*bromo*-1-*acetyl*-2 : 3-*diphenylindole*, colourless needles, m. p. 218°, from acetic acid, by shaking in acetone with aqueous potassium hydroxide (66%) and acetyl chloride (Found : N, 3·4%).

Bromination of 2-*Phenyl*-3-*methylindole.*—After a mixture of propiophenone (2 g.) and phenylhydrazine (1·5 g.) had been heated on the steam-bath for a short time and then refluxed for ½ hour with alcoholic hydrogen chloride, water precipitated 2-phenyl-3-methylindole, colourless plates, m. p. 91—92° (compare Collet, *Bull. Soc. chim.*, 1897, **17**, 74), from petroleum (b. p. 60—80°). When a solution of this compound in acetic acid was treated with an equimolecular amount of bromine, a yellow precipitate immediately formed, but this went into solution again after a short time. 4(or 6)-*Bromo*-2-*phenyl*-3-*methylindole*, colourless plates, m. p. 147°, from petroleum (b. p. 60—80°), then slowly separated (Found : C, 63·2; H, 4·2. $C_{15}H_{12}NBr$ requires C, 62·9; H, 4·2%). The primary yellow precipitate, even when prepared by the addition of a limited amount of bromine to avoid the presence of free halogen, readily liberated iodine from potassium iodide, and, when suspended in fresh acetic acid, gradually yielded the 4(or 6)-bromo-compound. The same bromo-compound (mixed m. p.) was prepared by a process similar to that given above for 2-phenyl-3-methylindole, but employing *m*-bromophenylhydrazine, while the use of *p*-bromophenylhydrazine led to 5-*bromo*-2-*phenyl*-3-*methylindole*, colourless plates, m. p. 141°, from petroleum (Found: N, 5·0. $C_{15}H_{12}NBr$ requires N, 4·9%).

THE DYSON PERRINS LABORATORY, OXFORD.

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