837. *Indoles derived from Aromatic Amines and 2-Hydroxy-ketones. The Synthesis of 7-Acetyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo(2′ : 3′-4 : 5)-indole.*

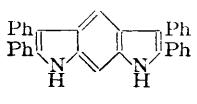
By N. A. Jones and Muriel L. Tomlinson.

The compound first obtained (Japp and Meldrum, *J.*, 1899, **75**, 1044) by condensation of benzoin with *m*-phenylenediamine has been proved to be 2 : 3 : 4′ : 5′-tetraphenylpyrrolo(2′ : 3′-4 : 5)indole and not its "linear" isomer, by synthesis of an acetyl derivative. Some tetrahydrocarbazoles and octahydroindolocarbazoles have been prepared from 2-hydroxy*cyclo*hexanone and aromatic amines.

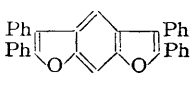
Japp and Meldrum (*J.*, 1899, **75**, 1044) prepared a tetraphenylpyrroloindole from *m*-phenylenediamine and benzoin, and Ruggli and Pettijean (*Helv. Chim. Acta*, 1936, **19**, 928) obtained the same substance from the bis-condensation product of deoxybenzoin and *m*-phenylenedihydrazine. Although syntheses of this kind generally afford compounds of "non-linear" structure, the latter authors assigned a "linear" structure (I) to Japp and Meldrum's compound by analogy with the tetraphenylfuranocoumarone (II) that Japp and Meldrum (*loc. cit.*, p. 1039) obtained from resorcinol and benzoin and from which Dischendorfer (*Monatsh.*, 1933, **62**, 69) obtained 4:6-dibenzoylresorcinol by oxidation and hydrolysis.

Japp and Meldrum's compound, unlike the corresponding methyl derivative (III; R = Me, R′ = H) now prepared from benzoin and 4-methyl-*m*-phenylenediamine, is very sparingly soluble in all common solvents and, although the very dilute methanol solution obtainable absorbs at wave-lengths similar to those observed for the methyl compound, establishment of the structure of the former by comparison of spectra was not satisfactory.

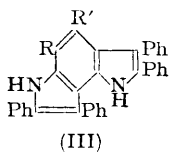
When, however, Japp and Meldrum's pyrroloindole was acetylated, a small quantity of 7-acetyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo(2′ : 3′-4 : 5)indole (III; R = Ac, R′ = H), identical (mixed m. p.) with an authentic specimen of that substance prepared by condensation of benzoin with 2 : 4-diaminoacetophenone, was obtained. The preparation of (III; R = Ac, R′ = H) in this way is unambiguous and must yield an "angular" product: Japp and Meldrum's compound must therefore be (III; R = R′ = H). Acetylation of 7-methyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo(2′ : 3′-4 : 5)indole yields a substance that must be 6-acetyl-7-methyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo(2′ : 3′-4 : 5)indole (III; R = Me, R′ = Ac) because it is stable to alkaline hydrolysis and it is unlikely that one of the four phenyl groups has been attacked.



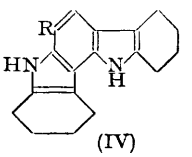
(I)



(II)



(III)



(IV)

While there are many examples in the literature of the preparation of diphenylindoles from aromatic amines and benzoin (*e.g.*, by Japp and Murray, *Ber.*, 1893, **26**, 2638; Fennell and Plant, *J.*, 1932, 2872; Ritchie, *J. Proc. Roy. Soc. N.S.W.*, 1946, **80**, 33), tetrahydrocarbazoles have not been prepared in a similar way using 1-hydroxy*cyclo*hexanone. It has now been shown that in many cases this reaction proceeds smoothly to give the expected product, frequently in good yield. It is interesting that, whereas *o*- and *p*-aminophenol give no tetrahydrohydroxycarbazole, *m*-aminophenol gives, in good yield, tetrahydro-7(or 5)-hydroxycarbazole, m. p. 163—164°, presumably identical with the substance, m. p. 164° (no analysis), described as obtained by heating *cyclo*hexanone and *m*-hydroxyphenylhydrazine with naphthalene-1 : 5-disulphonic acid (D.R.-P., 547,840; *Chem. Zentr.*, 1933, II, 622). *p*-Nitroaniline gives a substance $C_{12}H_{14}O_3N_2$ which must be either *p*-nitro-*N*-2-oxo*cyclo*hexylaniline or *N*-2-hydroxy*cyclo*hexylidene-*p*-nitroaniline. Cyclisation to the tetrahydrocarbazole did not occur even with zinc chloride or sulphuric acid.

5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-Octahydroindolo(3′ : 2′-1 : 2)carbazole (IV; R = H) was

originally prepared (Tomlinson, *J.*, 1951, 809) from bis*cyclo*hexanone *p*-phenylenedihydrazone but attempts to obtain (IV; R = Me) by an analogous method failed. The former has since been proved (Hall and Plant, *J.*, 1953, 116) to possess the "angular" structure first assigned to it on theoretical grounds. The original method used was unsuitable for the preparation of more than very small quantities of (IV; R = H) and the chemistry of this interesting compound has not therefore been investigated. Both (IV; R = H) and 5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-octahydro-3-methylindolo(3′ : 2′-1 : 2)carbazole (IV; R = Me) have now been obtained by condensation of 2-hydroxy*cyclo*hexanone with the appropriate diamine. The new method is far less laborious. It works best on a fairly small scale; yields are, however, somewhat variable. Experiments in which 2-chloro-*cyclo*hexanone was substituted for the hydroxy-compound have so far failed to produce indolocarbazole derivatives. *o*- and *p*-Phenylenediamines have not yielded octahydroindolocarbazoles with either chloro- or hydroxy-*cyclo*hexanone.

In view of the many interesting substances that have been obtained by nitrating and brominating tetrahydrocarbazole and its 9-acyl derivatives (*e.g.*, by Perkin and Plant, *J.*, 1923, 676; Plant and Tomlinson, *J.*, 1931, 3324; 1933, 995; 1950, 2127) and of the ready formation of tetrahydrocarbazolyl hydroperoxide which undergoes many reactions (Beer, McGrath, and Robertson, *J.*, 1950, 2118), the chemistry of octahydroindolocarbazoles calls for investigation. The preparation of *N*-acetyl derivatives has proved surprisingly difficult, and preliminary experiments on the bromination of (IV; R = H) have not yielded crystalline material. It appears that (IV; R = H) and (IV; R = Me) form hydroperoxides, the latter very rapidly. Their solutions darken in air, alcoholic solutions develop a green fluorescence, and benzene solutions, which liberate iodine from potassium iodide when fresh, soon deposit sparingly soluble amorphous material that does not oxidise potassium iodide.

Experimental

7-Methyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo(2′ : 3′-4 : 5)indole.—Concentrated hydrochloric acid (10 drops) was added to a mixture of 4-methyl-*m*-phenylenediamine (6·0 g.) and benzoin (22 g.) at 150° and after evolution of steam had subsided the temperature was raised to 200° during 30 min. Recrystallisation from ethyl acetate gave *7-methyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo-(2′ : 3′-4 : 5)indole* (17 g.) as colourless needles, m. p. 227—230°, containing solvent of crystallisation (Found: C, 83·6; H, 6·0; N, 4·7. $C_{35}H_{26}N_2,C_4H_8O_2$ requires C, 83·3; H, 6·0; N, 5·0%). Heating to constant weight at 160°/0·01 mm. gave the solvent-free *compound*, m. p. 234° (Found: C, 88·4; H, 5·6; N, 5·6. $C_{35}H_{26}N_2$ requires C, 88·6; H, 5·5; N, 5·9%). This substance (5 g.) was boiled with acetic anhydride (20 c.c.) and sulphuric acid (1 drop) for 2 hr. Water precipitated a solid which was recrystallised from alcohol (twice) and gave *6-acetyl-7-methyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo(2′ : 3′-4 : 5)indole* as needles, m. p. 248°, containing solvent of crystallisation (Found: C, 83·1; H, 6·0; loss *in vacuo* at 160°, 8·3. $C_{37}H_{28}ON_2,C_2H_6O$ requires C, 83·2; H, 6·0; C_2H_6O, 8·3%). This acetyl compound was unaffected by boiling alcoholic potassium hydroxide (10%) during 3 hr. The indole was unaffected by acetic anhydride in the absence of sulphuric acid.

7-Acetyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo(2′ : 3′-4 : 5)indole.—(*a*) The tetraphenylpyrroloindole (5 g.) was boiled with acetic anhydride (25 c.c.) and sulphuric acid (2 drops) for 12 hr. and, on cooling, solid (4·2 g.) was collected. (Boiling for 18 hr. or using camphorsulphonic for sulphuric acid produced similar results. In the absence of a catalyst the starting material was unchanged.) (i) Repeated recrystallisation from alcohol and then acetic acid finally gave a small quantity of yellow needles, m. p. 236—238°, unaffected by alcoholic potassium hydroxide. (ii) The crude acetylated material was refluxed with alcoholic potassium hydroxide (10%) for 6 hr., dried, and 0·45 g. in benzene (30 c.c.), was passed down an activated-alumina column. Development with benzene gave a lower yellow band that was eluted with acetone. After removal of solvent, the dried residue was recrystallised (twice) from glacial acetic acid from which it separated as yellow needles, m. p. 234—236°, not depressed by admixture with the above, or with an authentic specimen (see below) of *7-acetyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo-(2′ : 3′-4 : 5)indole*, m. p. 236—238°. In each specimen the crystals contained acetic acid of crystallisation, detectable with litmus paper on melting (Found: C, 83·2; H, 4·8; N, 4·8. $C_{36}H_{26}ON_2,\frac{1}{2}C_2H_4O_2$ requires C, 83·4; H, 5·2; H, 5·2%).

(*b*) 2 : 4-Diaminoacetophenone (0·09 g.) and benzoin (0·25 g.) were heated with hydrochloric

acid (1 drop) at 180° for 15 min., water being evolved. Recrystallisation of the product from acetic acid (twice) afforded 7-acetyl-2 : 3 : 4′ : 5′-tetraphenylpyrrolo(2′ : 3′-4 : 5)indole as pale yellow needles, m. p. 236—238°, identical with the above and containing acetic acid of crystallisation.

2 : 4-*Diaminoacetophenone*.—2-Amino-4-nitroacetophenone (1·08 g.) in alcohol (200 c.c.) with a little Adams catalyst was shaken in hydrogen until absorption ceased (15 min.; 420 c.c.; $3H_2$ requires 380 c.c.). The solvent was evaporated and the residue was extracted with ether, on removal of which 2 : 4-*diaminoacetophenone* remained. It crystallised from light petroleum (b. p. 100—120°) as colourless needles, m. p. 129·5—130·5° (Found : C, 64·0; H, 6·7. $C_8H_{10}ON_2$ requires C, 60·4; H, 6·7%).

2-Amino-4-nitroacetophenone was prepared from 1-acetyl-2 : 3-dimethylindole (Schofield and Theobald, *J.*, 1949, 796) but it was found that the nitroindole was more readily obtained by nitration of 9-acetyl-2 : 3-dimethylindole (Plant and Tomlinson, *J.*, 1933, 955) than from the cyclisation of the *m*-nitrophenylhydrazone employed by these authors.

Condensaiton of Aromatic Amines with 2-*Hydroxy*cyclo*hexanone*.—The amine (2 g.) was mixed with a molecular proportion of 2-hydroxy*cyclo*hexanone and a trace of hydrochloric acid and heated in an oil-bath as shown in the Table.

Amine	Temp.	Time (min.)	Carbazole deriv. produced	M. p.	Yield (%)
Aniline	140—160°	20	Tetrahydro-	116—117°	70
o-Chloroaniline ...	150—160	5	8-Chlorotetrahydro-	54—55	81
p-Chloroaniline ...	155—165	10	6-Chlorotetrahydro-	137	37
o-Toluidine	145—155	5	Tetrahydro-8-methyl-	94—97	77
p-Toluidine	150—160	5	Tetrahydro-6-methyl-	141—142	55
m-Toluidine	150—160	10	Mixture	—	—
Anthranilic acid ...	145—170	20	8-Carboxytetrahydro-	195—197	23
p-Anisidine	145—165	8	Tetrahydro-6-methoxy-	104—106	12
m-Aminophenol ...	140—160	10	* Tetrahydro-7(or 5)-hydroxy-	163—164	55

* Colourless needles from aqueous alcohol (Found : N, 7·5. $C_{12}H_{13}ON$ requires N, 7·5%).

p-Nitroaniline, heated with an equivalent of 2-hydroxy*cyclo*hexanone at 140—160° for 5 min., afforded yellow needles (2·3 g. from alcohol), m. p. 133° (Found : C, 62·1; H, 6·1; N, 11·5. $C_{12}H_{14}O_3N_2$ requires C, 61·6; H, 6·0; N, 11·9%), which were p-*nitro*-N-2-*oxo*cyclo*hexylaniline* or N-2-*hydroxy*cyclo*hexylidene*-p-*nitroaniline*. *o*- and *m*-Nitroaniline gave tars.

5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-*Octahydro*-3-*methylindolo*(3′ : 2′-1 : 2)*carbazole*.—4-Methyl-*m*-phenylenediamine (2·5 g.), 2-hydroxy*cyclo*hexanone (5·5 g.), and hydrochloric acid (2 drops) were heated at 150—175° for 15—20 min. The cooled product was extracted with cold benzene (75 c.c.), and the filtered solution was rapidly evaporated, avoiding contact with air as far as possible. Recrystallisation of the residue from acetone in an air-tight flask afforded 5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-*octahydro*-3-*methylindolo*(3′ : 2′-1 : 2)*carbazole* (2·6 g.) as colourless plates, m. p. 78—80°, containing acetone of crystallisation (Found : C, 76·1; H, 8·4; N, 7·2. $C_{19}H_{22}N_2,2C_3H_6O$ requires C, 76·1; H, 8·6; N, 7·1%). Sublimation *in vacuo* at 180° gave the solvent-free *octahydromethylindolocarbazole*, m. p. 137° (Found : C, 81·8; H, 7·9; N, 10·2. $C_{19}H_{22}N_2$ requires C, 82·0; H, 7·9; N, 10·1%). Acetylation was attempted by boiling this (2·5 g.) with acetic anhydride (12·5 c.c.) and sulphuric acid (1 drop) for 1 hr. The small amount of solid that separated on cooling was recrystallised (twice) from acetic acid, and a *diacetylmethyloctahydroindolocarbazole* (20 mg.) was obtained as dark green needles, m. p. 255° (Found : C, 76·0; H, 7·4. $C_{23}H_{26}O_2N_2$ requires C, 76·2; H, 7·2%).

5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 8′-*Octahydroindolo*(3′ : 2′-1 : 2)*carbazole*.—This was prepared from *m*-phenylenediamine as above, with heating at 140°—160° for 5—15 min. until effervescence ceased. Extraction with boiling acetic acid gave the octahydroindolocarbazole (yield, 17—30%), m. p. 225—227°, not depressed by admixture with a specimen, m. p. 228°, prepared by Tomlinson (*loc. cit.*). The product (2 g.) was boiled with acetic anhydride (17·5 c.c.; freshly distilled) for 8 hr. The solid that separated on cooling had m. p. 251—258°, raised by repeated recrystallisation from acetic acid to 259—260·5° (Found : C, 77·6; H, 7·4. Calc. for $C_{20}H_{22}ON_2$: C, 78·4; H, 7·2. Calc. for $C_{22}H_{24}O_2N_2$: C, 75·8; H, 6·9%). When boiled with alcoholic potassium hydroxide it was reconverted into the original octahydroindolocarbazole, m. p. 223—226°, alone or mixed with the starting material. In the presence of a trace of sulphuric acid acetic anhydride afforded an intractable product.

DYSON PERRINS LABORATORY, OXFORD. [*Received, August 20th*, 1953.]