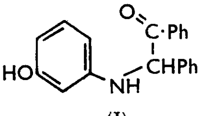
681. *4- and 6-Hydroxy-2,3-diphenylindole and 2,3-Diphenylindole-4,7- and -6,7-quinone.*

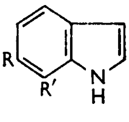
By Barbara Clifford, Patricia Nixon, Charlotte Salt, and Muriel Tomlinson.

An earlier report[1] that the compound, m. p. 168°, formed by reaction between *m*-aminophenol and benzoin, is 6- and not 4-hydroxy-2,3-diphenylindole, has been proved to be correct in spite of a claim[2] to the contrary. The quinone formed by oxidation of the 6-hydroxy-compound is now shown to be 2,3-diphenylindole-6,7-quinone, and not, as was claimed,[2] the 4,7-quinone. The latter compound has been prepared by oxidation of both 4-hydroxy- and 4,7-dihydroxy-2,3-diphenylindole, which proves its constitution.

Teuber and Schnee[2] disagreed with the findings of Orr and Tomlinson[1] who showed that the compound, m. p. 168°, made by cyclisation of *m*-*N*-(α-phenylphenacyl)aminophenol (I) was 6- (II; R = OH, R′ = H) and not 4-hydroxy-2,3-diphenylindole (III; R = OH, R′ = H). They repeated Orr and Tomlinson's work and claimed that removing the chlorine from 7-chloro-4-methoxy-2,3-diphenylindole (III; R = OMe, R′ = Cl) gave a methoxydiphenylindole, m. p. 202°, identical with the compound obtained either by methylating the substance, m. p. 168°, or from *m*-anisidine and benzoin. This led us to repeat our experiments.



(I)



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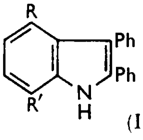

(III)

We prepared our 2-chloro-5-methoxyaniline from *p*-anisidine (acetylation, nitration, and hydrolysis, followed by conversion of the resulting 4-methoxy-2-nitroaniline into the amine by the Sandmeyer reaction and reduction). There is therefore no doubt about the constitution of this amine, or of the 7-chloro-4-methoxy-2,3-diphenylindole (III; R = OMe, R′ = Cl) obtained from it by condensation with benzoin. (Attempts to make this indole from deoxybenzoin 2-chloro-5-methoxyphenylhydrazone failed.) Removal of the chlorine now gave 4-methoxy-2,3-diphenylindole (III; R = OMe, R′ = H), m. p. 147—148°, and demethylation afforded 4-hydroxy-2,3-diphenylindole (III; R = OH, R′ = H), m. p. 149·5—151°, quite different from the 6-methoxy- and the 6-hydroxy-compound, m. p. 203° and 168°, respectively.

There is some evidence to support these structures in their very complex infrared spectra: the 6-methoxy-compound has maxima at 864, 834, and 812 cm.$^{-1}$ which are absent in the spectrum of the 4-methoxy-compound and could be attributed to the out-of-plane bending of one isolated, and two adjacent, hydrogen atoms on the benzenoid ring of the indole. Ockenden and Schofield[3] have, moreover, shown that 6- rather than 4-substituted indoles are normally obtained from phenylhydrazones which have strongly *ortho*- and *para*-directing substituents *meta* to the hydrazino-group, and they obtained only a substance, m. p. 204—207°, from deoxybenzoin *m*-methoxyphenylhydrazone.

It seemed possible that the discrepancies between the German authors' results and our own was a mistake about the identity of their starting material, namely, the 4-chloro-3-nitroanisole, which was a gift to them from Farbenwerken Hoechst A.G., and as a partial check on this we prepared a methoxydiphenylindole from *o*-anisidine (the most likely alternative if such a mistake had occurred). By a series of operations similar to those described for *p*-anisidine, we did obtain 6-methoxy-2,3-diphenylindole, m. p. 203°, but the

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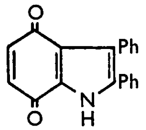
[1] Orr and Tomlinson, *J.*, 1957, 1025.
[2] Teuber and Schnee, *Ber.*, 1958, **91**, 2089.
[3] Ockenden and Schofield, *J.*, 1957, 3175.

melting point of the intermediate 5-chloro-6-methoxy-2,3-diphenylindole did not correspond with that of Teuber and Schnee's chloromethoxydiphenylindole.

These authors did not quote the melting point of their chloromethoxyaniline [its hydrochloride had m. p. 208° (decomp.); ours, m. p. 213—214° (decomp.)] but they made it by catalytic reduction in an autoclave at 80° and our experience shows that it could, therefore, have been contaminated with *m*-anisidine. In addition we have found that during the cyclisation of 2-chloro-5-methoxy-*N*-(α-phenylphenacyl)aniline, some chlorine is always extruded. We worked with analytically pure 2-chloro-5-methoxyaniline and yet we could isolate, from the product, 6-methoxy-2,3-diphenylindole which could not have arisen from *m*-anisidine in the starting material. Teuber and Schnee did not recrystallise their 7-chloro-4-methoxy-2,3-diphenylindole (it was distilled *in vacuo*). It could therefore have been contaminated with 6-methoxy-2,3-diphenylindole from either or both of the above sources, and, if it was, this very sparingly soluble compound would be isolated far more easily than the 4-isomer, after the dechlorination experiment: their yield was only 28%. (We can obtain an 84% yield of the 4-methoxy-compound.)



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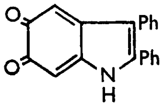

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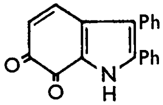

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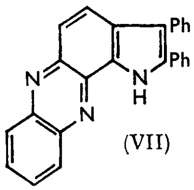

(VII)

Teuber and Schnee oxidised the hydroxy-2,3-diphenylindole, m. p. 168°, with potassium nitrosodisulphonate (Frémy's salt) and obtained a quinone, m. p. 235°, which they claim is 2,3-diphenylindole-4,7-quinone (IV). We have synthesised this quinone by demethylation and oxidation (sodium dichromate) of 4,7-dimethoxy-2,3-diphenylindole. Its infrared absorption spectrum is identical with that of the quinone which we got by oxidation of 4-hydroxy-2,3-diphenylindole with Fremy's salt.

Similar oxidation of 6-hydroxy-2,3-diphenylindole, which had been purified through the sodium salt or by conversion into the 6-methoxy-compound, gave a quinone which did not melt completely below 320°. Oxidation of 6-hydroxydiphenylindole which had been " purified " chromatographically gave this quinone, together with a small quantity of the above 4,7-quinone. The isolation of the 4,7-quinone here was our first indication that 4-hydroxy-2,3-diphenylindole is formed, together with the 6-isomer, from *m*-aminophenol and benzoin. We find now, however, that when the product of this reaction is methylated and chromatographed a little of the 4-methoxy-compound can be isolated from the first fractions.

The new quinone is an *o*-quinone because it forms a phenazine with *o*-phenylenediamine, and it must be either 2,3-diphenylindole-5,6- (V) or 2,3-diphenylindole-6,7-quinone (VI). Oxidation of 6-hydroxy-1-methyl-2,3-diphenylindole also gave an *o*-quinone which yielded a phenazine identical with that obtained by methylating the phenazine (VII). The infrared spectra of the quinone from 6-hydroxydiphenylindole, and of the phenazine derived from it, both contain a wide band at 2900—3400 cm.$^{-1}$, and this band is absent from the spectra of the corresponding *N*-methyl compounds. The hydrogen-bonding thus indicated suggests that these substances are 2,3-diphenylindole-6,7-quinone (VI) and 4′,5′-diphenylpyrrolo(2′,3′:1,2)phenazine (VII) respectively, because, although both indole-6,7-quinones and indole-5,6-quinones (in the imino-form) could be hydrogen-bonded, the phenazine from an indole-5,6-quinone is incapable of forming hydrogen bonds.

Teuber and Schnee stated that their quinone from the hydroxyindole, m. p. 168°, does not form a phenazine but gives, with *o*-phenylenediamine, a " dianil," m. p. 318—320°. We obtained the compound they describe (working under their conditions in pyridine), but the main product is the phenazine (VII) which they must have removed by washing the " dianil " with boiling benzene. The identity of this substance has not been established. It is not, as they suggest, 2,3-diphenylindole-4,7-quinone *oo'*-diaminodianil because the 4,7-quinone does not form this substance with *o*-phenylenediamine. The analysis accords with a formula, $C_{32}H_{23}N_5$, rather better than with the dianil formula, and the compound might have been formed by addition of *o*-phenylenediamine across the 4,5-double bond of the quinone (VI) followed by some oxidation: it is not formed when the phenazine (VII) is boiled with *o*-phenylenediamine in pyridine. It does not react with acetic anhydride and it is therefore unlikely that it contains an NH_2 group.

Experimental

6- *and* 4-*Methoxy*-2,3-*diphenylindole*.—*m*-Aminophenol (6 g.) and benzoin (5 g.) were converted into the indole[1] and the resulting gum, in benzene, was chromatographed on 5% deactivated alumina. Fractions collected from a wide grey band (mauve fluorescence) contained solids, m. p. 155—163°. This material (5·7 g.) was methylated,[1] dissolved in a minimum volume of benzene and chromatographed on activated alumina in benzene. A small quantity of gum in the first fraction gave, on recrystallisation from light petroleum (b. p. 60—80°), prisms, m. p. 136—140°, raised to 142° by admixture with 4-methoxy-2,3-diphenylindole, m. p. 146—147°. Later fractions gave the 6-methoxy-compound.

2-*Chloro*-5-*methoxyaniline*.—The corresponding nitro-compound has been reduced in various ways but the original method[4] produces the purest amine. Steam-distillation facilitates its isolation.

2-*Chloro*-5-*methoxyphenylhydrazine*.—The above amine (10 g.) was diazotised in hydrochloric acid (20 ml.) and water (25 ml.) with sodium nitrite (4·6 g.). The diazonium solution was reduced with stannous chloride (36 g.) in hydrochloric acid (50 ml.), and the *hydrazine* was liberated from the precipitated hydrochloride with sodium hydroxide. It separated from light petroleum (b. p. 60—80°) as needles, m. p. 70—72·5° (3·0 g.) (Found: C, 48·5; H, 5·1. $C_7H_9ClN_2O$ requires C, 48·6; H, 5·2%). When warmed with deoxybenzoin it gave *deoxybenzoin* 2-*chloro*-5-*methoxyphenylhydrazone*, needles, m. p. 100—101° (from methanol) (Found: C, 72·0; H, 5·4. $C_{21}H_{19}ClN_2O$ requires C, 72·0; H, 5·4%).

2-*Chloro*-5-*methoxy*-N-(α-*phenylphenacyl*)*aniline* has now been obtained in a second form, m. p. 116° (Found: C, 71·6; H, 5·0. $C_{21}H_{18}ClNO_2$ requires C, 71·4; H, 5·1%).

7-*Chloro*-4-*methoxy*-2,3-*diphenylindole*.—This was prepared as described earlier[1] from 2-chloro-5-methoxy-*N*-(α-phenylphenacyl)aniline (3·0 g.) and 2-chloro-5-methoxyaniline hydrochloride (1·5 g.), both made from 2-chloro-5-methoxyaniline (4·78 g.) (Found: C, 53·5; H, 5·2. Calc. for C_7H_8ClNO: C, 53·3; H, 5·2%). Chromatography of the reaction product in benzene on activated alumina gave, first, a yellow band which contained the chloromethoxyindole and some αβ-di-(2-chloro-5-methylanilino)stilbene. A second red band yielded a gum which, in contact with methanol, gave a solid, m. p. 190—192° (0·425 g.), and this, recrystallised from methanol, afforded 6-methoxy-2,3-diphenylindole, m. p. 200°.

5-*Chloro*-6-*methoxy*-2,3-*diphenylindole* was obtained from 4-chloro-3-methoxyaniline (1·0 g.) and benzoin (1·3 g.) heated with a little hydrochloric acid at 200° for 1 hr., as plates, m. p. 217° (from ethanol) (Found: C, 75·7; H, 5·0. $C_{21}H_{16}ClNO$ requires C, 75·6; H, 4·8%). When this was reduced with hydrogen and palladium–charcoal in mesitylene (cf. ref. 1) it gave 6-methoxy-2,3-diphenylindole.

4-*Hydroxy*-2,3-*diphenylindole*.—The 4-methoxy-compound (1·6 g.) in dry benzene (40 ml.) with aluminium chloride (5·0 g.) was heated under reflux in nitrogen for 8 hr. Ice and hydrochloric acid were added; 4-*hydroxy*-2,3-*diphenylindole* was isolated with ether and recrystallised from light petroleum (b. p. 60—80°) as prisms, m. p. 149—151·5° (0·41 g.) (Found: C, 84·2; H, 5·4. $C_{20}H_{15}NO$ requires C, 84·2; H, 5·3%). Methylation in aqueous acetone reconverted it into the 4-methoxy-compound.

7-*Chloro*-4-*hydroxy*-2,3-*diphenylindole* (0·78 g.) was made the same way from the corresponding methoxy-compound (1·2 g.). It formed plates, m. p. 174—175° (from light petroleum b. p. 80—100°) (Found: C, 75·1; H, 4·7. $C_{20}H_{14}ClNO$ requires C, 75·1; H, 4·4%.)

4,7-*Dimethoxy*-2,3-*diphenylindole*.—Heated together at 150—160°, with a drop of hydrochloric acid, 2,5-dimethoxyaniline (2·5 g.) and benzoin (3·5 g.) gave a gum which, chromatographed on activated alumina in benzene, yielded 2,5-*dimethoxy*-N-(α-*phenylphenacyl*)*aniline*,

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[4] Cummins and Tomlinson, *J.*, 1955, 3475.

prisms, m. p. 91—92° (from ethanol) (Found: C, 76·1; H, 6·2; N, 4·0. $C_{21}H_{21}NO_3$ requires C, 76·1; H, 6·1; N, 4·0%). This (1·55 g.), with 2,5-dimethoxyaniline hydrochloride (0·75 g.), at 210° gave a black mass which, chromatographed as above, gave the *indole* (from a yellow band), that crystallised from methanol as yellow plates, m. p. 133·5° (0·7 g.) (Found: C, 80·3; H, 5·9. $C_{22}H_{19}NO_2$ requires C, 80·2; H, 5·8%).

2,3-*Diphenylindole*-4,7-*quinone*.—(*a*) The above dimethoxyindole (1·0 g.) was demethylated as above with aluminium chloride (4·2 g.). After addition of acid, the product was extracted with ethyl acetate, and the dried organic layer was evaporated in nitrogen. The solid residue (0·6 g.) was immediately dissolved in acetone (70 ml.) and water (20 ml.) and oxidised with sodium dichromate (1·4 g.) in water (6 ml.) and concentrated sulphuric acid (2 ml.). After 30 min. the diluted solution was extracted with ether. Evaporation of the dried ether layer gave a dark red residue (0·48 g.) which was washed with a little benzene and then chromatographed on activated alumina in chloroform. Evaporation of the solvent which had eluted a red band left 2,3-diphenylindole-4,7-quinone which sublimed to form red needles above 190° and had m. p. 210° (decomp.).

(*b*) 4-Hydroxy-2,3-diphenylindole (0·3 g.) in acetone (15 ml.) was treated with potassium nitrosodisulphonate (0·7 g.) in water (30 ml.) and potassium dihydrogen phosphate (5 ml., M/6). The *quinone* recrystallised from aqueous alcohol as dark red needles which sublimed above 190° and had m. p. 216—218° (decomp.) (Found: C, 79·9; H, 4·5; N, 4·7. $C_{20}H_{13}NO_2$ requires C, 80·3; H, 4·3; N, 4·7%). The infrared spectra of the two samples were identical: $\nu_{max.}$ (in $CHCl_3$) 3400, 1660, 1645, 1595, 1435, 1280, 1105, 960, and a wide band 3300—2850 cm.$^{-1}$.

2,3-*Diphenylindole*-6,7-*quinone*.—(*a*) 6-Hydroxy-2,3-diphenylindole (made by demethylation of the 6-methoxy-compound) (0·5 g.) was oxidised with Fremy's salt (1·2 g.) as above. After ½ hr. the product was collected, washed, and dried. Chromatography in chloroform on activated alumina gave 2,3-diphenylindole-6,7-quinone, a red-brown solid which recrystallised from glacial acetic acid as dark red needles, not melting below 320° but decomposing slightly above 235° (Teuber and Schnee give m. p. 230°) (Found: C, 80·1; H, 4·5; N, 4·8. Calc. for $C_{20}H_{13}NO_2$: C, 80·3; H, 4·4; N, 4·7%), $\nu_{max.}$ (in $CHCl_3$) 3400, 1683, 1645, 1635, 1440, 1290, 982, 947, and a wide band 3300—2850 cm.$^{-1}$.

(*b*) 6-Hydroxydiphenylindole (purified chromatographically) (1·5 g.) was oxidised with Fremy's salt (3·6 g.). Chromatography as above gave a dark red band which was eluted rapidly, and evaporation of the solvent left the above 4,7-quinone (0·135 g.). Further elution slowly removed the 6,7-quinone.

4′,5′-*Diphenylpyrrolo*(2′,3′:1,2)*phenazine*.—(*a*) A mixture of the 6,7-quinone (1·0 g.) in acetic acid (100 ml.) and *o*-phenylenediamine (0·37 g.) in ethanol (8 ml.) was heated on a water-bath for 30 min. The solvents were partially removed *in vacuo* and dark orange crystals were collected and chromatographed in benzene on activated alumina. Elution of an orange band gave a solution which contained solid (0·8 g.), m. p. 120° (with frothing). This solid was melted and dissolved in boiling light petroleum (b. p. 60—80°) from which separated 4′,5′-*diphenylpyrrolo*(2′,3′:1,2)*phenazine*, orange needles, m. p. 143—145° (frothing above 150°) [Found (after drying at 150°): C, 84·0; H, 4·5. $C_{26}H_{17}N_3$ requires C, 84·1; H, 4·6%], $\nu_{max.}$ (in $CHCl_3$) 3600, 1625, 1600, 1470, 1440, 1350, 1325, 1290, 1133, 960, 905, and a wide band 3400—2850 with max. at 3375 and 3225 cm.$^{-1}$.

(*b*) The 6,7-quinone (0·5 g.) and *o*-phenylenediamine (0·37 g.) were heated in boiling pyridine (30 ml.) for 4 hr. The pyridine was distilled off and the brown residue was extracted with benzene which was then run on to activated alumina. The above phenazine (0·28 g.) was isolated by elution with benzene. The solid residue was recrystallised from xylene and gave yellow microcrystalline needles, m. p. 311—314° (0·1 g.) (Teuber and Schnee give m. p. 318—320°) (Found: C, 80·3; H, 4·9; N, 14·3. Calc. for $C_{32}H_{25}N_5$: C, 80·1; H, 5·25; N, 14·6. Calc. for $C_{32}H_{23}N_5$: C, 80·5; H, 4·8; N, 14·7%), unaltered by boiling acetic anhydride.

6-*Methoxy*-1-*methyl*-2,3-*diphenylindole*.—Dimethyl sulphate (5 ml.) was added during 1 hr. to a boiling solution of 6-hydroxydiphenylindole (2 g.) with powdered potassium hydroxide (3 g.) in acetone. After further boiling (1 hr.), water was added to precipitate the product which had m. p. 149° (from methanol) (Teuber and Schnee give m. p. 152°). Demethylation with aluminium chloride in benzene gave the corresponding 6-hydroxy-compound, m. p. 198—199° (Teuber and Schnee give m. p. 198—200°).

1-*Methyl*-2,3-*diphenylindole*-6,7-*quinone*.—This *quinone* was prepared from the above 6-hydroxy-*N*-methyl-compound (0·8 g.) with Fremy's salt (1·9 g.) and recrystallised from chloroform; it formed red needles which changed to plates at 210° and melted at 258—260° (Found: C, 80·3; H, 4·9; N, 4·6. $C_{21}H_{15}NO_2$ requires C, 80·5; H, 4·8; N, 4·5%), $\nu_{max.}$ (in $CHCl_3$) 1683, 1640, 1440, 1385, 1340, 1140, 1117, and 955 cm.$^{-1}$.

1′-Methyl-4′,5′-diphenylpyrrolo(2′,3′:1,2)phenazine was obtained from this *N*-methyl-6,7-quinone (0·4 g.) and *o*-phenylenediamine (0·14 g.) as above. It crystallised when the solvent was partially evaporated and recrystallisation from benzene gave yellow needles, m. p. 257—258° (0·24 g.) (Found: C, 83·8; H, 5·1. $C_{27}H_{19}N_3$ requires C, 84·1; H, 4·9%), $\nu_{max.}$ (in $CHCl_3$) 1605, 1555, 1465, 1427, 1355, 1335, 1143, 1120, 1090, and 890 cm.$^{-1}$.

The same compound (mixed m. p.) was obtained by methylating 4′,5′-diphenylpyrrolo-(2′,3′:1,2)phenazine with an excess of dimethyl sulphate and powdered potassium hydroxide in boiling acetone.

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