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The oxidative coupling of indole with three naphthols, 2-naphthol, 2,3-dihydroxynaphthalene and 2,7-dihydroxynaphthalene gave 1,1-bis(3'-indolyl)-2(1H)naphthalenone, 1,1-bis(3'-indolyl)-3-hydroxy-2(1H)naphthalenone and 1,1-bis(3'-indolyl)-7-hydroxy-2(1H)naphthalenone, respectively. The coupling of indole with protocatechuic aldehyde gave bis-(3-indolyl)-(3',4'-dihydroxyphenyl)methane and that of indole with homocatechol gave 3-(2'-methyl-3',4'-dihydroxyphenyl)indole.

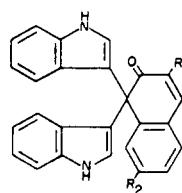
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In melanogenesis of DOPA the 4-7 or 3-7 linking of 5,6-dihydroxyindole is most probable (2), while other possibilities cannot be completely rejected. Horner (3) described the 3-6 linking, Harley-Mason (4) pointed out the possibility of dimerization at the position-2, and Bruce proposed the 3-4 linking. Bu'Lock and Harley-Mason (2a) and later Bruce (5) indicated that indole couples at the 3-position with quinones and the similar results were obtained by autoxidation of substituted 5,6-dihydroxyindoles (6). Recently we reported aminonaphthol oxidation (7) which is interesting as a model of melanochrome formation. As a further model experiment the oxidative coupling of indole with some phenolic compounds, naphthols and catechols, has been investigated.

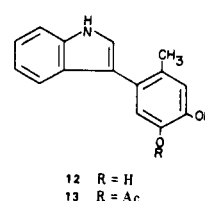
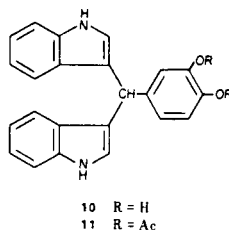
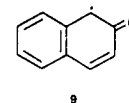
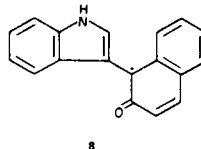
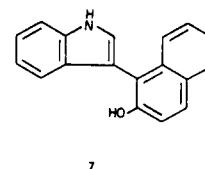
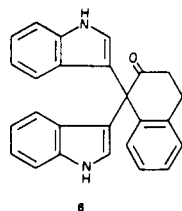
Coupling of Indole with Naphthols.

In spite of many examples of indole oxidation by air (8), oxygen (9), Fremy salt (10) or tetracyanoethylene (11) there is no report about the clear oxidative self-coupling of indole and preliminary experiment showed that 2-naphthol does not react with indole under the condition of melanogenesis. This means that indole is less active than 2-naphthol under the condition of oxidative coupling.

Three naphthols, 2-naphthol, 2,3-dihydroxynaphthalene and 2,7-dihydroxynaphthalene were oxidized with iron(III) or potassium ferricyanide in the presence of indole and the products were surveyed. From 2-naphthol and indole two products were obtained. One was 1,1'-bis-2-naphthol (12) and the other product with m.p. 291° was proved to be **1**, whose structure was in accord with the nmr and mass spectra and also supported by hydrogenation into **6**. It is of interest that the product is not an expected compound **7** which is an equimolecular coupling product of indole and 2-naphthol, but the trimer consisting of one molecule of naphthole and two molecules of indole. This means that an indolyl group stabilizes the intermediate radical **8** than **9**, and this effect fully covers the steric hindrance of indolyl group, furnishing further coupling with one more indole molecule. The formation



- 1 R₁ = R₂ = H
- 2 R₁ = OH, R₂ = H
- 3 R₁ = H, R₂ = OH
- 4 R₁ = OAc, R₂ = H
- 5 R₁ = H, R₂ = OAc



of **1** is analogous with the formation of trimeric product from 2-naphthol by manganese (III) acetylacetonate (13).

Coupling of Indole with Catechols.

Three catechols, protocatechuic aldehyde, homocatechol and catechol have been oxidized in the presence of indole under the similar condition of as melanogenesis of DOPA. Three kinds of conditions for oxidative coupling were used: autoxidation by bubbling air, oxidation by potassium ferricyanide and iron(III) chloride or MTA.

The autoxidation of protocatechuic aldehyde and indole in aqueous methanol in the presence of alkali gave a red solid of m.p. 151°. The structure **10** is supported by the ir and nmr spectra and also confirmed by the

physical data of the corresponding acetyl derivative **11**. The compound **10** was also obtained by the reaction of protocatechuic aldehyde and indole in the presence of potassium ferricyanide in alkaline solution or acidic iron(III) chloride solution of pH 4.0.

The oxidative coupling of indole with homocatechol by air-bubbling in methanol-water mixture containing sodium hydroxide at 40° for 12 hours gave **12** and an indole dimer. The acetylated compound **13** was also prepared for confirming the structure **12**. When indole and homocatechol were treated by iron(III) chloride in methanol-water mixture of pH 4.0 at room temperature for 12 hours the compound **12** and a homocatechol dimer were obtained. It was found that the coupling product **12** was formed specifically by autoxidation in alkaline solution, while both the coupling product and a homocatechol dimer were formed in case of iron(III) chloride oxidation. The attempted oxidative coupling of indole with catechol itself in the similar conditions described above gave no coupling products. This may be attributed to the fact that homocatechol is very sensitive to oxidizing reagents. It can be concluded that methyl group in homocatechol disturbs self-coupling but contributes hetero-coupling.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured as potassium bromide pellets on a Hitachi ESP-S2 spectrophotometer; the nmr spectra were determined at 60 MHz on a Hitachi H-60 nmr spectrophotometer with TMS as an internal reference.

1,1-Bis(3'-indolyl)-2(1H)naphthalene (**1**)

To a mixture of 2-naphthol (0.72 g.), indole (0.58 g.) and aqueous methanol (1:1) 50 ml., was added a solution of iron(III) chloride (2.4 g.) in water (20 ml.) in twenty minutes and stirred for two hours. When the reaction mixture became oily and a yellow solid began to precipitate the solution was acidified with 2N hydrochloric acid solution and extracted with ethyl acetate. The extract was washed with water and concentrated to dryness. The residue was chromatographed over silicagel and eluted with benzene to afford yellow powder, which gave yellow crystals from ethyl acetate-acetone (4:1, v/v), 0.26 g., m.p. 291°; ir: 3300, 1620, 1600, 1450, 1240, 1110, 660 cm⁻¹; uv (ethanol): nm 238 (20,000), 291 (18,100), 313 (10,400), 386 (1,280); nmr (DMSO-d₆, ppm): 6.05 (d, 1H, J = 10 Hz), 6.47 (d, 2H, J = 2.5 Hz), 6.6-7.1 (m, 12H) 7.55 (d, 1H, J = 10 Hz), 11.9 (br, disappeared with deuterium oxide).

Anal. Calcd. for C₂₆H₁₈N₂O: C, 83.40; H, 4.85; N, 7.48. Found: C, 83.40; H, 4.96; N, 7.48.

Another fraction eluted from benzene gave 1,1'-bis-2-naphthol (0.06 g.) as colorless crystals. The compound **1** (56 mg.) was hydrogenated with palladium black (60 mg.) in tetrahydrofuran (20 mg.) at room temperature and atmospheric pressure. Working up in the usual manner gave a crude product (50 mg.) which was subsequently crystallized from benzene-ethyl acetate (10:1), **6**; ir: 3450, 3350, 1695, 1450, 1335, 1240, 1150, 1100, 1010, and 735 cm⁻¹; uv (ethanol): nm 276, 282, 284, 291; nmr (DMSO-d₆): ppm 6.45 (d, 2H, J = 2.5 Hz), 6.6-7.4

(m, 12H), 2.6-3.0 (m, 4H), 10.87 (br, 2H, disappearing with deuterium oxide); ms: M⁺, m/e 376.

1,1-Bis(3'-indolyl)-3-hydroxy-2(1H)naphthalene (**2**)

A solution of iron(III) chloride (3.5 g.) in 25 ml. of water was added to a solution of indole (0.58 g.) and 2,3-dihydroxynaphthalene (0.8 g.) in 50 ml. of water-methanol (1:1, v/v) under stirring in twenty minutes and continued stirring for two hours at room temperature. The color of the reaction mixture began to change brownish yellow. Then the mixture was acidified with 2N hydrochloric acid. The brown precipitate was collected and purified by silicagel column chromatography eluted with benzene. The solvent was evaporated *in vacuo* and the residue was crystallized from ethyl acetate to afford 0.3 g. of yellow crystals, **2**, m.p. 251°; ir: 3400, 1660, 1480, 1455, 1400, 1230, 740 cm⁻¹; uv (ethanol): nm 283, 291, 340; nmr (DMSO-d₆): ppm 6.5 (d, J = 2.5 Hz, 2H), 6.65-7.45 (m, 13H), 9.1 (s, 1H), 10.9 (br, 2H, disappeared with deuterium oxide). After addition of deuterium oxide the following signals appeared: 6.5 (s, 2H); ms: M⁺, m/e 390.

Anal. Calcd. for C₂₆H₁₈N₂O₂: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.02; H, 4.91; N, 6.96.

The compound **2** (20 mg.) was added to 10 ml. of acetic anhydride and 3 drops of pyridine. The mixture was stirred at 60° for an hour and then poured into ice water under stirring. The colorless acetate was precipitated. The product was purified by silicagel column chromatography eluted with benzene-ethyl acetate (2:1, v/v), **4**, 10.5 mg; ir: 3400, 3060, 1765, 1670, 1460, 1420, 1200, and 740 cm⁻¹; nmr (deuteriochloroform): 2.05 (s, 3H), 6.4 (d, 2H), 6.7-7.3 (m, 13H), 8.0 (br, 2H, disappeared with deuterium oxide).

1,1-Bis(3'-indolyl)-7-hydroxy-2(1H)naphthalene (**3**)

A solution of iron(III) chloride (3.5 g.) in water (20 ml.) was gradually added to a solution of 2,7-dihydroxynaphthalene (0.8 g.) and indole (0.58 g.) in water-methanol (1:1, 50 ml.) at room temperature in 20 minutes with stirring. After stirring for further two hours under the same conditions the mixture was acidified with 2N hydrochloric acid, concentrated *in vacuo* and then extracted with ethyl acetate. The extract was washed with water, evaporated to dryness and chromatographed on silica gel eluted by benzene to give yellow needles from ethyl acetate, **3**, 0.3 g., m.p. 269°; ir: 3400, 3050, 1630, 1590, 1450, 1400, 1300, 1225, 1100, and 740 cm⁻¹; uv (ethanol): nm 283, 291, 345; nmr (acetone-d₆): ppm 5.90 (d, 1H, J = 10 Hz), 6.5-7.5 (m, 13H), 7.45 (d, 1H, J = 10 Hz), 8.60 (s, 1H), 10.0 (br, 2H).

Anal. Calcd. for C₂₆H₁₈N₂O₂: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.64; H, 4.68; N, 7.11.

The **3** (20 mg.) was dissolved in acetic anhydride (1.5 ml.) and pyridine (0.5 ml.) and the mixture was stirred at 60° for an hour. The reaction mixture was then worked up in the usual manner to give a monoacetate, **5**, which was crystallized from ethanol, colorless prisms; ir: 3400, 3050, 1750, 1660, 1490, 1455, 1230, and 740 cm⁻¹; nmr (DMSO-d₆): 2.10 (s, 3H), 6.02 (d, 1H, J = 10 Hz), 6.45-7.60 (m, 13H), 10.90 (br, 2H, disappeared with deuterium oxide); ms: M⁺ m/e 432.

Bis(3-indolyl)(3',4'-dihydroxyphenyl)methane (**10**)

To a solution of protocatechuic aldehyde (0.5 g.) in water (40 ml.) was added a solution of indole (0.5 g.) in water (40 ml.). After addition of 1N sodium hydroxide aqueous solution the mixture was stirred vigorously at 40° and air was bubbled through the solution for 12 hours. The reaction mixture was acidified to Congo red with 5N hydrochloric acid and extracted with ethyl acetate for several times. Evaporation of the extract afforded a

product which was chromatographed on silica gel column eluted by benzene-ethyl acetate (2:1) to yield **10**, 15% m.p. 151° dec.; ir: 3450, 1615, 1515, 1455, 1340, 1280, 1210, 1100, and 740 cm^{-1} ; uv (ethanol): nm 284.5, 295(sh); nmr (acetone- d_6): 5.75 (s, 1H, methine), 6.70-7.60 (m, 13H, aromatic protons), 7.20-7.60 (br, 2H, disappeared with deuterium oxide), 9.80 (br, 2H, disappeared with deuterium oxide); ms: M^+ m/e 354.

Anal. Calcd. for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.91. Found: C, 77.92; H, 5.35; N, 7.83.

Comparative yields of the compound **10** under various oxidative conditions were as follows: oxygen/sodium hydroxide +++, oxygen/barium hydroxide ++, potassium ferricyanide/sodium hydroxide +, ferric chloride (pH 4.0) +, MTA (manganese-tris-acetylacetonate), -.

3-(3',4'-Dihydroxy-6'-methylphenyl)indole (**12**).

To a solution of homocatechol (1.08 g.) in water (40 ml.) and a drop of 1N sodium hydroxide solution was added a solution of indole (1.0 g.) in methanol (40 ml.). The solution which showed reddish yellow color was stirred vigorously at 40° and air was bubbled through the solution. After stirring for 12 hours the reaction mixture was carefully acidified to Congo red with 5N hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the extracts gave 0.5 g. of deep brown gummy product, which was examined by tlc on silica gel eluting with benzene-ethyl acetate (10:1, v/v). On examination under uv light or iodine vapor four major spots were detected with Rf values of 0.73, 0.66, 0.19 and 0.14, respectively. Under these conditions indole had Rf 0.37 and homocatechol had Rf 0.19. A portion of the crude oxidation products (0.5 g.) was chromatographed on silica gel column eluted by benzene-ethyl acetate (10:1, v/v). The fraction of Rf 0.14 gave a pale brown solid which was rechromatographed to afford 40 mg. of **12**, 8%, m.p. 89°; ir: 3450, 2950, 1610, 1560, 1505, 1445, 1270, 870, and 730 cm^{-1} ; uv (ethanol): 284, 292; nmr (acetone- d_6): ppm 2.15 (s, 3H, methyl), 6.80-7.65 (m, 7H, indole and benzene), 7.70 (br, 2H, phenolic, disappeared with deuterium oxide), 10.23 (br, 1H, imine). The Gibbs reaction (14) for the compound **12** was negative indicating the absence of a free position to the phenolic hydroxyl groups; ms: M^+ m/e 239.

The formation of the compound **12** was as follows: oxygen/sodium hydroxide ++, oxygen/barium hydroxide +, ferric chloride (pH 4.0) ++, potassium ferricyanide -, MTA -. The formation of homocatechol dimer in these reactions was as follows which was identified with authentic sample (18): ferric chloride (pH 4.0) ++, other oxidants -.

3-(3',4'-Diacetoxy-6'-methylphenyl)indole (**13**).

A mixture of **12** (200 mg.), acetic anhydride (3 ml.) and a drop of pyridine was heated on the water bath for an hour. After two hours the solution was poured into water to give colorless powder which was purified by column chromatography on silica gel eluted by benzene-ethyl acetate (2:1), m.p. 59-60.5°; ir: 3450, 1765, 1620, 1500, 1370, 1210, 1000, and 740 cm^{-1} ; uv (ethanol): nm 275, 281, 291(sh); nmr (deuteriochloroform): ppm 2.18 (s, 3H, CH_3), 2.25 (d, 6H, CH_3CO), 6.80-7.50 (m, 7H, aromatic and 2-H), 8.50 (br, 1H, NH, disappeared with deuterium oxide); ms: M^+ m/e 323.

Indole Dimer.

Evaporation of the fraction of Rf 0.66 in the preceding section gave a brownish solid which was rechromatographed on a column

of silica gel in benzene, yield 10 mg. (2%); ir: 3450, 1620, 1450, 1330, 1080, and 730 cm^{-1} ; nmr (deuteriochloroform): ppm 6.80-7.80 (m, 10H, aromatic and 2-H, 2'-H), 7.60-7.90 (br, 2H, NH, disappearing with deuterium oxide, and 2'-H); ms: M^+ m/e 232, m/e 117, m/e 90.

Comparison of Oxidative Coupling of Indole 2-Naphthol and Homocatechol

Oxidant	(2-Naphthol)		(Homocatechol)	
	1	Polymer	12	Polymer
Oxygen/hydroxyl anion (15)	+	+	++	+
Potassium ferricyanide (16,17)	+	+	-	++
Ferric chloride (18)	+++	-	++	+
Vanadium oxychloride (19)	-	+	-	++
MTA (12)	-	+	-	+

Iron(III) chloride oxidation shows the best activity for the formation of **1** among the above oxidants. The polymer means that the products are black tar insoluble in common solvents.

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