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A REINVESTIGATION OF THE REACTIONS BETWEEN 5,6-DIHYDROXYINDOLES AND QUINONES

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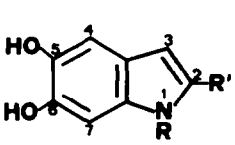
SUMMARY: 5,6-Dihydroxyindoles 1-3 react readily with 1,4-naphthoquinone to give mainly deep-violet monoadducts identified as 8-10 by chemical and spectral analysis. When an excess of 1,4-naphthoquinone is used, a more complex reaction takes place leading to the dinaphthocarbazole 17 rather than the diadduct 11, as previously reported. The same product (17) is also obtained by reaction of 2 with the 2,2'-dinaphthyl-1,4,1',4'-diquinone (18) in 30% yield. Interestingly, when 5,6-dihydroxyindoles are allowed to react with p-benzoquinone under similar conditions, no addition products are formed (UV and TLC evidence), owing to the tendency of the indoles to undergo oxidative coupling with formation, besides melanin-like products, of a complex mixture of oligomers. In the case of 2, reduction and subsequent acetylation of the reaction mixture, has allowed the isolation of two oligomers, identified as 12 and 13.

Since the early work of Möhlau and Redlich[1] in 1911, it has been known that indoles react readily with a variety of quinones affording adducts with a characteristic blue-violet chromophore. However, it was only in the fifties that the chemistry of these reactions received some attention[2,3] in relation to the mechanism of polymerization of 5,6-dihydroxyindoles to melanins.[4,5]

In order to throw some light on the possible ways in which the postulated intermediate of melanogenesis 5,6-indolequinone (4) might polymerize, Bu'Lock and Harley-Mason[2] investigated the reactions of simple indoles and quinones, as models. They reported that, in the presence of acids, p-benzoquinone reacted with indole to give the adduct 5. In the case of 1,4-naphthoquinone, in addition to the monoadduct 6, the reaction gave also a sparingly soluble compound which was for-



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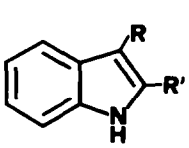
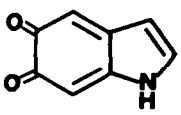
2 R=Me R'=H
3 R=H R'=Me





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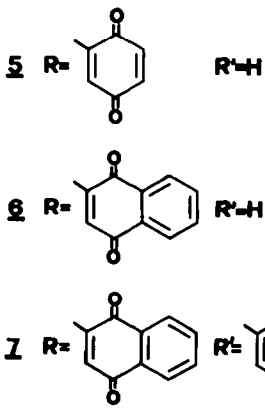
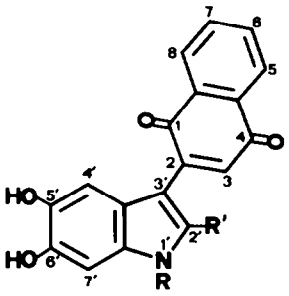


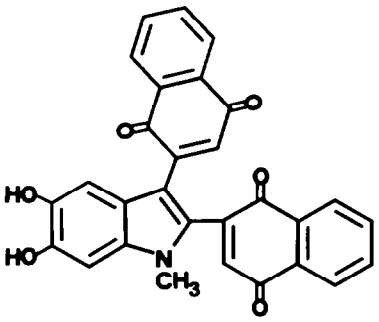
5 R= R'=H
6 R= R'=H
7 R= R'=



8 R=Me R'=H

9 R=H R'=H

10 R=H R'=Me



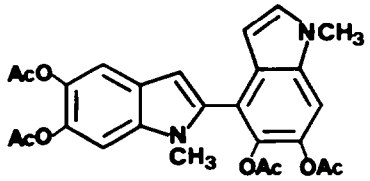
11

mulated as **7**, mainly on the basis of the failure of the 2-methyl substituted indole to give the analogous diadduct.

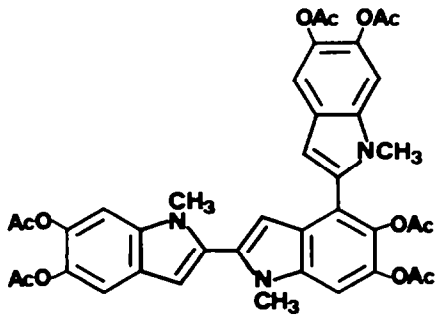
Attempts to extend these reactions to 5,6-dihydroxyindole (**1**) were unsuccessful owing to the intractable nature of the dark-brown material formed. However, in the case of the relatively more stable 5,6-dihydroxy-1-methylindole (**2**), Bu'Lock and Harley-Mason reported that, under appropriate conditions, the reaction of **2** with 1,4-naphthoquinone leads to similar mono and diadducts, identified as 2-(5',6'-dihydroxy-1'-methyl-3'-indolyl)-1,4-naphthoquinone (**8**) and 5,6-dihydroxy-1-methyl-2,3-di-(1',4'-naphthoquinol-2'-yl)-indole (**11**), respectively, on the basis of the similarity of their chromophores to those of the analogous adducts **6** and **7**.

While the formulation of **8** is consistent with a mechanism involving the nucleophilic addition of the indole to the α,β-unsaturated carbonyl system of the quinone, the formation of the diadduct **11** is intriguing since it is difficult to account for it in terms of a subsequent addition of 1,4-naphthoquinone to the indole system. In connection with our interest in the chemistry of melanogenesis, we have now reexamined the structures of the adducts **8** and **11**, and have extended the investigation to the reactions of some other 5,6-dihydroxyindoles with both p-benzoquinone and 1,4-naphthoquinone.

Initially, we repeated the reaction of **2** with p-benzoquinone and obtained, as reported,[2] a complex mixture of brown melanin-like products amongst which no addition products of the type **5** could be detected (UV and TLC evidence). Reduction and subsequent acetylation of the reaction mixture, followed by chromatographic fractionation, led to the isolation of two oligomeric products, which were identified as **12** and **13** by ^{1}H and ^{13}C NMR spectroscopy. The assignment of these structures was secured by comparison of the physical and chromatographic properties of the two oligomers with those of authentic samples of **12** and **13** obtained by enzymic oxidation of **2**, as



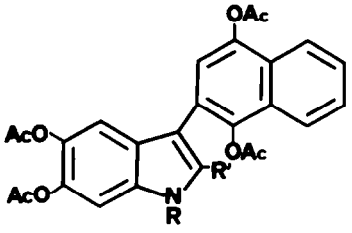
12



13

recently described.[6] Notably, a similar pattern of brown products, including the phenolic precursors of 12 and 13, was also obtained by reaction of 2 with chloranil, consistent with a mechanism involving the quinone induced oxidative coupling of the 5,6-dihydroxyindole system.

When 5,6-dihydroxy-1-methylindole (2) was allowed to react with 1,4-naphthoquinone, in aqueous acetic acid, the reaction proceeded, as reported,[2] to give a deep violet product $C_{19}H_{13}NO_4$ (M+ 319 requires 319.0844, found 319.0869). In agreement with the proposed structure 8, the ^{1}H-NMR spectrum shows, in addition to a singlet at δ 3.74 (3H, N-CH_3) and two broad signals (exchangeable by D_2O) attributable to the OH groups at δ 8.93 and δ 9.00, two multiplets centered at δ 7.80 (2H) and δ7.93 (2H) arising from the H-5, H-8 and H-6, H-7 protons of naphthoquinone system, and four sharp singlets at δ 8.02, δ7.27, δ7.03 and δ6.84 attributable to the H-2', H-3',[7] H-4' and H-7', respectively. The assignment of the singlets at δ8.02 and δ6.84 is supported by significant NOED effects measured between the N-CH_3 resonance at δ3.74 and the signals of the proximal H-7' and H-2' protons. A NOED effect is also observed between the H-4' proton of the indole system and the H-3 proton of the quinone moiety. Additional evidence for the proposed stucture was obtained by reductive acetylation of 8 leading to the expected tetraacetoxy derivative 14 .



14 R=Me R'=H

15 R=H R'=H

16 R=H R'=Me

5,6-dihydroxyindole (1) and 5,6-dihydroxy-2-methylindole (3) reacted similarly with 1,4-naphthoquinone to give the corresponding adducts 9 and 10 which on reductive acetylation were converted into the leucoacetates 15 and 16, respectively.

In further experiments, the reaction of 2 with an excess of 1,4-naphthoquinone in refluxing acetic acid was repeated as originally reported.[2] This gave a 70 % yield of a brown-red insoluble product which was described by Bu'Lock and Harley-Mason[2] as the diadduct 11. In contrast with this structure, the mass spectrum shows a molecular ion peak at m/e 473 suggesting the formula $C_{29}H_{15}NO_6$ (found 473.0934, requires 473.0899) with two hydrogen atoms less than that required for structure 11. Consistently, the ^{13}C NMR spectrum exhibits only ten CH signals, eight of which due to the naphthoquinone systems and the remaining two at δ111.92 and δ96.33 attributable to the C-4 and C-7 of the indole moiety, respectively. These latter assignments are supported by the ^{1}H-NMR spectrum showing, in addition to a multiplet centered at δ 8.06 (8H) for the two naphthoquinone units, two singlets at δ8.71 and δ7.04 arising from the H-4 and H-7, respectively. The strong deshielding of the former with respect to the H-7 is explainable in terms of its closeness to the carbonyl group of ring A.[8,9]

Taken together, these data suggest that the product described by Bu'Lock and Harley-Mason has the dinaphthocarbazole structure 17, arising by a subsequent ring closure of the diadduct 11. This latter step would explain the failure of 5,6-dihydroxy-2-methylindole (3) to react with 1,4-naphthoquinone to give a similar product.

It is difficult to speculate about the sequence of reactions leading to the formation of 17, owing to the present uncertainties on the general mechanism (radical or ionic) of addition of phenols to quinones.[10] The problem is further complicated by the observation that compound 17 can be obtained either by reaction of the monoadduct 8 with 1,4-naphthoquinone or by reaction of 2 with

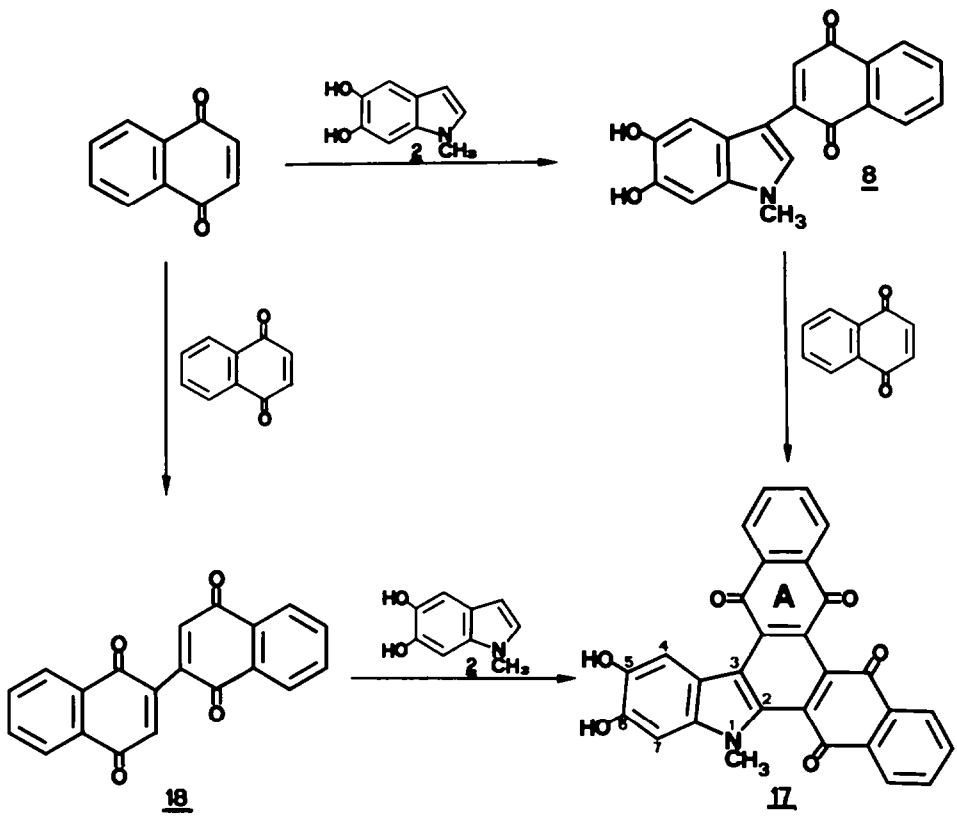


Fig. 1 Reactions of 2 with 1,4-naphthoquinone leading to the dinaphthocarbazole 17.

2,2'-dinaphthyl-1,4,1',4'-diquinone (18) (see fig.1). The formation of this latter compound, under the reaction conditions, has a precedent in literature[11] in the acid catalysed dimerization of naphthoquinones.

In conclusion, the results of our studies show that the reactions of quinones and 5,6-dihydroxyindoles are more complicated than previously believed, because of the tendency of these hydroxylated indole derivatives to undergo oxidative coupling. Although the number of reactions examined is still limited, it appears that quinones with low redox potential, e.g. 1,4-naphthoquinone, react with 5,6-dihydroxyindoles to give addition products of the type 8-10, whereas in the case of quinones with higher redox potentials e.g. p-benzoquinone and chloranil, dehydrogenation of 5,6-dihydroxyindoles takes place with formation of oligomers such as 12 and 13. An additional complexity, which has been observed in the case of 1,4-naphthoquinone, is due to the tendency of the 1,4-naphthoquinone system to undergo self-condensation giving rise eventually to cyclic products such as 17.

EXPERIMENTAL

M.ps. were determined with a Kofler hot-stage apparatus and are uncorrected. UV spectra are recorded with a Perkin-Elmer Mod. 141 spectrometer. ^{1}H-NMR (270 MHz) and ^{13}C-NMR (67.88 MHz) spectra were recorded on a Fourier trasform Bruker WH 270 spectrometer with Aspect 2000 computer 48K memory. The nuclear Overhauser effect difference FID's were obtained by gated decoupling with a microprogram virtually identical with one described in the Bruker Aspect 2000 NMR Software Manual 1.For each measurement, 80 scans with irradiation were subtracted from those with irradiation on resonance. A decoupler amplitude up to 15 Hz was utilized. A flip angle of about 50°

was applied. The sample concentration was 10-15 mg in 0.5 ml of $CDCl_3$ or DMSO-d_6 with TMS as internal reference. Electron impact mass spectrometry was determined with a Kratos MS-50 mass spectrometer. Besides the molecular ion the most abundant ions in the mass spectrum (above m/e 100) are given with their relative intensities. Analytical and preparative TLC were carried out on precoated silica gel F-254 plates (0.25 and 0.50 mm layer thickness,E. Merck). Proportion given for mixed solvents are by volume. The chromatograms were examined by UV irradiation at λ366 nm and λ 254 nm. 5,6-Dihydroxyindole[12], 5,6-dihydroxy-1-methylindole[8] and 5,6-dihydroxy-2-methylindole[13] were prepared as previously reported.

Reaction of 2 with p-benzoquinone.

5,6-Dihydroxy-1-methylindole (2) (800 mg) was dissolved in water (100 ml) containing a little ethanol (1%), and a solution of p-benzoquinone (530 mg) in water (200 ml) was added under vigorous stirring. After 5 minutes the reaction mixture was treated with $Na_2S_2O_4$ and repeatedly extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4 and evaporated to dryness. The brown residue so obtained was acetylated with acetic anhydride (2ml) and pyridine (100 μl) at room temperature for 12 h. After removal of the solvent, the reaction mixture (726 mg) was chromatographed on silica gel using benzene-ethyl acetate (70:30) to give, besides p-diacetoxybenzene (340 mg), a fraction (250 mg) consisting mainly of oligomers of 5,6-diacetoxy-1-methylindole. Subsequent fractionation by TLC (0.50 mm plates) with benzene-ethyl acetate (65:45) gave 12 (81 mg) and 13 (15 mg).

Reactions of 1,4-naphthoquinone with 5,6-dihydroxyindoles 1-3.

In a typical experiment, the appropriate indole (1.25 mmol) was dissolved in 20% acetic acid (10 ml) and a solution of 1,4-naphthoquinone (1.94 mmol) in acetic acid (5 ml) was added. The mixture became violet and a precipitate soon began to separate. After storage overnight at 5°C the precipitate was collected by centrifugation, washed twice with water and dried over P_2O_5 in vacuo.

Using this procedure 5,6-dihydroxy-1-methylindole (2), 5,6-dihydroxyindole (1) and 5,6-dihydroxy-2-methylindole (3) reacted with 1,4-naphthoquinone to give 8 (70% yield), 9 (42% yield) and 10 (65% yield), respectively.

Compound 8, deep-violet needles, m.p. 290-293°C(dec); λ_{max}(EtOH) 286, 301, 545 nm (logε 4.25, 4.25, 3.77); m/e 319 (M+, $C_{19}H_{13}NO_4$:found 319.0869, requires 319.0844); ^{1}H-NMR (DMSO-d_6): δ(ppm) 9.00 (1H, s broad, -OH, D_2O-exchangeable), 8.94(1H, s broad, -OH, D_2O-exchangeable), 8.02 (1H, s, H-2'), 7.94 (2H, m, H-5, H-8), 7.80(2H, m, H-6, H-7), 7.27(1H, s, H-3), 7.03 (1H, s, H-4'), 6.84 (1H, s, H-7'), 3.74 (3H, s, N-CH_3); ^{13}C-NMR (DMSO-d_6): δ(ppm) 185.34 (s), 183.86 (s), 143.81(s), 142.79 (s), 142.04 (s), 134.84 (d), 133.90 (d), 133.29 (d), 132.66 (s), 131.88 (s), 126.40 (d), 125.22 (s), 125.01 (d), 124.96 (d), 118.17 (s), 105.99 (s), 105.61 (d), 97.26 (d), 33.12 (q).

Compound 9, deep-violet needles, m.p. 287-290°C (dec); λ_{max}(EtOH) 284, 295(sh),540 nm (logε 4.22, 4.19, 3.65); m/e 305 (M+, $C_{18}H_{11}NO_4$: found 305.0698, requires 305.0688); ^{1}H-NMR (DMSO-d_6): δ (ppm) 8.92 (1H, s broad,-OH, D_2O-exchangeable), 8.86 (1H, s broad,-OH, D_2O-exchangeable), 8.07 (1H, s, H-2'), 8.04-7.83 (4H, m, H-5, H-6, H-7, H-8), 7.29 (1H, s, H-3), 7.11 (1H, s, H-4'), 6.90 (1H, s, H-7').

Compound 10, deep-violet needles, m.p. 291-294°C (dec); λ_{max}(EtOH) 298, 575 nm (logε 4.19, 3.49); m/e 319 (M+, $C_{19}H_{13}NO_4$: found 319.0786, requires 319.0844); ^{1}H-NMR (DMSO-d_6): δ (ppm) 11.13 (1H,s broad, -NH, D_2O-exchangeable), 8.70 (1H, s broad, -OH, D_2O exchangeable), 8.55 (1H, s broad, -OH, D_2O-exchangeable), 8.07 (2H, m, H-5, H-8), 7.90 (2H, m, H-6, H-7), 6.95 (1H, s, H-3), 6.90 (1H, s, H-4'), 6.75 (1H, s, H-7'), 2.37 (3H, s, -CH_3).

Reductive acetylation of 2-(5',6'-dihydroxy-3'-indolyl)-1,4-naphthoquinones 8-10.

To a refluxing mixture of zinc powder (0.5 g), acetic anhydride (2 ml) and a trace amount of pyridine (20μl), the appropriate 2-(5',6'-dihydroxy-3'-indolyl)-1,4-naphthoquinone (0.25 mmol) dissolved in acetic anhydride (10 ml), was added. The mixture was heated at 80 °C until the violet colour was discharged and then filtered to remove zinc. The filtrate was reduced to dryness, taken up with ethyl acetate and washed twice with water. The organic layer was dried over Na_2SO_4, taken to dryness and the residue crystallized from ethanol.

By this procedure the 2-(5',6'-dihydroxy-3'-indolyl)-1,4-naphthoquinones, 8-10 gave the leucoacetates 14 (90% yield), 15 (30% yield) and 16 (75% yield), respectively.

Compound 14, white prisms, m.p. 174-176 °C; λ_{max}(EtOH) 273, 308 (sh) nm (logε 4.48, 4.16); m/e 489 (M+, 60), 447 (75), 405 (100), 404(75), 363 (65), 321 (59), 320 (77); (found M+ 489.1425, $C_{27}H_{23}NO_8$ requires 489.1424); ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.86(2H, m), 7.54 (1H, s), 7.52 (2H, m), 7.41 (1H, s), 7.25 (1H, s), 7.18 (1H, s), 3.74 (3H, s), 2.44 (3H,s), 2.31 (3H, s), 2.29 (3H, s), 2.12 (3H, s); ^{13}C-NMR ($CDCl_3$): δ (ppm) 169.25 (s), 169.02 (s), 144.41 (s), 142.00 (s), 138.25 (s), 136.57 (s), 134.45 (s), 129.88 (d), 128.51 (s), 127.26 (d),126.39 (d), 124.13(s), 123.81 (s), 121.73 (d), 121.54 (d), 120.34 (d), 114.56 (d),112.27 (s), 103.93 (d), 33.24 (q), 21.00 (q), 20.63 (q).

Compound 15, white prisms, m.p. 202-204 °C; λ_{max}(EtOH) 272, 291 (sh), 306 (sh) nm (logε4.37, 4.16, 4.08); m/e 475 (M+, 18), 433 (46), 392 (21),391 (75), 349 (76), 348 (24),307 (100), 306

(50); ^{1}H-NMR ($CDCl_3$): δ(ppm) 8.57 (1H, s broad, D_2O-exchangeable), 7.85 (2H, m), 7.54 (2H, m), 7.49 (1H, s),7.35 (1H, s), 7.25 (1H,s), 7.19 (1H, s),2.41 (3H, s), 2.31 (6H, s), 2.10 (3H, s).

Compound 16, white prisms, m.p. 236-238 °C; λ_{max}(EtOH) 276, 308 (sh) nm (logε 4.42, 4.06); m/e 489 (M+, 35), 447 (69), 405 (79), 363 (82), 321 (100),320 (67); (found M+ 489.1359, $C_{27}H_{23}NO_8$ requires 489.1424); ^{1}H-NMR ($CDCl_3$): δ(ppm) 8.33 (1H, s broad, D_2O-exchangeable), 7.90 (2H, m), 7.55 (2H, m), 7.22 (1Hx2, s), 7.10 (1H, s), 2.38 (3H, s), 2.32 (3H, s), 2.30 (3H, s), 2.29 (3H, s), 1.96 (3H, s).

Synthesis of 17.

A) From 2 and 1,4-naphthoquinone.

According to the procedure of Bu'Lock and Harley-Mason[2], 1,4-naphthoquinone (150 mg) was added to a stirred solution of 2 (50 mg) in acetic acid (4 ml) and the reaction mixture was taken under reflux for 2h. The brown red precipitate which formed was collected by filtration and washed with ethanol to give 17 (100 mg, 69% yield), brownish red needles, m.p. 345°C (dec);λ_{max}(DMSO) 270, 321 438 nm (logε 4.54, 4.34, 4.12); m/e 473 (M+,100), 472 (23), 445 (14), 444 (16);(found M+ 473.0934, $C_{29}H_{15}NO_6$ requires 473.0899); ^{1}H-NMR (DMSO-d_6):δ(ppm) 9.94 (1H,s broad,-OH,D_2O-exchangeable, 9.34 (1H, s broad, -OH, D_2O-exchangeable), 8.71 (1H, s, H-4), 8.22-7.90 (8H, m), 7.04 (1H, s, H-7), 3.80 (3H, s, N-CH_3);^{13}C-NMR (DMSO-d_6): δ(ppm) 184.17(s), 183.80 (s), 183.53 (s), 182.22 (s), 150.12 (s), 142.23 (s), 141.63 (s), 140.90 (s), 134.46 (s), 134.16 (d), 133.99 (d), 133.84 (d), 133.62 (d), 131.19 (s), 129.91 (s), 126.52 (d), 126.34 (d), 125.65 (d), 125.51 (d), 123.56 (s), 112.74 (s), 111.92 (d), 96.33 (d), 36.24 (q).

B)From 2-(5',6'-dihydroxy-1'-methyl-3'-indolyl)-1,4-naphthoquinone (8) and 1,4-naphthoquinone.

To a solution of 1,4-naphthoquinone (74 mg)in acetic acid (4 ml), 8 (50 mg) was added under vigorous stirring and the reaction mixture was kept under reflux. After 90', the precipitate which separated was filtered and washed with ethanol to give 63 mg (85% yield) of 17.

C)From 2 and 2,2'-dinaphthyl-1,4,1',4'-diquinone (18).

To a suspension of 18[11] (144 mg) in acetic acid (8 ml), a solution of 2 (50 mg) in the same solvent (8 ml) was added. The reaction mixture was kept at 60 °C under vigorous strirring for 15'. The brown-red precipitate which formed was collected by filtration and washed with hot chloroform to give 46 mg of 17 (30% yield).

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REFERENCES AND NOTES

1) R. Möhlau and A. Redlich, Ber., 44, 3605 (1911).
2) J.D. Bu'Lock and J. Harley-Mason, J. Chem. Soc., 703 (1951).
3) J.D. Bu'Lock, J. Chem.Soc., 52 (1960).
4) R.A. Nicolaus, Melanins (Ed. E. Lederer), Hermann, Paris, 1968.
5) G.A. Swan, Fortsch. Chem. Org. Naturst (Eds. W. Herz, H. Grisebach and G.W. Kirby), Springer-Verlag, Wien, 1974, vol. 31, p.521.
6) M.G. Corradini, A. Napolitano and G. Prota, Tetrahedron, 42, 2083 (1986).
7) This assignment may be interchangeable with that of the singlet at δ 7.03 attributable to the H-4'.
8) S.J.Gabriel and O.R. Gottlieb, Phytochemistry, 11, 3035 (1982).
9) C.P. Falshaw, W.D. Ollis, J.A. Moore and K. Magnus, Tetrahedron, 7, 333 (1966).
10) H. Musso, Oxidative coupling of phenols (Eds. W.I. Taylor and A.R. Battersby), Marcel Dekker, INC., New York, 1967, p. 78.
11) R. Pummerer, A. Pfaff, G. Riegelbauer and E. Rosenhauer, Ber., 72, 1623 (1959).
12) J.D. Benigni and R.L. Minnis, J. Heterocyclic Chem., 2, 387 (1965).
13) R.J.S. Beer, K. Clarke , H.G. Khorana and A. Robertson, J. Chem. Soc., 2223 (1948).