Tetrahedron Vol. 44, No. 23, pp. 7265 to 7270, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

A PROFILE OF THE OXIDATION CHEMISTRY OF 5-HYDROXYINDOLE UNDER BIOMIMETIC CONDITIONS.

A. Napolitano, M. d'Ischia and G. Prota *

Department of Organic and Biological Chemistry
University of Naples
Via Mezzocannone 16, I-80134 Napoli, Italy.

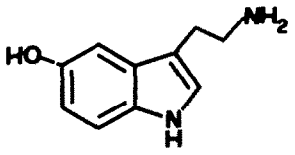
(*Received in UK* 29 *July* 1988)

Abstract. In aqueous buffer, at physiological pHs, 5-hydroxyindole (3) is rapidly oxidised by the H_2O_2/horseradish peroxidase system to give a complex mixture of oligomeric products, five of which could be isolated after acetylation, and identified as the diacetoxybiindolyls 4 and 5, and the trimers 6, 7 and 8. A similar pattern of products was obtained from the reaction of 3 with other oxidising agents, e.g. potassium ferricyanide, ammonium persulphate and sodium periodate. The observed reactivity suggests that oxidation of 3 proceeds probably through the intermediacy of the labile quinone imine 9. This could be trapped in the form of the adduct 12 when 3 was oxidised with o-chloranil in dry ether.

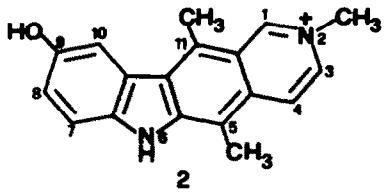
In the last few years there has been an upsurge of interest in the chemistry of biologically active compounds containing the 5-hydroxyindole ring, especially 5-hydroxytryptamine (serotonin, 1) which plays a key role in nervous trasmission. Following an early suggestion that a faulty oxidative pathway of 1 might be the underlying cause of certain types of mental disorders, such as depression and schizophrenia,[1-3] Dryhurst and coworkers[4] recently investigated the electrochemical oxidation of 1 in 0.01 M HCl. As a result of this work, an oxidative pathway of 1 was proposed, involving the initial formation of phenoxyl and nitrogen centred radicals which could either couple to give C(4)-C(4') and N(1)-C(4') dimers, or lose a second electron to generate an unstable quinone imine. This latter is rapidly attacked by water to give tryptamine-4,5-dione and, on further oxidation, 5-hydroxytryptamine-4,7-dione and a related dimer.

In the course of their studies on the antitumour activity of the plant alkaloid ellipticine, Potier and coworkers[5] reported that on reaction with the horseradish peroxidase-H_2O_2 system the hydroxy derivative 2 was readily converted into the corresponding quinone imine, which survived long enough to be detected spectrophotometrically[6]. When generated in the presence of nucleophilic species, e.g. alcohols,[7,8] thiols,[8] aminoacids,[9] nucleosides,[5,7] this quinone imine underwent regiospecific attack at the electrophilic 10-position with formation of the corresponding adducts.

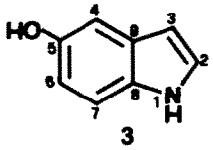
Apart from the foregoing studies on the reactivity of 1 and 2, no further work has recently appeared on the oxidation chemistry of the 5-hydroxyindole system. As a part of our continuing studies on the chemistry of hydroxyindoles,[10,11] we report now the results of a detailed investigation on the oxidative behaviour of the parent 5-hydroxyindole (3) under biomimetic conditions. As the oxidising system for this study, the horseradish peroxidase/H_2O_2 couple was preferably used, in



1



2



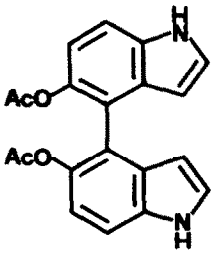
3

view of its postulated role in biological oxidation processes.[12]

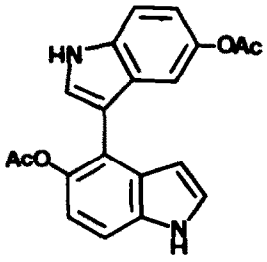
When a solution of 3 in phosphate buffer at pH 6.8 was exposed to H_2O_2, no oxidation took place. Addition of horseradish peroxidase caused an immediate reaction to occur, leading eventually to the formation of a copious yellowish brown precipitate. Direct analysis of the mixture proved to be difficult, owing to both the instability and the unfavourable chromatographic properties of the products. However, acetylation and subsequent fractionation of the mixture on silica gel, coupled in some cases with preparative HPLC, led to the isolation of four major oligomers of 3. A similar pattern of oligomeric products was obtained when 3 was allowed to react with other oxidising agents such as potassium ferricyanide, ammonium persulphate, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and sodium periodate.

Two of the oligomers thus obtained were readily identified as the isomeric 5,5'-diacetoxy-4,4'-biindolyl (4) and 5,5'-diacetoxy-3,4'-biindolyl (5) by straightforward analysis of their ^{1}H- and ^{13}C-NMR spectra.

The mass spectrum of the third oligomer showed a molecular ion peak at m/z 479, corresponding to the formula $C_{28}H_{21}N_3O_5$, and two relevant peaks at m/z 437 and 395, resulting from the consecutive losses of two acetyl groups. The ^{1}H NMR spectrum revealed the presence of twelve protons in the aromatic region which, coupled with the lack of H-4 resonances, suggested the trimeric structure 6, having two units linked through an oxygen bridge. Consistent with this structural assignment, the ^{13}C-NMR spectrum exhibited three singlets for the C-4, C-4' and C-4" carbons, one of which (δ 141.49, C-4") deshielded by the adjacent bridging oxygen.



4



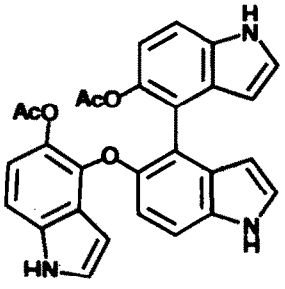
5

The fourth oligomer, $C_{28}H_{21}N_3O_5$, was yellow in colour (λ max 390 and 284 nm) and its ^{1}H-NMR spectrum was characterised by two sets of indolic signals with areas in the ratio of 2:1. The first set (relative area 2) lacked the H-3 proton resonance, while in the second set (relative area 1) the H-4 proton was clearly missing. The ^{13}C-NMR spectrum showed as most prominent features a carbonyl resonance at δ 201.16 and an aliphatic quaternary carbon at δ 56.27. On this basis, the compound was assigned the symmetrical structure 7 in which a 5(4H)-indolone moiety bears at the C-4 carbon two geminal 5-acetoxyindole units attached through the 3-position.

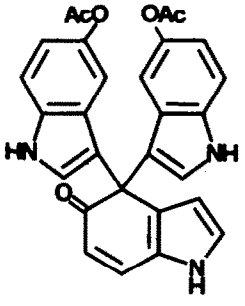
In separate experiments, it was found that in the course of the chemical or enzymic oxidation of 3 another major oligomer was formed which, under the acetylation conditions used, partially decomposed without undergoing esterification. By fractionation of the crude oxidation mixture on silica, the compound was eventually obtained as yellow prisms, m.p. 203-205° C, $C_{24}H_{15}N_3O_3$, λ max 420 ,322 nm. The ^{1}H-NMR spectrum exhibited twelve aromatic protons, four of which due to a 4-disubstituted 5(4H)-indolone moiety, and the remaining eight attributable to two 4-substituted 5-hydroxyindole units mutually linked in an asymmetric fashion. In line with this interpretation, the ^{13}C-NMR spectrum showed a carbonyl resonance at δ 193.08 and two singlets for the C-4 carbons of the two 5-hydroxyindole rings at δ 121.22 and 142.73, the latter shifted downfield by an adjacent oxygen atom. Taken together, these data could only be accommodated by the unusual structure 8, featuring a 1,4-dioxepin-spiro-indol-5(4H)-one ring.

Mechanistically, formation of compound 8 could be envisaged as involving oxidation of the phenolic precursor of the trimer 6, followed by an intramolecular attack of the 5''-hydroxyl group to the substituted 4-position of the outer indole unit.

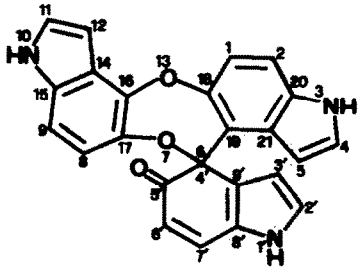
From consideration of the structure of compounds 4-8 it seems that polymerisation of 3 invariably involves coupling of the 4-position of one indole ring with either the 4- or 3-position



6



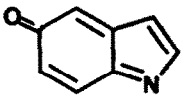
7



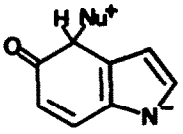
8

or the hydroxyl group of another indole ring. Such a reactivity can be accounted for in terms of either a free radical mechanism or an ionic process in which the electrophilic 4-position of the transiently generated quinone imine 9 is attacked by the nucleophilic sites of a 5-hydroxyindole counterpart. This latter mechanism, however, appears more likely considering that the same pattern of compounds 4-8 is formed with either one electron oxidising agents, e.g. ammonium persulphate,[13] or with two electron oxidants, such as sodium periodate.[14] Noteworthy is also the lack of formation of C3-C3', C3-O and C3-N1 dimers which would supposedly be produced in the case of a statistical coupling of radical species.

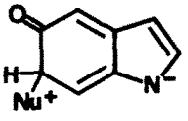
The proclivity of the quinoneimine 9 to undergo nucleophilic attack at the 4-position would fit well into the general pattern of reactivity of quinone imines.[15] The regiospecificity of the reaction is consistent with the higher stability of the initially formed C-4 adduct 10 with respect to the other possible adducts, e.g. 11, in which the aromatic character of the condensed pyrrole moiety is disrupted.



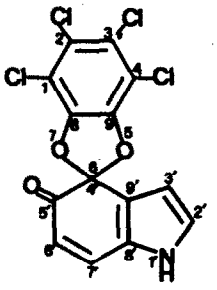
9



10



11



12

Interestingly, when 3 was oxidised with o-chloranil in dry ether the reaction gave as the major product a yellow adduct, $C_{14}H_5NO_3Cl_4$, which was identified as the 1,3-benzodioxol-spiro-indol-5(4H)-one 12. This could well arise from trapping of the quinone imine 9 by the nucleophilic hydroxyl groups of the reduced o-quinone.

As a final consideration, it should be noted that, under all the conditions used, the 6-position of the 5-hydroxyindole ring was not found to be involved in the oxidative process. Unless specific, yet unknown, enzymatic systems are present, this would rule out the possibility envisioned by Udenfriend that tryptophan or a 5-hydroxylated derivative can oxidatively give rise to melanin via the formation of an intermediate 5,6-dihydroxytryptophan.[16]

EXPERIMENTAL

M.ps. were determined with a Kofler hot-stage apparatus and are uncorrected. UV spectra were recorded with a Perkin-Elmer Mod. 550-S spectrophotometer. ^1H NMR (270 MHz) and ^{13}C NMR (67.9 MHz) spectra were performed on a Bruker AC 270 spectrometer. Electron impact mass spectra were determined with a Kratos MS-50 mass spectrometer. Besides the molecular ions, the most abundant ions in the mass spectra (above m/z 100) are given with their relative intensities. Analytical and preparative TLC were carried out on a precoated silica gel F-254 plates from Merck (0.25 and 0.50 mm layer thickness). The chromatograms were examined by UV irradiation at 366 and 254 nm. Flash chromatography was performed on a silica column packed with Merck Kieselgel (230-400 mesh). Preparative HPLC was carried out on a Waters model 6000 A instrument using a 1x25 cm RP18 Lichrosorb Hibar column (E. Merck). The mobile phase was CH_3CN-H_2O (40:60) and the flow rate was maintained at 4 ml/min. Detection was carried out with a UV spectrophotometer Waters model 480 (λ = 290 nm). Horseradish peroxidase (donor-H_2O_2 oxidoreductase, EC 1.11.1.7) type II was purchased as a lyophilized powder (210 units/mg, RZ E430/E275 =2.0) from Sigma Chemical Co. (St. Louis, MO, USA). 5-Hydroxyindole (3) was from Aldrich Chemie (Steinheim,FRG).

Enzymic oxidation of 3.

To a solution of 3 (400 mg, 3 mmol) and horseradish peroxidase (30 mg) in 0.2 M phosphate buffer at pH 6.8 (140 ml), 260 µl (0.294 g, 3 mmol) of a 35% solution of hydrogen peroxide were added under vigorous stirring. The reaction mixture immediately turned to yellowish brown and a precipitate soon began to separate. After 30 min, conversion of the starting material was complete, as evidenced by TLC analysis and the mixture was repeatedly extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4 and taken to dryness. The yellowish brown residue thus obtained was chromatographed on preparative TLC with benzene-ethyl acetate (50:50) to give 8 (Rf 0.36, 26 mg, 7%).
For the isolation of compounds 4-7, the residue was acetylated with acetic anhydride and pyridine at room temperature for 12 h. After removal of the solvents, the mixture was thin layer chromatographed on silica with benzene-AcOEt (50:50) to give four bands at Rf 0.61, 0.57, 0.44, and 0.23.
The less polar band (Rf 0.61, 64 mg) was crystallised from $CHCl_3$ to give 4 (59 mg, 11%).
The second band at Rf 0.57 (56 mg) was further chromatographed on silica gel plates (benzene-AcOEt 60:40) affording 5 (50 mg, 10%).
The band at Rf 0.44 (51 mg) was purified by preparative HPLC giving 6 (15 mg, 3%).
The more polar band (Rf 0.23, 37 mg), consisting of a yellow oil, was purified by preparative TLC using $CHCl_3$-MeOH (92:8) as the eluent to yield 7 (27 mg, 6%).

Chemical oxidation of 3.

1) by potassium ferricyanide, ammonium persulphate, 2,3-dichloro-5,6-dicyanobenzoquinone, sodium periodate.
Oxidation of 3 (100 mg, 0.75 mmol) was carried out with a) potassium ferricyanide (495 mg, 1.50 mmol) in 2% bicarbonate solution (40 ml), b) ammonium persulphate (170 mg, 0.75 mmol) with trace amount of $AgNO_3$ as the catalyst in 0.2 M acetate buffer, pH 6.5 (40 ml), c) 2,3-dichloro-5,6-dicyanobenzoquinone (170 mg, 0.75 mmol) in 0.2 M phosphate buffer-MeOH, 50:50 (40 ml), d) sodium periodate (160 mg, 0.75 mmol) in 0.2 M phosphate buffer, pH 7 (40 ml). In all cases, work up of the resulting yellow-brown mixture as above afforded compounds 4-8 in comparable yields.

2) by o-chloranil.
To an ice-cold solution of 3 (50 mg, 0.37 mmol) in peroxide free ether (35 ml), a solution of o-chloranil (92 mg, 0.37 mmol) in the same solvent (15 ml) was added under stirring. After 10 min the resulting yellow mixture was reduced to small volume (5 ml) in vacuo at 25°C and flash chromatographed on a 1.5X16 cm column with Et_2O-AcOEt (50:50) as the eluent to afford 10 (49 mg, 35%).

5,5'-diacetoxy-4,4'-biindolyl (4)
Colourless prisms from $CHCl_3$, m.p. 200-202 °C; λ max (EtOH) 293 nm (log ε 4.14); HRMS m/z 348.1146 (M+) (calc. for $C_{20}H_{16}N_2O_4$: 348.1110); EIMS m/z 348 (M+,10), 306 (28), 264 (100); ^{1}H-NMR (acetone-d_6): δ1.89 (3H x 2, s, $-CH_3$), 6.01 (1H x 2, ddd, J=3.0, 2.4, 0.8 Hz, H-3, H-3'), 7.03 (1H x 2, d, J=8.8 Hz, H-6, H-6'), 7.27 (1H x 2, dd, J=3.0, 2.8 Hz, H-2, H-2'), 7.47 (1H x 2, dd, J=8.8, 0.8 Hz, H-7, H-7'), 10.35 (1H x 2, bs, NH, NH'); ^{13}C-NMR (acetone-d_6): δ21.20 (q, CH_3CO-), 103.77 (d, C-3, C-3'), 111.97 (d, C-6, C-6'), 117.91 (d, C-2, C-2'), 121.02 (s, C-4, C-4'), 126.54 (d, C-7, C-7'), 129.60 (s, C-9, C-9'), 135.00 (s, C-8, C-8'), 143.02 (s, C-5, C-5'), 170.38 (s, $COCH_3$).

5,5'-diacetoxy-3,4'-biindolyl (5).
Colourless oil; λmax (EtOH) 284 nm; HRMS m/z 348.1133 (M+) (calc. for $C_{20}H_{16}N_2O_4$ 348.1110); EIMS m/z 348 (M+,16), 306(38), 264 (100); ^{1}H-NMR (acetone-d_6) δ: 1.96 (3H, s, $-CH_3$), 2.27 (3H, s, $-CH_3$), 6.45 (1H, ddd, J=3.0, 2.4, 0.8 Hz, H-3'), 6.94 (1H, dd, J=8.6, 2.2 Hz, H-6), 6.98 (1H, d, J=8.8 Hz, H-6'), 7.23 (1H, d, J=2.2 Hz, H-4), 7.33 (1H, dd, J=3.0, 2.8 Hz, H-2'), 7.42 (1H, dd, J=8.8, 0.8 Hz, H-7'), 7.49 (1H, d, J=8.6 Hz, H-7), 7.55 (1H, d, J=2.6 Hz, H-2), 10.36 (1H, bs, NH'), 10.45 (1H, bs, NH); ^{13}C-NMR (acetone-d_6) :δ21.36 (q, $-CH_3$), 21.40 (q, $-CH_3$), 103.65 (d, C-3'), 111.42 (d, C-6'), 112.66 (s, C-3), 113.11 (d, C-6), 114.28 (d, C-4), 117.22 (d, C-2'), 118.15 (d, C-2), 120.44 (s, C-4'), 126.95 (d, C-7'), 127.30 (d, C-7), 128.21, 129.88 (s, s, C-9, C-9'), 135.59, 135.68 (s, s, C-8, C-8'), 142.93 (s, C-5'), 145.72 (s, C-5), 170.95, 171.01 (s, s, -CO-).

5-acetoxy-5'-(5"-acetoxy-indolyl-4"-oxy-)-4,4'-biindolyl (6).
Colourless prisms from EtOH, m.p. 285-287 °C; λ max (EtOH) 294, 274 (sh) (log ε 3.92, 3.86); HRMS m/z 479.1460 (M+) (calc. for $C_{28}H_{21}N_3O_5$: 479.1481); EIMS m/z 479 (M+,40), 437 (100), 395 (96), 306 (20), 264 (89); ^{1}H-NMR (acetone-d_6), :δ1.89 (3H, s, $-CH_3$), 2.12 (3H, s, $-CH_3$), 6.02 (1H, ddd, J=2.9, 2.2, 0.9 Hz, H-3'), 6.04 (1H, ddd, J=2.7, 2.2, 0.9 Hz, H-3), 6.27 (1H, ddd, J=2.9, 2.1, 0.9 Hz, H-3"), 6.72 (1H, d, J=8.8 Hz, H-6'), 6.82 (1H, d, J=8.6 Hz, H-6), 7.01 (1H, d, J=8.7 Hz, H-6"), 7.08 (1H, dd, J= 2.9, 2.8 Hz, H-2'), 7.10 (1H, dd, J=8.6, 0.9 Hz, H-7), 7.25 (1H, dd, J=2.7,

2.5 Hz, H-2), 7.26 (1H, dd, J=8.8, 0.9 Hz, H-7'), 7.31 (1H, dd, J=2.9, 2.8 Hz, H-2''), 7.41 (1H, dd, J= 8.7, 0.9 Hz, H-7"), 10.18, 10.23, 10.28 (1H each, bs, NH,NH',NH"); ^{13}C-NMR (acetone-d_6), δ: 20.74 (q,-CH_3), 21.00 (q, -CH_3), 101.49 (d, C-3'), 102.94 (d, C-3), 103.65 (d, C-3"), 107.22 (d, C-6'), 111.25 (d, C-6), 111.52 (d, C-6"), 113.08 (d, C-2'), 117.35 (s, C-4'), 117.54 (d, C-2), 117.80 (d, C-2'), 121.68 (s, C-4), 122.38 (s, C-9"), 125.44(d, C-7), 125.96 (d, C-7'), 126.12 (d, C-7"), 129.62, 129.74 (s,s, C-9, C-9'), 133.11, 134.68, 135.87 (s,s,s, C-8, C-8', C-8"), 136.98 (s, C-5"), 141.49 (s, C-4"), 143.19 (s, C-5), 149.79 (s, C-5'), 169.74 (s,-CO).

4,4-bis-(5'-acetoxyindol-3'-yl)-indol-5(4H)-one (7).
Yellow needles from ethyl acetate, m.p. 214-216°C ; λ max (EtOH) 390, 284 nm (log ε 3.81, 4.18); HRMS m/z 479.1495 (M+) (calc. for $C_{28}H_{21}N_3O_5$: 479.1481); EIMS m/z 479 (M+,0.5), 437 (1.5), 395 (1), 348 (3), 306 (16), 264 (68), 175 (10), 133 (100); ^{1}H-NMR (acetone-d_6) δ: 2.15 (3H x 2, s, -CH_3), 5.65 (1H, d, J=9.7 Hz, H-6), 5.81 (1H,ddd, J=2.5, 1.7, 0.8 Hz, H-3), 6.75 (1H x 2, d, J=2.5 Hz, H-2'), 6.80 (1H x 2, dd, J=8.7, 2.3 Hz, H-6'), 6.93 (1H, dd, J=2.5, 2.4 Hz, H-2), 7.02 (1H x 2, d, J=2.3 Hz, H-4'), 7.33 (1H x 2, d,J=8.7 Hz, H-7'), 7.42 (1H, dd, J=9.7, 0.8 Hz, H-7), 10.12 (1H x 2, bs, NH'), 10.55 (1H, bs, NH); ^{13}C-NMR (acetone-d_6) δ : 20.99 (q, -CH_3), 56.27 (s, C-4), 111.34 (d, C-6), 112.36 (d, C-6'), 114.39 (d, C-4'), 116.54 (d, C-2'), 117.98 (s, C-3'), 119.26 (d, C-3), 122.86 (d, C-2), 125.03 (s, C-9), 127.35 (s, C-9'), 127.39 (d, C-7'), 132.99 (s, C-8), 133.92 (d, C-7), 136.03 (s, C-8'), 144.53 (s, C-5'), 170.35 (s, -$COCH_3$), 201.16 (C-5).

Diindolo [5,4-b:5',4'-e][1,4]dioxepin-6-spiro-4'-indol-5'(4H)-one (8).
Yellow needles from acetone, m.p. 203-205 °C (dec.); λ max (EtOH) 420, 322 (sh), 310 (log ε 3.70, 4.11, 4.16);HRMS m/z 393.1120 (M+) (calc. for $C_{24}H_{15}N_3O_3$: 393.1113); EIMS m/z 393 (M+,31), 264 (100), 133 (62); ^{1}H-NMR (acetone-d_6) δ: 5.60 (1H,ddd, J=2.6, 2.2, 0.7 Hz, H-3'), 5.70 (1H,d, J=9.8 Hz, H-6'), 6.43 (1H,ddd, J=2.4, 2.2, 0.7 Hz, H-5), 6.49 (1H, ddd, J=2.6, 2.2, 0.7 Hz, H-12), 6.70 (1H, d, J=8.5 Hz, H-8), 6.78 (1H, dd, J=2.6, 2.5 Hz, H-2'), 6.86 (1H, d, J=8.5 Hz, H-1), 7.32 (1H, dd, J=2.4, 2.3 Hz, H-4), 7.38 (1H, dd, J=8.5, 0.7 Hz, H-2), 7.39 (1H, dd, J=2.6, 2.5 Hz, H-11), 7.40 (1H, dd, J=8.5, 0.7 Hz, H-9), 7.42 (1H, dd, J=9.8, 0.7 Hz, H-7'), 10.25, 10.35 (1H each, bs, N10H, N3H), 10.53 (1H, bs, N1'H); ^{13}C-NMR (DMSO-d_6) δ : 102.80 (d, C-5), 102.97 (d, C-12), 106.27 (s, C-4'), 110.39 (d, C-6'), 110.59 (d, C-8), 110.61 (d, C-1), 117.57 (d, C-3'), 117.59 (d, C-4), 117.74 (d, C-11), 121.22 (s, C-19), 121.78 (d, C-2'), 122.69 (s, C-14), 123.90 (s, C-9'), 125.32 (d, C-2), 125.46 (s, C-21), 125.65 (d, C-9), 126.07, 126.14, 133.89 (s,s,s, C-20, C-15, C-8'), 134.22 (s, C-17), 135.40 (d, C-7'), 142.73 (s, C-16), 144.31 (s, C-18), 193.08 (s, C-5').

Tetrachloro[1,3]benzodioxol-6-spiro-4'-indol-5'(4H)-one (12).
Yellow prisms from ethyl acetate-benzene, m.p. 181-183 ° C (dec); λmax(EtOH) 428,280 nm (log ε 3.53, 3.78); HRMS m/z 374.9019 (M+) (calc. for $C_{14}H_5NO_3Cl_4$: 374.9023); EIMS m/z 379/375 (M+,13,25,18) , 250/246 (47,99,79), 133 (100);^{1}H-NMR (DMSO-d_6) δ:5.77 (1H,d, J=9.9 Hz, H-6'), 6.67 (1H, ddd, J=2.6, 2.2, 0.7 Hz, H-3'), 7.16 (1H, dd, J=2.6, 2.5 Hz, H-2'), 7.64 (1H, dd, J=9.9, 0.7 Hz, H-7'), 11.92 (1H, bs, N'H);^{13} C-NMR (DMSO-d_6) δ: 105.83(s, C-4'), 111.10 (d, C-6'), 111.16 (s, C-2,C-3), 115.88 (d, C-3'), 117.95 (s, C-9'), 123.80 (s, C-8'), 124.55 (d, C-2'), 127.91 (s, C-1,C-4), 137.90 (d, C-7'), 145.04 (s, C-8, C-9), 191.38 (s, C-5').

ACKNOWLEDGEMENTS

This work was supported by grants from C.N.R. (Rome) and M.P.I. (Rome).

REFERENCES

1. D.W. Woolley, E. Shaw, Proc. Natl. Sci. U.S.A., 40, 228, 1954.
2. J. H. Gaddum, J. Physiol. (London), 119, 363, 1953.
3. D.W. Woolley, The Biochemical Bases of Psychoses, Wiley, New York, 1962.
4. M.Z. Wrona, G. Dryhurst, J. Org. Chem., 52, 2817, 1987.
5. V.K. Kansal, S. Funakoshi, P. Mangeney, B. Gillet, E. Guittet, J.Y. Lallemand, P. Potier, Tetrahedron, 41, 5107, 1985.
6. C. Auclair, C. Paoletti, J. Med. Chem., 24, 289, 1981.
7. G. Meunier,B. Meunier, C. Auclair, J. Bernadou, C. Paoletti, Tetrahedron Letters, 24, 365,1983.
8. V.K. Kansal, S. Funakoshi, P. Mangeney, P. Potier, B. Gillet, E. Guittet, J.Y. Lallemand, Tetrahedron Letters, 25, 2351, 1984.
9. V.K. Kansal, R. Sundaramoorthi, B.C. Das, P. Potier, Tetrahedron Letters, 26, 4933, 1985.
10. M.G. Corradini, A. Napolitano, G. Prota, Tetrahedron, 42, 2083, 1986.
11. M. d'Ischia, A. Napolitano, G. Prota, Tetrahedron, 43, 5351, 1987.
12. B.C. Saunders, A.G. Holmes-Siedle, B.P. Stark, Peroxidase, Butterworths, London, 1964.
13. F. Minisci, A. Citterio, C. Giordano, Acc. Chem. Res.,16, 27, 1983.
14. A.J. Fatiadi in "Synthetic Reagents", ed. J.S. Pizey, J. Wiley, NewYork, 1981, vol.IV, p.147.
15. P. Grunanger in "Methoden Der Organischen Chemie", (Houben-Weyl), ed. C. Grundmann, George Thieme Verlag, Stuttgard, 1979, vol. VII/3b, p. 235.
16. S. Undenfriend, E. Titus, H. Weissbach, R.E. Peterson, J. Biol. Chem., 219, 335, 1956.