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Reactions of Ninhydrin with Activated Anilines: Formation of Indole Derivatives

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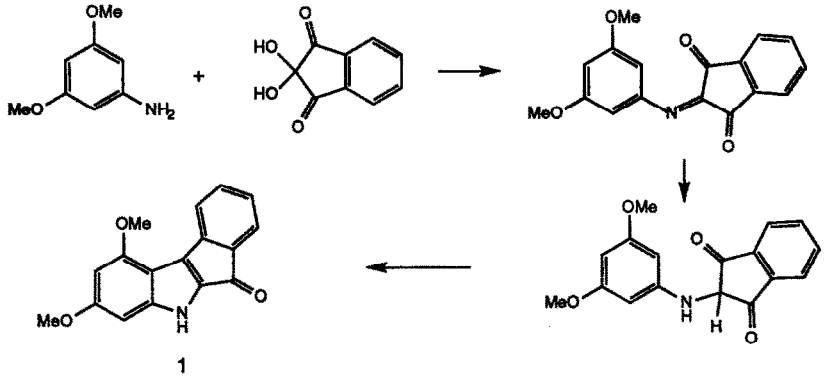
Abstract: In benzene, ninhydrin undergoes electrophilic substitution at C2 of 3,5-dimethoxyaniline, leading to the indeno[1,2-b]indole (7), which can in turn be transformed into the fused indole derivatives (9), (17) and (19), the indolenines (15) and (16), the indolone (18), and the dihydroindole (8). The corresponding reaction in water undergoes electrophilic substitution at C4 to give compound (11)

INTRODUCTION

In connection with other work, we were interested in the synthesis of the indeno-indolinone compound (1) and sought to obtain it from the reaction of ninhydrin with 3,5-dimethoxyaniline, followed by reduction and Bischler-type cyclisation of the product, as shown in Scheme 1.



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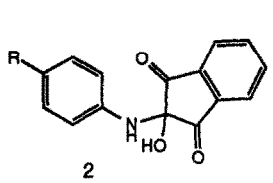
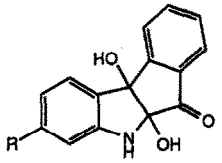
Scheme 1

The chemistry of ninhydrin, and especially its reactions with anilines, has been comprehensively reviewed by Joullié and co-workers [1]. Moubasher has reported that reaction of ninhydrin with 4-aminophenol in acetic acid, or 4-aminobenzoic acid in benzene gave the corresponding 2-hydroxy-2-anilino-indane-1,3-diones (2) [2]. Friedman elaborated on these findings and reported that ortho- and para- activated anilines gave imines

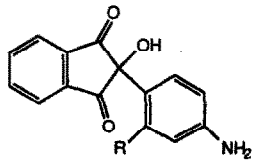
corresponding to the dehydration products of hydroxy compounds analogous to (2) [3]. In contrast, Roth and Kok have claimed that substitution para to the amino group occurs in electron rich anilines[4]. Re-examination of Friedman's work by Shapiro and Chatterjie concluded that the product of the reaction between ninhydrin and 3-hydroxyaniline was not the proposed hydroxy-anilino derivative, but the cyclised compound (3) [5]. A related structure (4) was also proposed for the product from 3-methoxyaniline. We now present our results, which establish that these structures are also incorrect, and should be the structurally isomeric compounds (5 and 6). A recent report by Bullington and Dodd has independently reached the same conclusion [6]. Our results provide even more conclusive evidence, which supports most of their findings, but also corrects yet another erroneous structural assignment.



2
R = OH or COOH



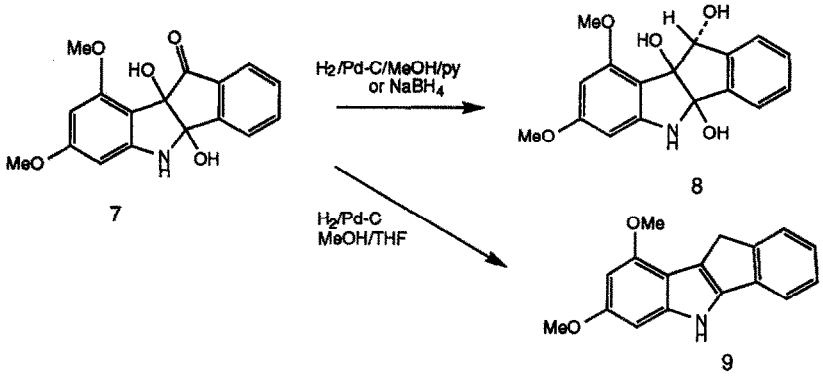
3 R = OH
4 R = OMe



5 R = OH
6 R = OMe

RESULTS AND DISCUSSION

Our reaction of ninhydrin with 3,5-dimethoxyaniline in anhydrous benzene at 60^0 gave a yellow precipitate, which was purified by boiling in acetonitrile, and obtained in 75% yield. This was hydrogenated in methanol containing pyridine to give a colourless compound in 75% yield. The same product could be obtained quantitatively by borohydride reduction. The structure of this reduction product was established by X-ray crystallography to be (8) (see Fig. 1), and therefore the initial reaction product is assigned structure (7).



7

8

9

Hydrogenation of compound (7) in methanol and tetrahydrofuran gave the indeno-indole (9), as the result of a more extensive reduction. This reaction presumably proceeds via dehydration of (7) to the indolenine, followed by reduction of both imine and carbonyl groups, and then another dehydration to give a 3-hydroxymethylindole: such compounds are known to undergo further reduction via indolenine derivatives [7,8].

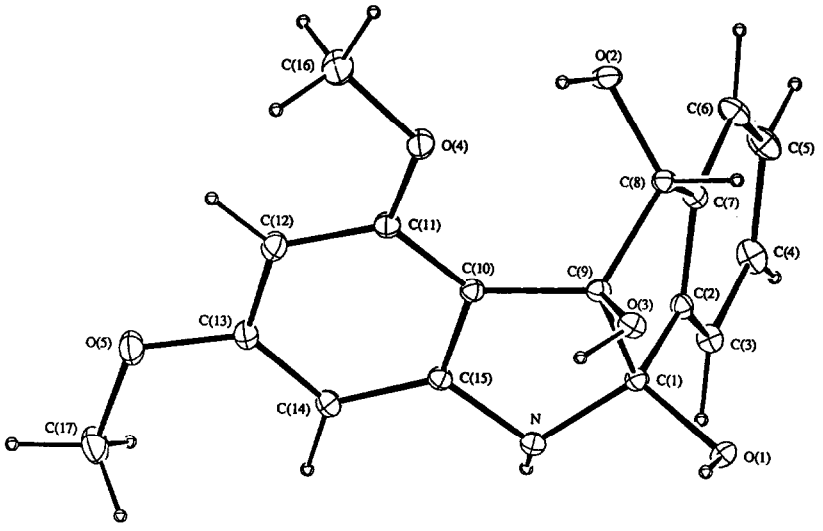
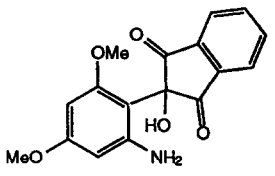


Fig. 1 : X-Ray crystal structure of compound (8).

The formation of the indeno[1,2-b]indole ring system in compound (7) requires that the initial step in the reaction of ninhydrin and the aniline is an electrophilic substitution ortho to the amino group to give the intermediate (10), which subsequently undergoes cyclisation. This contrasts with earlier indications of nucleophilic addition of the aniline nitrogen atom to the hydrated central carbonyl group of ninhydrin. Presumably the electrophilic substitution is a result of the electron-rich nature of the dimethoxy aniline.



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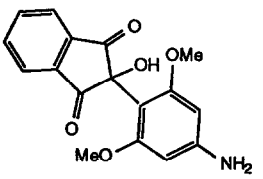


11

It seemed reasonable to assume that whilst electrophilic substitution could be facilitated by the solvent benzene, reaction in a polar solvent could promote the alternative nucleophilic addition. Reaction of 3,5-dimethoxyaniline with ninhydrin in water gave the immediate formation of a deep yellow precipitate, which was a 1:3 mixture of compound (7) to a different substitution product. Spectroscopic data clearly showed that the latter structure was symmetrical and consistent with the less detailed data reported by Shapiro and Chatterjie for the reaction products from 2-hydroxy- and 2-methoxy-aniline [5]. The structure of our reaction product was confirmed by X-ray crystallography to be the 4-substituted aniline (11) (see Fig. 2). Formation of this product is consistent with the earlier work of Roth and Kok [4], but contrary to the assignment of the 2-substituted aniline (10) made by

Bullington and Dodd [6]. These latter workers based their assignment on the observation that their product could be converted on further reaction to the cyclised compound (7). Presumably the 4-substituted aniline (11) must undergo reversal to starting materials to allow the corresponding 2- substituted aniline (10) to form and lead directly to product (7). Indeed, it appears from all the available evidence that the ortho-substituted product is never isolated because it rapidly undergoes cyclisation. Preferential electrophilic substitution at C2 in benzene and C4 in water is probably related to the hydration of the amino group in water, resulting in a serious steric impediment to attack at C2. On the basis of our work, the structures (5 and 6) are assigned to the products of reaction of ninhydrin with 3-hydroxy- and 3-methoxy-aniline reported by Shapiro and Chatterjie [5]. These assignments are also made by Bullington and Dodd [6]. It should, however, be pointed out that the alternative 6-substituted aniline cannot be ruled out conclusively at this stage. ^{1}H Nmr spectroscopic data includes two doublet resonances at 6.30 and 7.35ppm, together with a singlet at 6.10ppm. This clearly establishes that substitution has not taken place at C2, but does not distinguish between C4 and C6 substitution. C4 substitution is considered more likely because of the above steric argument.

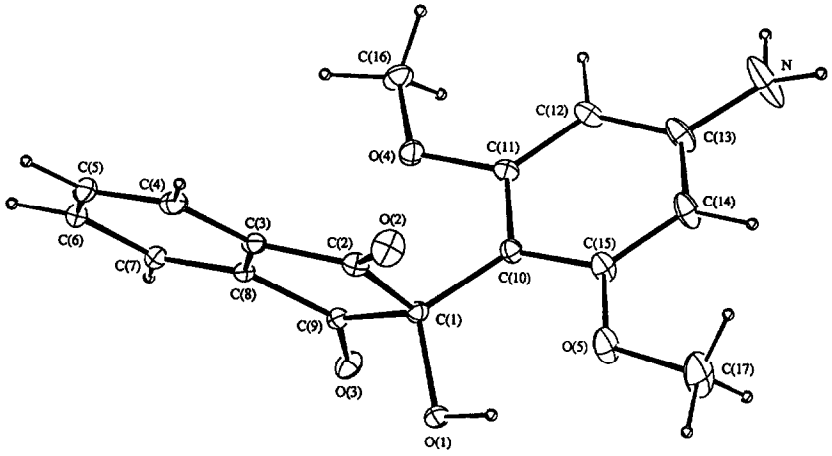
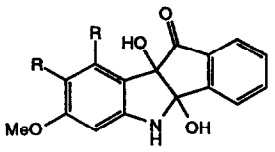
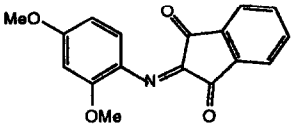


Fig. 2 : X-Ray crystal structure of compound (11).

Reaction of ninhydrin with 3-methoxyaniline in benzene resulted in formation of a black tar, from which only a 9% yield of the cyclised product (12) could be obtained. Structural assignment is based on nmr data and especially a comparison of it with that of compound (7). In our hands, a similar reaction in water gave a 55% yield of the substitution product (6).In an attempt to establish the generality of these reactions, combination of ninhydrin with 3,4,5-trimethoxyaniline in dichloromethane gave the indeno[1,2-b]indole (13) in 25% yield. Contrary to the results of Bullington and Dodd the corresponding reaction in water gave no addition product and only a 6% yield of the cyclised product (13) could be isolated from a complex mixture. Related reaction of ninhydrin with 2,4-dimethoxyaniline in either benzene or water gave the same imine product (14), consistent with



12 R = H
13 R = OMe



14

the findings of Friedman [3] and also Shapiro and Chatterjie [5]. Imine (14) was characterised by spectroscopic data but was relatively unstable and could not be obtained analytically pure.

Despite the fact that the reaction of 3,5-dimethoxyaniline with ninhydrin did not yield our desired structure, it represents a very simple and effective route to the analogous indeno[1,2-b]indole ring system, which has received some attention because of the anti-oxidant properties of some examples[9,10]. Some further exploratory transformations of compound (7) were therefore investigated. Treatment of compound (7) with sulfuric acid and methanol gave the indolenine (15) in 90% yield. The lability of the diol (7) towards dehydration was further demonstrated by the formation of the methoxy-imine (16) after compound (7) was stirred in methanol for 7 days. Reduction of the hydroxy-indolenine (15) with lithium aluminium hydride gave a single hygroscopic product, which was characterised as the 2-aryl indole (17) on the basis of nmr and mass spectroscopic data. Formation of this product is probably initiated by hydride attack at the carbonyl group, resulting in ring opening to give an indoxyl aldehyde. Reduction of both carbonyl groups, followed by dehydration of the hydroxy-indoline ring would then afford the indole(17). Compound (7) was found to undergo rapid attack by hydroxide ion to afford the spiro-lactone (19) as a white solid in almost quantitative yield. The structure was indicated by spectroscopic

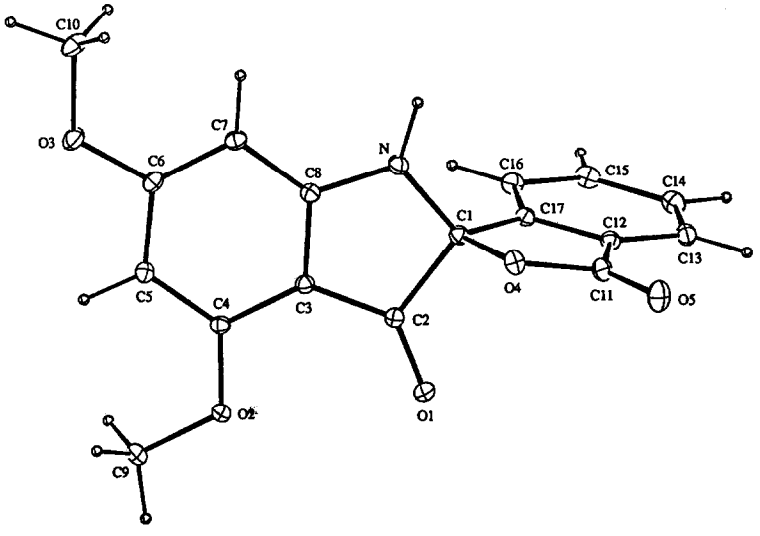
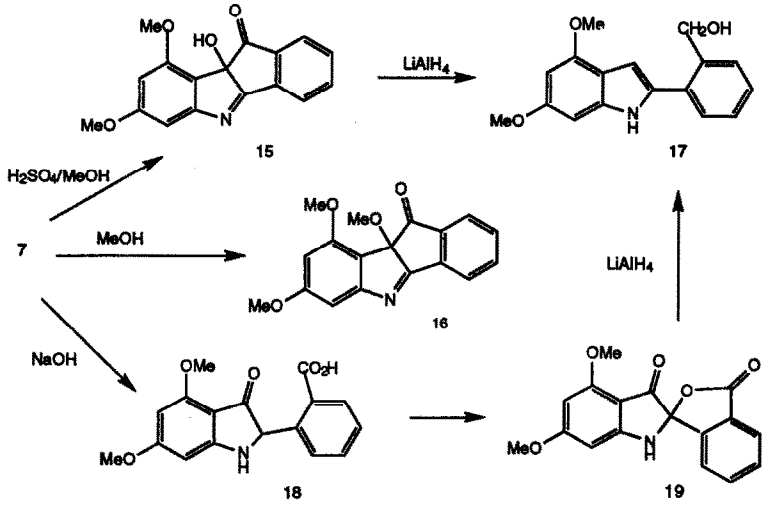
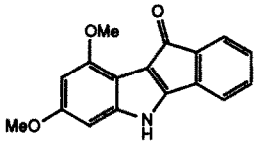


Fig. 3: X-Ray crystal structure of compound (19).

data and confirmed by X-ray crystallography (see Fig. 3). The lactone (19) is presumably formed via the initially-formed indoxyl derivative (18), which could undergo rapid oxidation to an imine susceptible to nucleophilic attack by the carboxylate ion. Reduction of the lactone (19) with lithium aluminium hydride in dry tetrahydrofuran gave the indole (17) in 47% yield.



It would be particularly useful if a direct conversion of the vicinal diol (7) to the indole (20) could be achieved. Numerous methods for such a transformation have been attempted, but so far the desired conversion has not been realised.



20

Crystallography

Crystal data. (8) $(C_{17}H_{17}NO_5)_2.CH_2Cl_2$, M 715.6, triclinic, space group $P\bar{1}$, a 11.232(1), b 11.854(1), c 13.145(1)Å, α 99.667(4), β 103.107(2), γ 100.386(4)°, V 1636.2(2)Å^3, D_c 1.45 g cm^{-3}, Z 2, μ_{Cu} 23.33 cm^{-1}. Crystal size 0.16 by 0.18 by 0.50 mm, $2\theta_{max}$ 140°, min. and max.transmission factors 0.36 and 0.74. The number of reflexions was 5078 considered observed out of 6203 unique data. Final residuals R, R_w were 0.039, 0.064.

Crystal data. (11) $C_{17}H_{15}NO_5$, M 313.3, monoclinic, space group $P2_1/c$, a 11.6346(7), b 8.1907(3), c 19.5722(10)Å, β 124.827(2)°, V 1531.0(1)Å^3, D_c 1.36 g cm^{-3}, Z 4, μ_{Cu} 8.02 cm^{-1}. Crystal size 0.13 by 0.42 by 0.45 mm, $2\theta_{max}$ 140°, min. and max.transmission factors 0.82 and 0.96 The number of reflexions was 2138 considered observed out of 2892 unique data, with R_{merge} 0.012 for 70 pairs of equivalent hk0 data.. Final residuals R, R_w were 0.044, 0.059.

Crystal data (19). $C_{17}H_{13}NO_5$, M 311.3, monoclinic, space group $P2_1/c$, a 8.6585(5), b 7.5056(3), c 22.5331(15)Å, β 99.983(3)°, V 1442.2(1)Å^3, D_c 1.43 g cm^{-3}, Z 4, μ_{Cu} 8.51 cm^{-1}. Crystal size 0.15 by 0.20 by 0.25 mm, $2\theta_{max}$ 140°, min. and max.transmission factors 0.81 and 0.87 The number of reflexions was 2321 considered observed out of 2707 unique data, with R_{merge} 0.010 for 160 pairs of equivalent hk0 data.. Final residuals R, R_w were 0.043, 0.064.

Structure Determination. Reflexion data were measured with an Enraf-Nonius CAD-4 diffractometer in θ/2θ scan mode using nickel filtered copper radiation (λ 1.5418Å). Data were corrected for absorption. Reflexions with $I > 3\sigma(I)$ were considered observed. The structures were determined by direct phasing and Fourier methods. Hydrogen atoms were included in calculated positions, and were assigned thermal parameters equal to those of the atom to which bonded. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined using full matrix least squares. Reflexion weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o) = [\sigma^2(I_o) + (0.04I_o)^2]^{1/2}$. The weighted residual is defined as $R_w=(\Sigma w\Delta^2/\Sigma wF_o^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography[11]. Structure solution was by MULTAN80[12] and refinement used BLOCKLS, a local version of ORFLS[13] ORTEP-II[14] running on a Macintosh IIcx was used for the structural diagram, and an IBM 3090 computer was used for calculations.

The structures and atom numbering schemes are shown in Fig. 1 for molecule A of (8), in Fig. 2 for (11), and in Fig. 3 for (19). Material deposited with this journal comprises all atom and thermal parameters, interatomic distances, angles and torsional angles, and observed and calculated structure factors.

EXPERIMENTAL

General information . Melting points are uncorrected. Microanalyses were performed by Dr. H. P. Pham of the University of New South Wales. ^{1}H n.m.r. spectra were obtained in the designated solvents on a Bruker CXP 300 (300 MHz), a Bruker AC300F (300 MHz) or a Bruker AM 500 (500 MHz) spectrometer. ^{13}C n.m.r. were obtained in the designated solvents on a Bruker AC300F (300 MHz) or a Bruker AM 500 (500 MHz) spectrometer. Ultraviolet spectra were measured on a Hitachi U-3200 spectrometer and refer to solutions in absolute methanol. Infrared spectra were recorded on a Perkin-Elmer 298 or a Perkin-Elmer 580B spectrometer and refer to paraffin mulls. The E.I. Mass Spectra were recorded on an AEI MS 12 mass spectrometer at 70eV ionising potential and 8000 V accelerating voltage with an ion source temperature of 210°C. FAB spectra were recorded on an AutoSpecQ mass spectrometer. Flash column chromatography was carried out using Merck silica gel 7736 60H, whilst preparative thin layer chromatography was performed on 3 mm plates using Merck silica gel 7730 60GF_{254}.

5,10-Dihydro-4b,9b-dihydroxy-7,9-dimethoxyindeno[1,2-b]indol-10-one *(7)*

Ninhydrin (4.64 g, 0.03 mol) was added to a solution of benzene containing 3,5-dimethoxyaniline (4.0 g, 0.03 mol). The suspension was then gradually warmed to 60°C at which time a yellow precipitate began to form in the reaction vessel. Heating was maintained for 5 h. Upon cooling, the precipitate was filtered and washed with methanol / benzene (1:5). Further purification was then accomplished by boiling the solid for a short time in a

small quantity of acetonitrile. The desired product was obtained as a pale yellow powder (6.12 g, 75%) m.p. 188-190°C. (Found: C, 63.5; H, 4.9; N, 4.2. $C_{17}H_{15}NO_5$ 1/2H_2O requires C, 63.4; H, 5.0; N, 4.3%). γ_{max} (KBr Disc) 3457, 3393, 3301, 1710, 1611, 1507, 1462, 1406, 1344, 1225, 1201, 1138, 1099, 1070, 994 cm^{-1}. ^1H n.m.r. δ (d^6 DMSO) 3.60 and 3.70, s, 6H, OCH_3; 5.65, s, OH; 5.70, s, H8; 5.75, d (J=2.6 Hz), H6; 6.00, d (J=2.6 Hz), H7; 7.45, s, NH; 7.50-7.90, m, 4H , ArH. ^{13}C n.m.r. δ (d^6 DMSO): 55.29, (OCH_3); 84.37, (C); 87.05, (C8); 88.86, (C6); 92.90, (C); 103.93, (C); 122.62, (CH); 124.99, (CH); 129.68, (CH); 134.78, (C); 135.61, (CH); 150.63 and 151.38, (COH); 159.30 and 163.43, ($COCH_3$); 199.25, (C=O). *m/z:* 314, (M+1, 12%); 313, (M, 43); 295, (100); 280, (65);.180, (50).

5,10-Dihydro-7,9-dimethoxy-4b,9b,10-trihydroxy-indeno[1,2-b]indole (8)

Method 1

Indenoindole (7) (0.5 g, 1.6 mmol) was dissolved in a mixture of tetrahydrofuran and methanol (4:1) containing 1 mL of pyridine. Palladium catalyst (10% on carbon) (120 mg) was then added and the flask evacuated and flushed several times with an atmosphere of hydrogen. The reaction was stirred for 48 h at room temperature before being examined by thin layer chromatography. The single product which formed was isolated and recrystallised from dichloromethane / petroleum ether to give a white solid (0.43g, 75%) which was found to be hygroscopic. m.p. 75°C. (Found: C, 63.3; H, 6.1 N, 3.8. $C_{17}H_{17}NO_5$. 1/2H_2O requires C, 63.0; H, 5.6; N, 4.3%). γ_{max} (KBr Disc) 3490, 3250, 2950, 1690, 1620, 1600, 1344, 1310, 1240, 1205, 1150, 1110 1065, 945 cm^{-1}. ^1H n.m.r. δ (d^6 DMSO) 3.65, 3.75, s, 6H, OCH_3; 4.75, d (J=4.62 Hz), CHOH; δ5.05, s, OH; 5.20, d (J=4.62 Hz), CHOH; 5.55, s, OH; 5.65, d (J=2.31 Hz), H8; δ5.85, d (J=2.31 Hz), H6; 6.90, s, NH; 7.20-7.60, m, 4H , ArH. ^{13}C n.m.r. δ (d^6 DMSO) 59.04 and 59.32, (OCH_3); 85.81, (CH); 91.62, (CH); 92.56, (CH); 93.31, (C); 100.84, (C); 110.34, (C); 127.39, (CH); 128.2, (CH); 132.16, (CH); 132.43, (CH); 146.45, (C); 146.57, (C); 155.38, (C); 162.11 and 166.40 ($COCH_3$). *m/z*: 316, (M+1, 1%); 315, (M, 3); 279, (100); 280, (65); 250, (35).

Method 2

The indenoindole (7) (1.0 g, 0.32 mol) was dissolved in a solution of dry tetrahydrofuran (100 mL) and stirred at room temperature under a nitrogen atmosphere. Sodium borohydride (0.11 g) was then added in a single portion and was allowed to continue stirring until decolourization of the solution had occurred. The solvent was then removed under reduced pressure to give the trihydroxy compound as a white hygroscopic solid (1.00 g, 100 %).

5,10-Dihydro-7,9-dimethoxyindeno[1,2-b]indole (9)

The indenoindole (7) (1.0 g, 3.0 mmol) in a solution of methanol and tetrahydrofuran (1:3) was hydrogenated over 10% palladium / charcoal (0.15 g) for 48 h. After filtration of the catalyst and evaporation of the filtrate, a white solid was obtained. Chromatography through a short plug of silica gave the pure indenoindole as a white solid (0.6 g, 65%) m.p. 206-208 °C. (Found: C, 76.8; H, 5.9; N, 5.2. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%). γ_{max} (KBr Disc) 3414, 2935, 2901, 1629, 1609, 1579, 1527, 1512, 1461, 1269, 1215, 1148, 1125 cm^{-1}. ^1H n.m.r. δ (d^6 DMSO) 3.70, s, 2H, CH_2; 3.80 and 3.90, s, 6H, OCH_3; 6.22, s, H8; δ6.65, s, H6; 7.20-7.55, m, 4H , ArH; 11.40, s, NH. ^{13}C n.m.r. δ : 32.44, (CH_2); 56.21 and 56.37, (OCH_3); 90.12, (CH); 92.92, (CH); 111.72, (C); 118.16, (CH); 120.9, (CH); 126.29, (CH); 127.66, (CH); 142.58, (C); 144.10, (C); 148.61, (C); 154.63 and 158.38, ($COCH_3$). *m/z:* 266, (M+1, 16%); 265, (M, 83); 250, (100); 207, (23).

2-Hydroxy-2-(4-amino-2,6-dimethoxyphenyl)indan-1,3-dione (11)

Ninhydrin (4.64 g, 0.03 mol) was dissolved in water (50 mL) and stirred with an aqueous suspension of 3,5-dimethoxyaniline (4.0g, 0.03 mol). The yellow precipitate which formed immediately was allowed to continue stirring for several hours at room temperature. The precipitate was filtered, washed and dried before being recrystallised from ethanol to give the product as a yellow solid (3.0 g, 36%) m.p. 168-169°C. (Found: C, 65.2, H, 4.4 N, 4.2. $C_{17}H_{15}NO_5$ requires C, 65.2; H, 4.8, N, 4.5%). γ_{max}: 3550, 3460, 3410, 2990, 2910, 1730, 1640, 1590, 1480, 1385, 1240, 1120 cm^{-1}. ^1H n.m.r. (d^6 DMSO) 3.50, s, 6H, OCH_3; 5.40, s, 2H, NH_2; 5.90, s, 2H, H3 and H5 (aniline); 6.70, s, OH; 8.02, s, 4H, ArH. ^{13}C n.m.r. δ (d^6 DMSO): 59.10, ($O\underline{C}H_3$); 80.88, (C); 95.13, (CH); 102.83, (C); 126.80, (CH); 139.68, (CH); 142.87, (C); 154.21, (C); 162.51, (C); 202.49, (C=O). *m/z*: 314, (M+1, 9%); 314, (M, 35); 180, (28); 153, (100), 124, (35), 104, (45).

The cyclised product (7) (1.0g, 12%) could also be isolated from the mother liquors.

2-Hydroxy-2-(4-amino-2-methoxyphenyl)indan-1,3-dione (6)

Ninhydrin (2.9 g, 0.016 mol) was dissolved in warm water (50 mL)and heated with an aqueous suspension of 3-methoxyaniline (2.0 g, 0.0163 mol) in water. The yellow gum which formed was allowed to continue stirring for several hours at room temperature. The precipitate was filtered, washed and taken up in ethanol. Treatment with activated charcoal followed by recrystallisation gave the pure product as a yellow solid (2.5 g, 55%).m.p. 214-215°C, (Lit. 212-214°C)[5]. γ_{max}: 3400, 3300, 3410, 2900, 2830, 1740, 1700, 1600, 1580, 1500, 1460, 1360, 1300, 1240, 1200 cm^{-1}; ^1H n.m.r. (d^6 DMSO) 3.10, s, 3H, OCH_3; 5.20, s, 2H, NH_2; 6.10, s, H3; 6.30, d, H5; 6.80, s, OH; 7.35, d, H6; 8.00, s, 4H, ArH. ^{13}C n.m.r. δ (d^6 DMSO): 58.74, ($O\underline{C}H_3$); 79.51, (C); 101.01, (CH); 110.01, (CH); 117.74, (C); 127.08, (CH); 132.38, (CH); 140.11, (CH); 143.88, (C); 154.20, (C); 159.63, (C); 204.63, (C=O).

5,10-Dihydro-4b,9b-dihydroxy-7-methoxyindeno[1,2-b]indol-10-one (12)

Ninhydrin (7.2 g, 0.04 mol) was added to a solution of benzene containing 3-methoxyaniline (5.0g, 0.04 mol). The dark orange solution was heated for 8h at 60°C. Upon cooling, the tar which formed was dissolved in acetone causing a small amount of product to crystallise. The solid was filtered and dried to give the indenoindole as a cream material (1.0 g, 9%) m.p. 140-142 °C. (Found: C, 64.1; H, 5.2 N, 4.4.$C_{16}H_{13}NO_4.H_2O$ requires C, 63.8; H, 5.0; N, 4.6%). γ_{max}: 3295, 2940, 2850, 1720, 1700, 1619, 1470, 1380, 1300, 1225, 1210, 1180, 1160, 1150, 1100 cm^{-1}. ^1H n.m.r. δ (d^6 DMSO) 3.65, s, 3H, OCH_3; 6.05, d (J=2.3 Hz), H6; 6.08, s, OH; 6.15, s, OH; 6.20, d (J=2.3 Hz), H8; 7.15, d (J=2.4 Hz), H9; 7.45, s, NH; 7.50-8.00, m, 4H , ArH. ^{13}C n.m.r. δ (d^6 DMSO): 58.97, ($O\underline{C}H_3$); 87.14, (C); 96.41, (C); 98.16, (CH); 108.21, (CH); 121.02, (C); 126.68, (CH); 128.95, (CH); 130.30, (CH); 133.78, (CH); 137.86, (C); 140.39, (CH); 152.97, (C); 156.19, (C); 166.17, (C); 205.12, (C=O). *m/z:* 284, (M+1, 5%); 283, (M, 15); 265, (25); 250, (20); 150, (100).

5,10-Dihydro-4b,9b-dihydroxy-7,8,9-trihydroxy-indeno[1,2-b]indol-10-one (13)

3,4,5-Trimethoxyaniline (0.5 g, 2.7 mmol) was dissolved in a minimum amount of dichloromethane and added to a flask containing finely powdered ninhydrin (0.49 g, 2.7 mmol) suspended in benzene. The reaction vessel was then protected from light using sheet foil and left to stir for 48 h. The precipitated solid was filtered to give the indenoindole (13) as a white solid (0.23 g, 25%) in a state of high purity m.p. 137-139°C. (Found: C, 63.1; H, 4.8; N,4.0;. $C_{18}H_{17}NO_6$ requires C, 63.0; H, 5.0; N, 4.1%). γ_{max} 3560, 3200, 2900, 2860, 1710, 1600,

1450, 1370, 1340, 1290, 1240, 1200, 1120, 1050, 1000, 930, 920, 805 cm^{-1}. ^1H n.m.r. δ (d^6 DMSO) 3.61, 3.70 and 3.85, s, 9H, OCH_3; 5.75, s, OH; 5.85, s, H6; 6.15, s, OH; 7.30-7.90, m, 4H, ArH; ^{13}C n.m.r. δ (d^6 DMSO) 55.93, 60.85 and 61.32, ($O\underline{C}H_3$); 85.00, (C); 89.20, (CH); 92.85, (C); 108.98, (C); 122.71, (CH); 125.13, (CH); 129.84, (CH); 133.96 (C); 134.81, (C); 135.88, (CH); 145.43, (C); 151.63, 152.71 and 156.23, ($COCH_3$); 199.23, (C=O). *m/z:* 344, (M+1, 4%); 343, (M, 17); 325, (100); 310, (90).

2-(2,4-dimethoxyphenylimino)indan-1,3-dione (14)

2,4-Dimethoxyaniline (0.5 g, 3.3 mmol) was dissolved in a minimum amount of dichloromethane and added to a suspension of finely powdered ninhydrin (0.6 g, 3.4 mmol) in benzene. A slow initial colour change from clear to yellow was followed by the formation of a deep green solution. The solvent was evaporated after 48 hours to give a green / purple.solid which was chromatographed (dichloromethane) to give the imine (14) as a green solid (0.53 g, 55%) m.p. 162-1648°C γ_{max} 2920, 1760, 1720, 1600, 1460, 1380, 1310, 1210, 1165, 1140, 1045, 995 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 3.85 and 3.90, s, 6H, OCH_3; 6.55, m, 2H, H5', H6', ; 7.60, d, H3'; 7.20-8.2, m, 4H, ArH. ^{13}C n.m.r. δ ($CDCl_3$) 55.68 and 55.89, (OCH_3); 98.53, (CH); 104.61, (CH); 123.89, (CH); 124.23, (CH); 126.22, (CH); 130.84 (C); 136.12, (CH); 155.18, (C); 163.31, (C). *m/z*: 296, (M+1, 15%); 294, (M, 45%); 104, (100) .

10H-9b-hydroxy-7,9-dimethoxyindeno[1,2-b]indol-10-one (15)

Indenoindole (7) (1.0 g, 0.003 mol) was suspended in a solution of methanol and water (1:5) and cooled to 0°C in an ice bath. Concentrated sulphuric acid, (5 drops) was then added slowly to the rapidly stirring solution. An immediate darkening of the suspension occurred. Stirring was allowed to continue for a further 20 min before the mixture was cooled and filtered. The isolated yellow product was recrystallised from ethanol as a bright yellow solid (0.85 g, 90%) m.p. 272-274 °C. (Found: C, 69.0; H, 4.6 N, 4.6. $C_{17}H_{13}NO_4$ requires C, 69.1; H, 4.5; N, 4.7%). γ_{max}: 3427, 2963, 2842, 1709, 1690, 1623, 1582, 1550, 1533, 1361, 1312, 1203, 1157, 1129 cm^{-1}. ^1H n.m.r. δ (d^6 DMSO) 3.85 and 3.92, s, 6H, OCH_3; 6.26, d (J=1.8 Hz),H8; 6.60, (J=1.8 Hz), H6; 7.40-8.25, m, 4H , ArH; 11.80, s, OH. ^{13}C n.m.r. δ (d^6 DMSO); 55.61 and 55.67, (OCH_3); 87.35, (C8); 92.52, (C6); 101.98, (C); 114.73, (C); 117.62, (C); 120.26, (CH); 126.53, (CH); 130.87, (C); 131.01, (CH); 134.45, (C); 135.56, (CH); 137.56, (C); 153.65, (C); 159.35 and 162.02 (C); *m/z*: 296, (M+1, 26%); 295, (M, 100); 280, (50); 252, (35).

10H-7,9,9b-Trimethoxyindeno[1,2-b]indol-10-one (16)

The dihydroxyindenoindole (7) (1.0 g, 0.003 mol) was stirred in methanol at room temperature for 7 days. During this period the solution was observed to darkened from pale to deep yellow. The solvent was removed under reduced pressure and the product isolated as a yellow-orange solid (0.46 g, 46%) m.p. 150-152°C. (Found: C, 65.6; H, 4.9 N, 4.2.$C_{18}H_{15}NO_4.H_2O$ requires C, 66.0; H ,5.2; N, 4.3%). γ_{max}: 3415, 2953, 2842, 1716, 1633, 1598, 1585, 1474, 1434, 1377, 1314, 1284, 1224, 1097, 1088 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 3.80, 3.90 and 3.95 s, 9H, OCH_3; 6.26, (J=1.8 Hz),H8; 6.67, (J=1.8 Hz), H6; 7.50-7.75, m, 4H , ArH. ^{13}C n.m.r. δ ($CDCl_3$); 52.48, 55.61 and 55.67, ($O\underline{C}H_3$); 97.10, (C5); 103.52, (C); 103.69, (C7); 129.77, (CH); 129.89, (CH); 130.60, (CH); 131.50, (C); 131.60, (C); 132.33, (CH); 160.48, (C); 163.68, (C); 167.16, (C); 168.99, (C); 170.17 and 185.78 (C). *m/z:* 310, (M+1, 19%); 309, (M, 100); 164, (44).

4,6-Dimethoxy-2-phenylindol-2'-yl methanol (17)

Compound (15) (2.0 g, 6.7 mmol) was dissolved in dry tetrahydrofuran (50 mL) and heated to reflux. Lithium aluminium hydride (0.7 g) was then carefully added in small portions and the solution refluxed for 24 h. The excess hydride was then cautiously destroyed by the slow addition of water. The solution was then neutralised and swirled with dichloromethane. Drying of the solvent over anhydrous magnesium sulfate followed by evaporation under reduced pressure gave the alcohol as a hygroscopic solid (0.79 g, 42%) m.p. 88°C. (Found: C, 70.8; H, 6.2; N, 4.5. $C_{17}H_{17}NO_3$ requires C, 72.1; H, 6.0; N, 5.0%). ^{1}H n.m.r. δ ($CDCl_3$) 3.20, bs, OH, 3.80 and 3.95, s, 6H, OCH_3; 4.70, s,2H, CH_2; 6.30, d (J=2.2 Hz), H5; 6.55, d (J=2.2 Hz), H7; δ6.90, d (J=2.5 Hz), H3; 7.40-7.80, m, 4H, ArH; 10.20, bd, NH. ^{13}C n.m.r. ($CDCl_3$) δ55.23 and 55.52, (OCH_3); 64.37, (CH_2); 86.99, (CH); 91.67, (CH); 98.75, (CH); 113.98, (C); 127.17, (CH); 128.83, (CH); 129.40, (CH); 130.60, (CH); 133.74, (C); 135.04, (C); 135.46, (C); 137.92, (C); 153.43 and 157.34, ($\underline{C}OCH_3$). m/z: 284, (M+1, 15%); 283, (M, 80); 250, (100); 207, (30).

Spiro[2,3-dihydro-4,6-dimethoxy-3-oxoindole-2,3'-phthalide] (19)

Indole (7) (0.3 g, 1.0 mmol) was dissolved in pyridine (2 ml) and added to a solution of sodium hydroxide (10 ml, 2.5M). After stirring for 3h, neutralisation gave a cream precipitate, which was chromatographed in dichloromethane on silica to give the lactone (19) (0.27 g, 90%) as a white solid.m.p. 228-229°C. (Found: C, 65.4; H, 4.5; N, 4.2. $C_{17}H_{13}NO_5$ requires C, 65.6; H, 4.2; N, 4.5%). υ_{max} 3330, 2942, 2865, 1755, 1700, 1620, 1590, 1515, 1470, 1375, 1345, 1224, 1174, 1105 cm^{-1}. ^{1}H n.m.r. δ (d^6DMSO) 3.75 and 3.80, s, OCH_3; 5.90, s, H5; 6.10, s, H7; 7.45 - 8.00, m, ArH; 8.50, s, NH. ^{13}C n.m.r. d (d^6DMSO) 56.20, 56.41, (OCH_3); 88.66 (CH); 91.00, (CH); 95.40, (C); 100.30, (C); 122.83, (CH); 125.26, (CH); 127.22,(C); 131.36, (CH); 135.40, (CH); 144.54, (C); 160.73, (C); 163.82, (C); 166.43, (C); 170.94, 187.91, (CO). m/z: 311, (M, 42%); 283, (100); 282, (40); 266, (36); 252, (31); 238, (28); 210, (26); 209, (42); 206, (30).

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REFERENCES

1. Joullié, M.M.; Thompson, T.R.; Nermeroff, N.H. *Tetrahedron*, **1991**, *47*, 8791-8827.
2. Moubasher, R., *J. Chem. Soc.* **1948**, 1038-1041.
3. Friedman, M., *Can. J. Chem.* **1967**, *45*, 2271-2275.
4. Roth, H.J.; Kok, W., *Arch. Pharm.* **1975**, *308*, 301-307.
5. Shapiro, R.; Chatterjie, N., *J. Org. Chem.* **1970**, *35*, 447-450.
6. Bullington, J.L.; Dodd, J.H., *J. Org. Chem.* **1993**, *58*, 4833-4836.
7. Leete, E.E., *J. Am. Chem. Soc.* **1959**, *81*, 6023-6026.
8. Black, D.St.C.; Kumar, N.; Wong, L.C.H., *Aust. J. Chem.* **1986**, *39*, 15-20.
9. Brown, D.W.; Graupner, P.R.; Sainsbury, M.; Shertzer, H.G. *Tetrahedron* **1991**, *47*, 4383-4408.
10. Graham, J.; Ninan, A.; Reza, K.; Sainsbury, M.; Shertzer, H. G. *Tetrahedron* **1992**, *48*, 167-176.

11. Ibers, J.A. and Hamilton, W.C., (Eds) 'International Tables for X-Ray Crystallography' Vol. 4, Kynoch Press, Birmingham, **1974.**
12. Main, P.,'MULTAN80', University of York, England, **1980.**
13. Busing, W.R., Martin, K.O., and Levy, H.A.,'ORFLS', Oak Ridge National Laboratory, Tennessee, U.S.A., **1962.**
14. Johnson, C.K.,'ORTEP-II', Oak Ridge National Laboratory, Tennessee, U.S.A., **1976.**

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