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SYNTHESIS OF LAVENDAMYCIN

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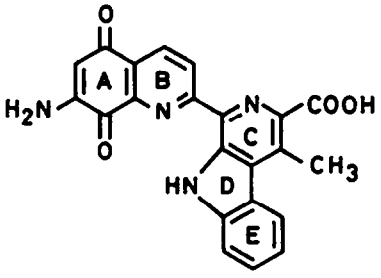
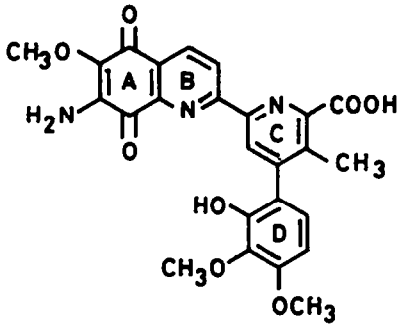
Abstract - A regiospecific and convergent synthesis of Lavendamycin (1) starting from 8-hydroxyquinoline and indole via Bischler-Napieralski cyclisation is described.

The isolation of lavendamycin (1), a novel antitumour antibiotic from the fermentation broths of Streptomyces lavendulae by Doyle et al[1] has triggered off another synthetic puzzle to organic chemists. Lavendamycin, a dark red quinone was shown to possess a β-carboline skeleton accompanied by varied functional groups.

Lavendamycin bears a striking similarity with that of a tetracyclic antitumour antibiotic, streptonigrin (2). It was demonstrated by biosynthetic studies due to Gould and co-workers[2] that streptonigrin was originated from β-methyltryptophan via the formation of β-carboline skeleton and since lavendamycin also possesses a β-carboline system, it might have a biosynthetic link between β-methyltryptophan and streptonigrin. The recent reports on the total synthesis of 1 by Kende et al[3] and Hibino et al[4] have prompted us to record our findings on its total synthesis.



(1)



(2)

Fascinating structural features coupled with interesting biological activity of lavendamycin led us to undertake the synthesis of this complex molecule and of its analogues with a view to find better activity than the parent compound.

The retrosynthesis (Scheme-I) of the molecule called for judicious planning and revealed us two key intermediates, namely, β-methyltryptophan (4) and suitably substituted quinaldic acid 3 which in turn could be obtained from easily accessible indole (6) and 8-hydroxyquinoline (5) respectively.

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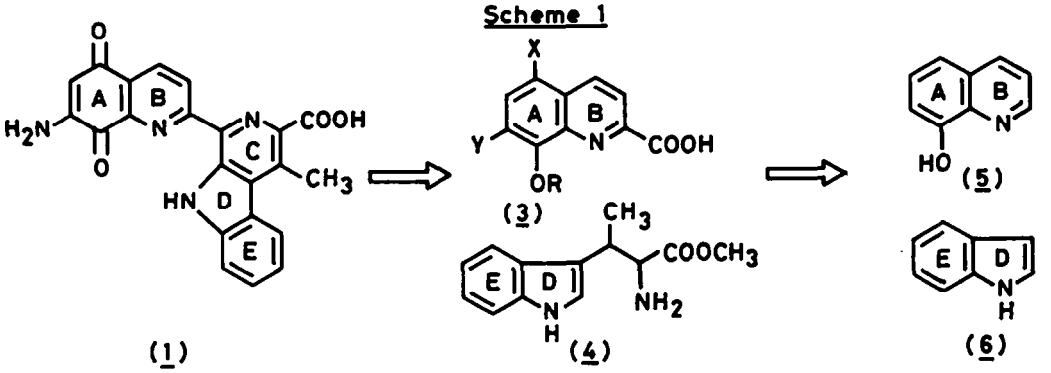
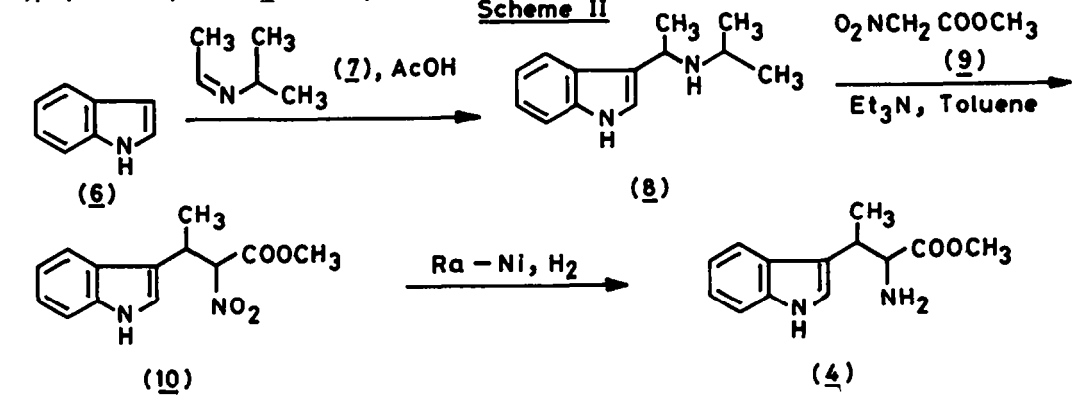
Scheme 1



Thus, our synthetic strategy comprised of constructing first AB and DE rings followed by C ring at the later stages. In our earlier communication[5] we have demonstrated the efficacy of the above synthetic plan.

β-Methyltryptophan methyl ester was prepared from indole in three high yielding steps (Scheme-II). Indole (6) was subjected to Mannich reaction[6] with ethylidene isopropylamine (7) to give 3-(Isopropylamino ethylidene)-indole (8) in 60% yield. Condensation[7] of the amine 8 with methyl nitroacetate (9) in refluxing toluene gave rise to diastereomeric mixture of methyl- β-(3-indolyl)- β-methyl-α-nitropropionate (10) in 85% yield. Hydrogenation of the nitroester 10 with Raney nickel at normal pressure afforded β-methyltryptophan methyl ester (4) in 71% yield.

Scheme II

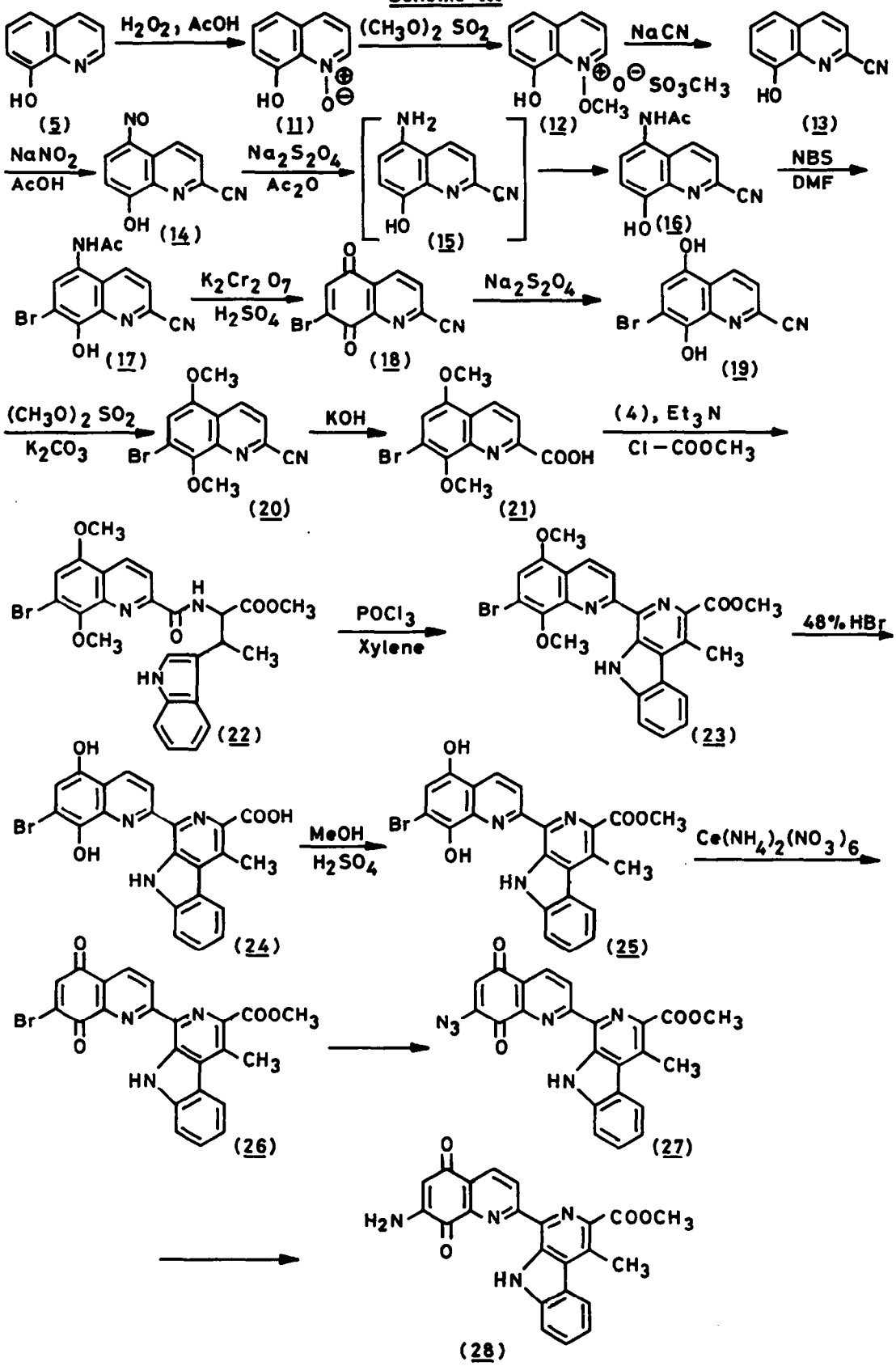


After successfully completing the indole part, attention was directed towards properly substituted 8-hydroxyquinaldic acid from 8-hydroxyquinoline (5) (Scheme-III). 8-Hydroxyquinoline (5) was converted into N-oxide 11 by treatment with hydrogen peroxide in hot acetic acid according to modified literature procedure[8]. Alternately, the same reaction was conducted efficiently by employing m-CPBA as the oxidising agent to obtain 11 in 83% yield. Treatment of 11 with dimethylsulphate gave the salt 12 which was directly converted into 8-hydroxyquinaldonitrile (13) by treatment with sodium cyanide[9] in 72% yield. 13 was then subjected to nitrosation reaction in acetic acid to give 5-nitroso-8-hydroxyquinaldonitrile (14) in 74% yield. Reduction of the nitroso compound 14 with aqueous sodium dithionite yielded the amine 15 which was isolated as amide 16.

The reactivity of the amine was curtailed due to the amide formation and therefore advantage was taken of the free hydroxyl group as a better ortho directing group towards electrophilic bromination. Introduction of bromine at C-7 position as latent amine (which could be derived at the later stages) was envisaged. Bromination of the phenolic compound 16 employing variety of brominating conditions led to irretrievable devastation of the molecule. The propensity of NBS as a nuclear brominating agent is well documented in literature. Bromination of phenolic compound 16 employing one equivalent of NBS in DMF at 0° smoothly furnished 5-acetamido-7-bromo-8-hydroxyquinaldonitrile (17) in 83% yield.

Two-phase oxidation of amidophenol 17 with acidic potassium dichromate at 0° furnished 2-cyano-7-bromo quinoline-5,8-dione (18) in 73% yield. Reduction of 18 using aqueous sodium dithionite gave 7-bromo-5,8-dihydroxyquinaldonitrile (19) in 94% yield, which was protected as its dimethyl ether 20. Alternately, the amidophenol 17 was oxidised and the resultant quinolinedione 18 was directly subjected

Scheme III


H2O2, AcOH
(CH3O)2 SO2
NaCN
(5)
(11)
(12)
(13)
NaNO2
AcOH
Na2S2O4
Ac2O
(14)
(15)
(16)
NBS
DMF
(17)
K2Cr2O7
H2SO4
(18)
Na2S2O4
(19)
(CH3O)2 SO2
K2CO3
(20)
KOH
(21)
(4), Et3N
Cl-COOCH3
(22)
POCl3
Xylene
(23)
48% HBr
(24)
MeOH
H2SO4
(25)
Ce(NH4)2(NO3)6
(26)
(27)
(28)

without purification to dithionite reduction and subsequently methylated to 20 in 43% overall yield. Hydrolysis of the nitrile 20 in a refluxing ethanolic solution of aqueous potassium hydroxide gave 7-bromo-5,8-dimethoxyquinaldic acid (21) in 86% yield. Condensation of the acid 21 with β-methyltryptophan 4 furnished the amide 22 in excellent yield. Cyclisation of amide 22 was effected with $POCl_3$ in refluxing xylene to give the β-carboline 23 in 85% yield. Direct oxidation of 23 with oxidising agents like ammonium cerric nitrate or argentic oxide to the bromoquinone 26 were marred with low conversion with most of the starting material remaining in tact. However, this problem was later circumvented as follows. Exhaustive demethylation in refluxing 48% HBr afforded 24 which was esterified using methanolic sulphuric acid to 25. Subsequent oxidation of 25 with CAN or $K_2Cr_2O_7$ gave the bromoquinone 26. This bromoquinone was found to be identical in all respects with that of reported sample.

Since the transformation of bromoquinone 26 to lavendamycin methyl ester 28 via azidoquinone 27 had already been reported by Kende et al[3], this communication would constitute a formal total synthesis of lavendamycin.

Experimental

Melting points were determined, either in open capillaries or on Koffler block instrument, and are uncorrected. Infrared spectra (IR) ($\tilde{\nu}_{max}$ in cm^{-1}) were recorded in nujol or chloroform or neat in a Perkin Elmer model 683 spectrophotometer with sodium chloride optics. ^{1}H-NMR spectra were recorded on a Varian T-60/Varian FT-80A/Jeol PMX-60/Bruker WH-90 spectrometer in CCl_4/$CDCl_3$/ DMSO-d_6/ Acetone-d_6 containing TMS as an internal standard. All chemical shifts are reported in parts per million (δ) downfield from TMS. Mass spectra were recorded on AEI MS 30 double beam mass spectrometer/CEG 21-110B spectrometer. All solvents and reagents were purified and dried by standard techniques. Progress of the reactions was monitored by thin layer chromatography (TLC) on 0.2 mm layers of silica gel, prepared with Acme silica gel (400 mesh) and the chromatograms were exposed in iodine vapours or ultraviolet lamp for visualisation. Column chromatography was carried out using silica gel (60-120 mesh, Acme make).

5-(isopropyl amino ethylidene)-indole (8)

This was prepared by the reaction of indole and ethylidene isopropylamine according to the reported procedure[6].

Methyl-β-(3-indolyl)-β-methyl-α-nitropropionate (10)

In a 100 ml two-necked round bottom flask fitted with a reflux condenser, a guard tube and a gas inlet, were placed 3-(isopropylamino ethylidene)-indole (8) (2.02 g, 0.01 mol), methylnitroacetate (1.42 g, 0.012 mol) and triethylamine (5 drops) in dry toluene (50 ml). The resulting mixture was heated with stirring at 110-120° in a stream of nitrogen gas for 15 hr. The solid was filtered, the filtrate rotary evaporated and the residue chromatographed (silica gel) using benzene-ethylacetate (9:1) as eluent to furnish the nitroester (2.26 g, 85% yield), m.p. 92-95°.

IR (Nujol) : 3370 (NH), 1750 ($COOCH_3$) cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 1.50 (d, 3H, CH_3, J=6Hz), 3.50, 3.80 (s, 3H, OCH_3, diastereomers), 3.90-4.30 (m, 1H), 5.30, 5.35 (d, 1H, $NO_2\underline{CH}COOCH_3$, diastereomers), 6.90-7.70 (m, 5H, Ar), 8.00 (br. s, 1H, NH). m/e 262. Analysis : calculated for $C_{13}H_{14}N_2O_2$; C, 67.26; H, 6.90; N, 12.17; Found : C, 67.18; H, 7.11; N, 12.10 %.

β-methyltryptophan methyl ester (4)

A solution of nitroester 10 (3.5 g, 0.0134 mol) in ethanol (40 ml) was stirred at room temperature in the presence of Raney nickel (3 g) in an atmosphere of hydrogen. The reaction was monitored by TLC. After 24 hr, the catalyst was filtered and the filtrate concentrated to a gummy product. This compound was taken in ether, extracted with dilute hydrochloric acid (4 x 25 ml) and then, the aqueous extract was rendered neutral ($NaHCO_3$). The resulting solution was extracted with ether, dried (Na_2SO_4) and concentrated to afford a viscous liquid which solidified gradually on keeping to furnish the amine (2.2 g, 71% yield). m.p. 76-80°.

IR (Nujol) : 3400, 3300 (-NH_2), 1740 ($COOCH_3$) cm^{-1}, ^{1}H-NMR ($CDCl_3$) : δ 1.2, 1.35 (d, 3H, J=6.3 Hz, CH_3), 1.75 (br. s, 2H, exchanges with D_2O), 3.55, 3.65 (s, 3H, OCH_3), 3.80 (m, 2H, $\underline{CH}CH_3$, NH_2-$\underline{CH}COOCH_3$), 6.7-7.7 (m, 5H, Ar), 8.2 (br. s, 1H, NH, exchanges with D_2O). m/e 232.

8-Hydroxyquinaldonitrile (13)

This was prepared from 8-hydroxyquinoline by a modified literature procedure[9].

5-Nitroso-8-hydroxyquinaldonitrile (14)

To a stirred solution of 8-hydroxyquinaldonitrile (13.7 g, 0.081 mol) in acetic acid (400 ml) at 0° was added dropwise an aqueous solution of sodium nitrite (11.1 g, 0.161 mol). The reaction mixture was allowed to attain room temperature and further stirred for 4 hr. It was diluted with cold water (500 ml) and the solid was filtered and dried to give 5-nitroso-8-hydroxyquinaldonitrile (11 g, 74%) as yellow solid. m.p. $> 250°$.

IR (Nujol) : 3100 (br, -OH), 2240 (CN), 1670 cm^{-1}, ^{1}H-NMR (DMSO) : δ 6.78 (d, 1H, J=10H, Ar), 8.05 (d, 1H, J=10 Hz, Ar), 8.20 (d, 1H, J=8 Hz, Ar), 8.73 (d, 1H, J=8 Hz, Ar).

5-Acetamido-8-hydroxyquinaldonitrile (16)

A suspension of 5-nitroso-8-hydroxyquinaldonitrile (4.3 g, 0.025 mol) in ethylacetate was shaken vigorously with aqueous sodium dithionite (10 g dissolved in minimum amount of water) in a separatory funnel. The reaction was exothermic and the solution became red. After the suspended solid had dissolved, the layers were separated and then the aqueous solution was repeatedly extracted with ethylacetate. The combined ethyl acetate extract was treated with acetic anhydride (20 ml) and the solution was boiled on water bath. On cooling, solid separated which was filtered and dried to furnish 5-acetamido-8-hydroxyqinaldonitrile (16, 4.3 g, 88% yield). The compound was recrystallised from acetone m.p. 275°.

IR (Nujol) : 3340, 3280 (NH and OH), 2260 (-CN), 1660 (amide) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) : δ 2.24 (s, 3H, $COCH_3$), 7.20 (d, 1H, J=8 Hz, Ar), 7.63 (d, 1H, J=10 Hz, Ar), 9.42 (br. s, exchanges with D_2O), 9.64 (br. s, exchanges with D_2O).

5-Acetamido-7-bromo-8-hydroxyquinaldonitrile (17)

To a stirred solution of amidophenol 16 (5.64 g, 0.025 mol) in dimethylformamide (50 ml) at 0° was added dropwise a solution of NBS (4.86 g, 0.027 mol) in dimethylformamide (40 ml). The reaction mixture was allowed to come to room temperature. After 4 hr the solution was cooled to 0°, diluted with cold water and stirred for 15 minutes. The solid was separated which was filtered and dried to yield 5-acetamido-7-bromo-8-hydroxyquinaldonitrile (17, 6.33 g, 83% yield). Recrystallisation from acetone furnished yellow crystals which melted at 248-250° (dec).

IR (Nujol) : 3300, 3240 (NH and OH), 2200 (-CN), 1660 (NHCO) cm^{-1}. ^{1}H-NMR (DMSO-d_6) : δ 2.19 (s, 3H, $COCH_3$), 8.00 (s, 1H, Ar), 8.14 (d, 1H, J=7.6 Hz, Ar), 8.66 (d, 1H, J=7.6 Hz, Ar), 10.04 (s, 1H). m/e 305, 307. Analysis calculated for $C_{12}H_8N_3O_2Br$: C, 47.06, H, 2.60, N, 13.73; Found C, 47.32, H, 2.80, N, 13.85%.

2-Cyano-7-bromo quinoline-5,8-dione (18)

To a stirred cold suspension of 5-acetamido-7-bromoquinaldonitrile (0.43 g, 1.41 mmol) in ethylacetate at 0°, was added 12N sulphuric acid (15 ml) followed by potassium dichromate (0.5 g in minimum water). The reaction was allowed to attain room temperature. The progress of the reaction was indicated by the disappearance of the suspension and formation of two clear layers. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford a residue which was purified by column chromatography on silica gel using benzene as eluent to furnish the bromoquinone 18 (0.315 g, 73% yield), as yellow solid. m.p. 165°.

IR (Nujol) : 2230 (-CN), 1700, 1670, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) : δ 7.65 (s, 1H, Ar), 8.17 (d, 1H, J=7.54 Hz, Ar), 8.55 (d, 1H, J=7.54 Hz, Ar). m/e 261, 263. Analysis calculated for $C_{10}H_3N_2BrO_2$: C, 45.63, H, 1.14, N, 10.65; Found : C, 45.52, H, 1.14, N, 10.45%.

7-Bromo-5,8-dihydroxyquinaldonitrile (19)

2-Cyano-7-bromo quinoline-5,8-dione (18, 2.12 g, 0.0081 mol) dissolved in ethyl acetate (100ml) was vigorously shaken with aqueous sodium dithionite solution (5 g dissolved in minimum water) in a separatory funnel. An exothermic reaction ensued and the original yellow colour of the solution darkened slightly. The product had identical R_f value with the starting material on TLC. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined non aqueous layer was dried (Na_2SO_4) and rotary evaporated under vacuum to yield the hydroquinone (2.19 g, 94% yield),

recrystallised from benzene to give yellow crystals. m.p. 216-218° (dec).

IR (Nujol) : 3340 (-OH), 2260 (-CN) cm^{-1}. ^{1}H-NMR (Acetone-d_6) : δ 7.31 (s, 1H, Ar), 6.88 (d, 1H, J=10 Hz, Ar), 7.71 (d, 1H, J=10 Hz, Ar), 9.27 (s, 1H, exchanges with D_2O), 9.69 (s, 1H, exchanges with D_2O). m/e 265, 267. Analysis calculated for $C_{10}H_5N_2BrO_2$: C, 45.28, H, 1.89, N, 10.57; Found C, 45.28, H, 2.09, N, 10.43%.

7-Bromo-5,8-dimethoxyquinaldonitrile (20)

7-Bromo-5,8-dihydroxyquinaldonitrile (19, 2.12 g, 0.008 mmol) was treated with dimethylsulphate (5 ml) in the presence of anhydrous potassium carbonate (10 g) in boiling acetone for 4 hr. Acetone was distilled off and water was added to the residue. After stirring for 0.5 hr at room temperature, the solid obtained was filtered and dried. The compound was purified on a short column of silica gel using benzene as eluent to furnish 7-bromo-5,8-dimethoxyquinaldonitrile (1.19 g, 56%) as yellow solid. m.p. 180°.

IR (Nujol) : 2260 (-CN) cm^{-1}, ^{1}H-NMR ($CDCl_3$) : δ 4.00 (s, 3H, OCH_3), 4.10 (s, 3H, -OCH_3), 7.05 (s, 1H, Ar), 7.65 (d, 1H, J=8 Hz, Ar), 8.65 (d, 1H, J=8 Hz, Ar). m/e 291, 293. Analysis calculated for $C_{12}H_9N_2O_2Br$: C, 49.15, H, 3.07, N, 9.56; Found : C, 48.96, H, 3.28, N, 9.25%.

7-Bromo-5,8-dimethoxyquinaldic acid (21)

To a stirred solution of 7-bromo-5,8-dimethoxyquinaldonitrile (2.12 g, 0.007 mol) in ethanol (150 ml), was added an aqueous solution of potassium hydroxide (8 g in 20 ml). The resulting mixture was heated under reflux for 12 hr. Ethanol was removed and the solid was dissolved in hot water, cooled and acidified (conc. HCl) to give 7-bromo-5,8-dimethoxyqinaldic acid (1.95 g, 86% yield) as a yellow solid, m.p. 186-188° (dec).

IR (Nujol) : 3340 (br, -OH), 1720 (-COOH) cm^{-1}, ^{1}H-NMR ($CDCl_3$) : δ 4.00 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 6.90 (broad, exchanges with D_2O), 7.05 (s, 1H, Ar), 8.23 (d, 1H, J=6.3 Hz, Ar), 8.72 (d, 1H, J=6.3 Hz, Ar), m/e 311, 313. Analysis calculated for $C_{12}H_{10}NO_4Br$: C, 46.15, H, 3.21, N, 4.4; Found : C, 45.99, H, 3.32, N, 4.28 %.

Methyl-β-methyl-Nb (7-bromo-5,8-dimethoxyquinaldoyl) tryptophan (22)

To a stirred solution of 7-bromo-5,8-dimethoxyquinaldic acid (0.1 g, 0.321 mmol) in dry tetrahydrofuran (10 ml) was added triethylamine (0.032 g, 0.317 mmol). The mixture was cooled to 0° and then methylchloroformate (0.030 g, 0.32 mmol) was introduced. After 0.5 hr β-methyltryptophan (0.089 g, 0.384 mmol) in dry tetrahydrofuran (5 ml) was added to the above cold solution in one lot. Stirring was continued for 4 hr during which it was allowed to come to room temperature. Tetrahydrofuran was rotary evaporated and the residue was resolved by column chromatography using benzene as eluent to furnish the amide 22 (0.164 g, 97% yield) as a white solid. m.p. 85-90°.

IR (Nujol) : 3400 (-NH), 1750 (-$COOCH_3$), 1690 (amide) cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 1.50 (t, 3H, $CHCH_3$), 5.17 (m, 1H, $NHCHCOOCH_3$), 7.04 (s, 1H, Ar), 7.07-7.84 (m, 5H, Ar), 8.38 (d, 1H, J=9 Hz, Ar), 8.56 (d, 1H, J=9 Hz, Ar), 8.69 (d, 1H, J=9 Hz, Ar), 8.73 (d, 1H, J=9 Hz, Ar). m/e 525, 527. Analysis calculated for $C_{25}H_{24}N_3O_5Br$: C, 57.03, H, 4.56, N, 7.98; Found : C, 57.39, H, 4.76, N, 7.66%.

1-[2-(7'-bromo-5',8'-dimethoxyquinolyl)]-3-methoxycarbonyl-4-methyl-β-carboline (23)

A solution of amide 22 (0.28 g, 0.53 mmol) and $POCl_3$ (2 ml) in dry xylene (20 ml) was heated under reflux with stirring for 4 hr. The flask was cooled and the contents poured over crushed ice with stirring. The pH of the resulting solution was adjusted at 8 with sodium carbonate. Xylene was separated and the solid was extracted with dichloromethane. The combined organic layer was washed with water and dried (Na_2SO_4) and rotary evaporated to dryness. The crude product was purified by boiling in refluxing acetone followed by cooling to yield 23 (0.238 g, 88% yield). Alternately, the crude product was purified by chromatography using benzene as eluent. m.p. 280°.

IR ($CHCl_3$) : 3340 (NH), 1730 (-$COOCH_3$) cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 3.2 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.07 (s, 3H, -OCH_3), 4.26 (s, 3H, OCH_3), 6.97 (s, 1H, Ar), 7.23-7.57 (m, 2H, Ar), 7.66 (d, 1H, J=7.5 Hz, Ar), 8.38 (d, 1H, J=7.5 Hz, Ar), 8.62 (d, 1H, J=9 Hz, Ar), 8.85 (d, 1H, J=9 Hz, Ar), 12.37 (br. s, 1H, NH, D_2O exchangeable). m/e 505, 507. Analysis calculated for $C_{25}H_{20}N_3O_4Br$: C, 59.28, H, 3.95, N, 8.29; Found : C, 59.01, H, 4.03, N, 8.23%.

1-[2-(7'-bromo-5',8'-quinolinedionyl)]-3-methoxycarbonyl-4-methyl-β-carboline (26)

A suspension of the β-carboline 23 (0.095 g, 0.188 mmol) with 48% aqueous HBr (10 ml) was refluxed with stirring under nitrogen atmosphere for 8 hr. The reaction mixture was cooled and poured over crushed ice and the precipitate was filtered and dried to give 24 (0.069 g) as a brown solid. This was used for esterification without further purification.

The suspension of 24 (0.069 g) in dry methanol (30 ml) containing concentrated sulphuric acid (1 ml) was refluxed for 12 hr. Methanol was removed under reduced pressure and cold water added to the reaction mixture. The solid was formed which was filtered and dried to yield 25 (0.07 g) as brown solid. This was subjected to oxidation without further purification.

A suspension of 25 (0.07 g) in methylene chloride (50 ml) was vigorously stirred at room temperature with aqueous solution of cerric ammonium nitrate (0.5 g in 10 ml water) for 6 hr. As the reaction progressed, the suspension dissolved and the colour of the solution changed from brown to red. The organic layer was separated and the aqueous layer extracted repeatedly with chloroform. The combined organic layer was washed with water, brine, dried (Na_2SO_4) and evaporated to dryness to yield a red residue which was purified by chromatography using benzene as eluent to furnish the bromoquinone 26 (0.038 g, 43% yield). m.p. 286-289° (lit.[3] m.p. 285-287°).

IR ($CHCl_3$) : 3360 (NH), 1730 (-$COOCH_3$), 1700, 1670. ^{1}H-NMR ($CDCl_3$) : δ 3.20 (s, 3H, CH_3), 4.10 (s, 3H, -OCH_3), 7.36 (t, 1H, Ar), 7.57 (s, 1H, Ar), 7.63 (t, 1H, Ar), 7.67 (d, 1H, J=8 Hz, Ar), 8.34 (d, 1H, J=8 Hz, Ar), 8.36 (d, 1H, J=8 Hz, Ar), 8.98 (d, 1H, J=8 Hz, Ar), 11.77 (bs, NH), m/e 475, 477. Analysis calculated for $C_{23}H_{14}N_3O_4Br$: C, 57.98, H, 2.94, N, 8.82; Found : C, 57.83, H, 3.09, N, 8.88%.

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