Synthesis and Reactions of 10,10-Dimethyl-10*H*-pyrido[1,2-*a*]indol-6-ones

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Cyclocondensation of 2,3,3-trimethyl-3*H*-indoles **2** with malonates **3** gives 8-hydroxy-10,10-dimethyl-10*H*-pyrido[1,2-*a*]indol-6-ones **4**, which were halogenated in position 7, 8 and 9 with sulfuryl chloride, bromine or phosphoroxychloride to give the corresponding halo-10,10-dimethyl-10*H*-pyrido[1,2-*a*]indoles **5, 6, 7** and **8**. Amination affords the 8-amino-10,10-dimethyl-10*H*-pyrido[1,2-*a*]indol-6-one **9**. Nitration gives either the 10,10-dimethyl-7-nitro-10*H*-pyrido[1,2-*a*]indoles **10** or 10,10-dimethyl-7-hydroxy-10*H*-pyrido[1,2-*a*]indoles **11**, depending on the conditions.

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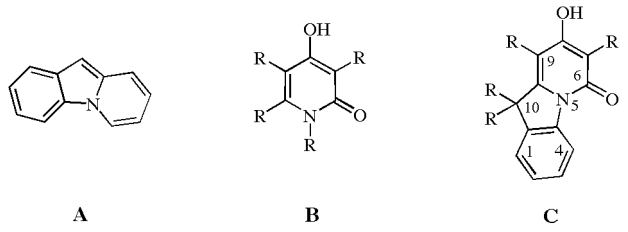
Pyrido[1,2-*a*]indole (**A**) is a ring system which is only described in a few samples in the literature mainly because of its difficult approach. There are two reaction sequences described which lead either *via* a high-temperature reaction (>500 °C) to the fully aromatic system of pyrido[1,2-*a*]indole [1-3] or by intramolecular alkylation to the ring system with an saturated pyridine ring [1,4]. Further reactions described hitherto are hydrogenations or acylations of the pyridine ring [1,2,5], or nitrosation of the benzene ring [1]. Due to our projects for new syntheses of fused heterocycles containing the biologically active 4-hydroxy-2-pyridone moiety **B**, the synthesis of the target molecule **C** containing both the hydroxypyridone structure element of **B** and the pyrido[1,2-*a*]indole structure **A** was of interest.

Scheme 1



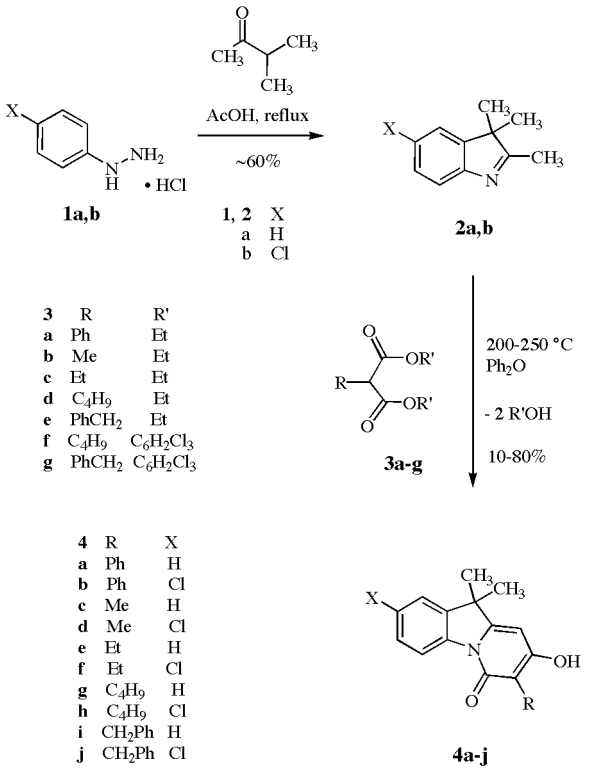
A **B** **C**

We were able to show in a large number of reactions that malonates react easily by cyclocondensation with enamines to 4-hydroxypyridones [6]; as synthon for the synthesis of pyrido[1,2-*a*]indoles we chosed 2,3,3-trimethyl-3*H*-indoles **2**, which are either commercially available or easily obtained by reaction of phenylhydrazinium chlorides **1** with 3-methylbutanone in a Fischer indole synthesis. In the next step the cyclocondensation of **2** with malonates was planned taking advantage of our previous researches on the cyclocondensation of enamines with commercially available diethyl malonates instead of highly reactive bis(2,4,6-trichlorophenyl)malonates (*e.g.* **3f,g**) [6,7].

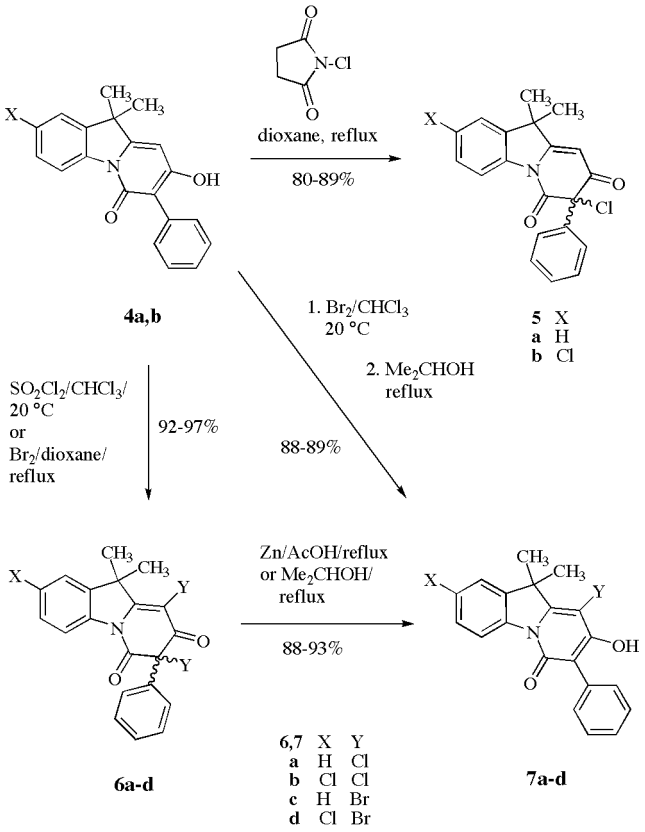
The reaction of diethyl phenylmalonate (**3a**) with 2,3,3-trimethyl-3*H*-indoles **2** without solvent at temperatures of 250-280 °C gave rather impure products; performing the reactions in refluxing diphenylether as solvent, 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-ones **4a**,**b** were obtained in about 80% yield and excellent purity. With methyl-, ethyl-, butyl- and benzylmalonates **3b-e**, the yields of 8-hydroxy-10,10-dimethyl-10*H*-pyrido[1,2-*a*]indol-6-ones **4c-j** were lower (10-60%), but the simple, cheap and quick reaction overcomes this disadvantage. The reason for the lower yields compared with **4a**,**b** are probably the lower boiling points of the malonates, which prohibit the necessary high reaction temperatures and the formation of an intermediate α-oxo ketene [6]. In order to test the higher reactivity of bis(2,4,6-trichlorophenyl)malonates, the reactive butyl- and benzylmalonates **3f,g** were reacted with 2,3,3-trimethyl-3*H*-indole **2a** to compare the yields: with butylmalonates, the simple diethylester method using **3d** afforded the better yield of **4g** (method A, 61%) compared with the bis(2,4,6-trichlorophenyl)malonate method of **3f** (**4g** in method B, 53%) probably caused by the more difficult workup in method B. With benzylmalonates, the bis(2,4,6-trichlorophenyl)malonate method with **3g** (method B) afforded **4i** in 53%, in contrast to the simple diethylester method using **3e** (method A), which gave **4i** only in 25% yield.

The halogenation in the pyridine part of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-ones **4** can be achieved regioselectively at positions 7, 8 or 9, depending on the halogenation reagents and conditions. Chlorination with *N*-chlorosuccinimide in dioxane gives a mono-chlorination at position 7 and forms in 80-90% 7-chloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-diones **5a,b** as the fixed 6,8-dioxo tautomers, shown by the addidional infrared carbonyl signal at C-8 at 1720 cm^{-1}; the introduction of the additional substituent at C-7 generated racemic molecules **5** with an asymmetric center at C-7. The use of sulfurylchloride as chlorination agent caused the introduction of an additional chloro substituent at position 9 and gives 7,9-dichloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-

Scheme 2



Scheme 3



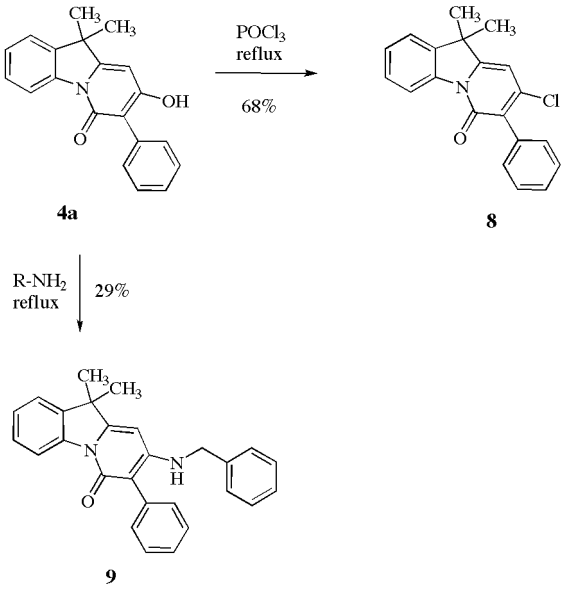
a]indole-6,8(7*H*)-diones **6a,b**. We noticed that in the preparation of **6a** only a 3-fold excess of sulfurylchloride was necessary, whereas **6b** needed a 4-fold excess for a complete reaction. The position of the second chloro substituent can be determined easily by the disappearance of the H-9 signal in the ^{1}H nmr at about δ = 5.90 ppm. The reduction with zinc in glacial acetic acid removes the aliphatic chloro atom in position 7. The olefinic chloro atom in position 9 and the chloro atom in the benzo part of **7b** remained unchanged. As products, the tautomeric 9-chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6(7*H*)-ones **7a**,**b** were obtained, shown by the lack of the C-8 carbonyl signals at 1720 cm^{-1} and the appearance of the C-8 hydroxy bands at 3200 cm^{-1} in the infrared spectra.

The bromination of **4a,b** with elementary bromine using dioxane as the solvent at reflux temperature gives the racemic dibromo products with the tautomeric oxo group at C-8, 7,9-dibromo-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-diones **6c,d**. When the reaction of **4a,b** with bromine was carried out in chloroform at room temperature and the reaction mixture was then heated subsequently with 2-propanol, the monobromo products at C-9 with the tautomeric hydroxy group at C-8, 9-bromo-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6(7*H*)-ones **7c,d** were obtained.

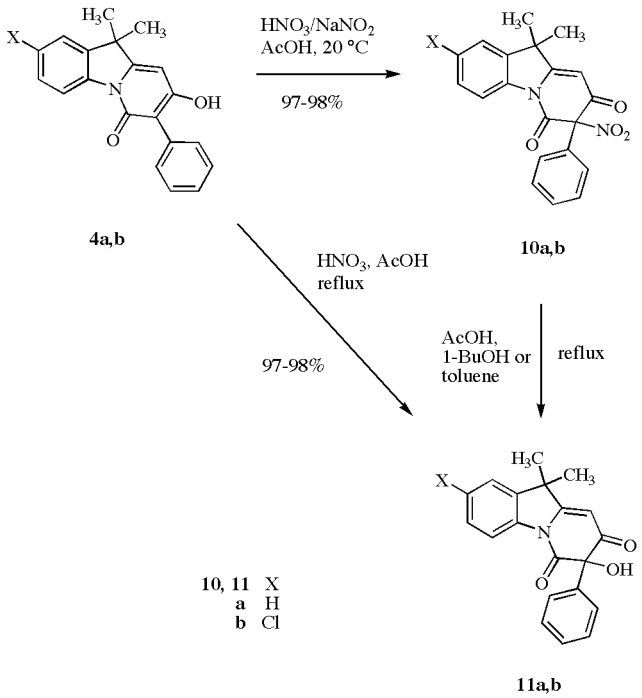
Whereas the halogenation reactions carried out in Scheme 3 follow an electrophilic substitution of hydrogen either at the CH-acidic carbon of the enolized 1,3-dicarbonyl system (C-7) or at the enamine position (C-9), nucleophilic displacement of the 8-hydroxy group of **4a** by reaction with phosphorylchloride leads to the 8-chloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6(7*H*)-one **8**. The necessary reaction time (2.5 hours) and temperature (105 °C) reveals that the reactivity of the hydroxy group in **4a** is lower than in 4-hydroxy-3-phenyl-2-quinolines [8]. Aminolysis of the 8-hydroxy group of **4a** with benzylamine afforded after 12 hours reaction time in rather moderate yields 8-amino-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6(7*H*)-ones **9**; again in the 4-hydroxy-3-phenyl-2-quinoline series a higher reactivity and better yields in the reaction with amines has been observed [9].

The reaction of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-ones **4a,b** with nitric acid showed the formation of two products. By adaptation of the reaction conditions we were able to isolate both compounds. Nitration of **4a,b** with nitric acid in glacial acetic acid at room temperature using a small amount of sodium nitrite as catalyst afforded 10,10-dimethyl-7-nitro-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-diones **10a**,**b**. The dioxo structure was again proved by the ir bands at

Scheme 4



Scheme 5



1720 cm^{-1}. When the nitration was performed with nitric acid in glacial acetic acid at reflux temperatures, the second product was formed, which could be assigned to the structure of 7-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-diones **11a**,**b** by elemental analysis and the ir signals for both the 6,8-dioxo structure at 1705-1730 and 1655-1670 cm^{-1}, and the hydroxy group with a sharp OH signal at 3450-3470 cm^{-1}, which is in accordance with similar hydroxy compounds of quinolines [7]. The formation of the 7-hydroxy compounds **11** by reaction with nitric acid cannot be explained in terms of a simple oxidation of **4**, because we found that nitro compounds **10** decompose on heating in glacial acetic acid, but also in 1-butanol or toluene to hydroxy compounds **11**.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Model MFB-595 in open capillary tubes. Infrared spectra were taken as potassium bromide pellets on a Perkin-Elmer 298 spectrophotometer. The ^{1}H nmr spectra were recorded on a Varian Gemini 200 (200 MHz) or a Bruker AM 360 instrument (360 MHz); ^{13}C nmr spectra were recorded on a Bruker AM 360 instrument (90 MHz). Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. The solvent for NMR spectra was deuteriodimethylsulfoxide unless otherwise stated. Microanalyses were performed on a Fisons elemental analyzer, Mod. EA1108 and are within ±0.4 of the theoretical percentages. Mass spectra were taken on on a FINNIGAN 4000 (EI: 70 eV, CI: 120 eV, methane). All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using uv light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

General Procedure for the Synthesis of 2,3,3-Trimethyl-3*H*-indoles **2**.

This procedure was performed following a general textbook procedure [10]: A suspension of the appropriate phenylhydraziniumchloride **1a,b** (0.5 mol) in glacial acetic acid was warmed and to this mixture a solution of 3-methyl-2-butanone (43.07 g, 0.5 mol) in glacial acetic acid (50 mL) was added under stirring. The reaction was exothermic and started to reflux. After the addition, the reaction mixture was heated under reflux for further 2 hours, then the mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was diluted with water (100 mL) and made alkaline with 2 *M* sodium hydroxide solution. Then the product was extracted with diethylether (2 x 100 mL), dried with sodium sulfate and the solvent evaporated under reduced pressure. The residue was then distilled *in vacuo*.

2,3,3-Trimethyl-3*H*-indole (**2a**).

The yield was 44.3 g (56%), light yellow oil, bp 110-115 °C (20-23 mbar); lit. bp 228-229 °C (744 mm Hg) [11].

5-Chloro-2,3,3-trimethyl-3*H*-indole (**2b**).

The yield was 58.2 g (60%) light yellow oil, bp. 115-116 °C (2 mm Hg), lit. bp 80-82 °C (0.3 mm Hg) [12].

General Procedure for the Synthesis of Pyrido[1,2-*a*]indoles **4a-j**.

Method A.

A mixture of the appropriate trimethylindole **2a,b** and the corresponding diethyl malonate **3a-e** in diphenylether was heated in a metal bath using a 25 cm Vigreux column as air condenser for the time and temperature (bath temperature) given at the individual procedure. During this time, ethanol was liberated and removed by distillation equipment. When the formation of

ethanol had stopped, the reaction mixture was cooled to room temperature and diluted with the same volume of diethyl ether. The obtained solid was isolated by suction filtration and washed with diethylether.

Method B.

A mixture of the appropriate trimethylindole **2a,b** and the corresponding bis-(2,4,6-trichlorophenyl)malonate **3f**,**g** [13] was heated for 30 minutes to 200-220 °C (bath temperature). Then the mixture was cooled to room temperature and triturated several times with diethylether and hexane until the formed 2,4,6-trichlorophenol was removed and the gum-like reaction product became solid. Then the precipitate was recrystallized from the solvent listed below.

8-Hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4a**).

Method A: **4a** was obtained from trimethylindole **2a** (15.9 g, 0.1 mol), phenylmalonate **3a** (26.0 g, 0.11 mol) and diphenylether (50 g) after heating for 1 hour to 260 °C. The yield was 24.4 g (81%), pale yellow prisms, mp 274-276.5 °C (glacial acetic acid); ir: 3350-2700 b, 1640 s, 1610 s, 1545 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.50 (s, 6 H, 2 Me), 6.30 (s, 1 H, H-9), 7.10-7.60 (m, 8 H, ArH), 8.45 (d, J = 8 Hz, 1 H, H-4), 10.50 (s, 1 H, OH).

Anal. Calcd. for $C_{20}H_{17}NO_2$ (303.36): C, 79.19; H, 5.65; N, 4.62. Found: C, 78.79; H, 5.81; N, 4.53.

2-Chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4b**).

Method A: **4b** was obtained from chloro-trimethylindole **2b** (19.3 g, 0.1 mol), phenylmalonate **3a** (26.0 g, 0.11 mol) and diphenylether (50 g) after heating for 1 hour to 260 °C. The yield was 26.3 g (78%), pale yellow prisms, mp 256-259 °C (ethanol); ir: 3250-2600 b, 1655 s, 1610 m, 1545 cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.50 (s, 6 H, 2 Me), 6.30 (s, 1 H, H-9), 7.10-7.50 (m, 6 H, ArH), 7.70 (d, J = 2 Hz, 1 H, H-1), 8.45 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{16}ClNO_2$ (337.81): C, 71.11; H, 4.77; N, 4.15. Found: C, 71.45; H, 4.78; N, 4.14.

8-Hydroxy-7,10,10-trimethyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4c**).

Method A: **4c** was obtained from trimethylindole **2a** (7.95 g, 50 mmol), methylmalonate **3b** (9.6 g, 55 mmol) and diphenylether (25 g) after heating for 3 hours at 220 °C and 1 hour at 250 °C. The yield was 3.71 g (31%), light yellow prisms, mp 296.5 °C (glacial acetic acid); ir: 3250-2800 m, b, 2660 w, 1665 sh, 1650 s, 1610 s, 1575 m cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.44 (s, 6 H, 2 Me at C-10), 1.88 (s, 3 H, 7-Me), 6.20 (s, 1 H, H-9), 7.25 and 7.33 (2 dd, J = 2 and 8 Hz, H-2 and H-3), 7.53 (dd, J = 2 and 8 Hz, H-1), 8.53 (dd, J = 2 and 8 Hz, H-4).

Anal. Calcd. for $C_{15}H_{15}NO_2$ (241.29): C, 74.67; H, 6.27; N, 5.80. Found: C, 74.34; H, 6.38; N, 5.65.

2-Chloro-8-hydroxy-7,10,10-trimethyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4d**).

Method A: **4d** was obtained from chloro-trimethylindole **2b** (9.65 g, 50 mmol), methylmalonate **3b** (9.6 g, 55 mmol) and diphenylether (25 g) after heating for 3 hours at 220 °C and 1 hour at 250 °C. The yield was 4.21 g (31%) light yellow prisms, mp 297 °C (dec) (glacial acetic acid); ir: 3270 - 2820 m, b, 2615 w, 1660 sh, 1650 s, 1605 m, 1595w, 1580 m cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.46 (s, 6 H, 2 Me at C-10), 1.87 (s, 3 H, 7-Me), 6.20 (s, 1 H, H-9), 7.42 (dd, J = 2 and 8 Hz, H-3), 7.70 (d, J = 2 Hz, 1 H, H-1), 8.51 (dd, J = 2 and 8 Hz, 1 H, H-4), 10.52 (s, b, OH).

Anal. Calcd. for $C_{15}H_{14}ClNO_2$ (275.74): C, 65.34; H, 5.12; N, 5.08. Found: C, 65.62; H, 5.01; N, 5.31.

7-Ethyl-8-hydroxy-10,10-dimethyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4e**).

Method A: **4e** was obtained from trimethylindole **2a** (7.95 g, 50 mmol), ethylmalonate **3c** (10.35 g, 55 mmol) and diphenylether (25 g) after heating for 3 hours at 220 °C and 1 hour at 250 °C. The yield was 6.82 g (50%) light yellow prisms, mp 264 °C (dec.) (glacial acetic acid); ir: 3160 - 2850 m, b, 2620 w, 1660 sh, 1650 s, 1610 s, 1580 m cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.00 (t, J = 7 Hz, 3 H, Et-CH_3), 1.44 (s, 6 H, 2 Me), 2.42 (q, J = 7 Hz, 2 H, CH_2), 6.18 (s, 1 H, H-9), 7.25 and 7.33 (2 dd, J = 2 and 8 Hz, 2 H, H-2, H-3), 7.53 (dd, J = 2 and 8 Hz, 1 H, H-1), 8. 53 (dd, J = 2 and 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{16}H_{17}NO_2$ (255.32): C, 75.27; H, 6.71; N, 5.49. Found: C, 75.55; H, 6.65; N, 5.36.

2-Chloro-7-ethyl-8-hydroxy-10,10-dimethyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4f**).

Method A: **4f** was obtained from chloro-trimethylindole **2b** (9.65 g, 50 mmol), ethylmalonate **3c** (10.35 g, 55 mmol) and diphenylether (25 g) after heating for 3 hours at 220 °C and 1 hour at 250 °C. The yield was 4.08 g (28%) light yellow prisms, mp 279 °C (glacial acetic acid); ir: 3250-3020 m, b, 2980 w, 2920 w, 1670 s, 1655 m, 1610 s, 1595 m cm^{-1}; ^1H nmr (DMSO-d_6): δ = 0.99 (t, J = 7 Hz, 3 H, Et-CH_3), 1.45 (s, 6 H, 2 Me), 2.44 (q, J = 7 Hz, 2 H, CH_2), 6.19 (s, 1 H, H-9), 7. 41 (dd, J = 2 and 8 Hz, H-3), 7.69 (d, J = 2 Hz, 1 H, H-1), 8.51 (dd, J = 2 and 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{16}H_{16}ClNO_2$ (289.76): C, 66.32; H, 5.57; N, 4.83. Found: C, 66.65; H, 5.32; N, 4.67.

7-Butyl-8-hydroxy-10,10-dimethyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4g**).

Method A: **4g** was obtained from trimethylindole **2a** (3.18 g, 20 mmol), butylmalonate **3d** (4.75 g, 22 mmol) and diphenylether (10 g) after heating for 1 hour to 260 °C. The yield was 3.45 g (61%), colorless prisms, mp 213-215 °C (methanol).

Method B: **4g** was obtained from trimethylindole **2a** (1.0 g, 63 mmol) and butylmalonate **3f** (3.15 g, 65 mmol). The yield was 0.90 g (53%), colorless prisms, mp 204 °C (tetrachloromethane); ir: 3200-2400 m, 1660 s, 1625 s, 550 m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 0.80-1.10 (m, 7 H, CH_3-CH_2CH_2), 1.40 (s, 6 H, 2 Me), 2.50-2.80 (m, 2 H, CH_2), 6.55-7.35 (m, 4 H, ArH), 8.5 (s, 1 H, H-4), 10.2 (s, 1 H, OH); MS: m/e (%) = 283 (28.6, M^+), 241 (100), 268 (10.9), 266 (8.7), 254 (30.5), 250 (5.4), 226 (62.0), 169 (32,6).

Anal. Calcd. for $C_{18}H_{21}NO_2$ (283.37): C, 76.30; H, 7.47; N, 4.94. Found: C, 76.03; H, 7.38; N, 4.88.

7-Butyl-2-chloro-8-hydroxy-10,10-dimethyl-10*H*-pyrido[1,2-*a*]-indol-6-one (**4h**).

Method A: **4h** was obtained from chloro-trimethylindole **2b** (3.86 g, 20 mmol), butylmalonate **3d** (4.75 g, 22 mmol) and diphenylether (10 g) after heating for 1 hour to 260 °C. The yield was 4.0 g (63%), pale yellow prisms, mp 220-222.5 °C (methanol); ir: 3300-2500 b, 1650 s, 1610 m, 1580 m, 1545 s cm^{-1}; ^1H nmr (DMSO-d_6): δ = 0.90 (t, J = 7 Hz, 3 H, Bu-CH_3), 1.20-1.70 (m, 10 H, 2 Me and 2 Bu-CH_2), 2.50 (t, J = 7 Hz, 2 H,

Bu-CH_2), 6.20 (s, 1 H, H-9), 7.35 (dd, J = 8 and 2 Hz, 1 H, H-3), 7.60 (d, J = 2 Hz, 1 H, H-1), 8.50 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{18}H_{20}ClNO_2$ (317.82): C, 68.03; H, 6.34; N, 4.41. Found: C, 67.85; H, 6.30; N, 4.30.

7-Benzyl-8-hydroxy-10,10-dimethyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4i**).

Method A: **4i** was obtained from trimethylindole **2a** (7.95 g, 50 mmol), benzylmalonate **3e** (13.67 g, 55 mmol) and diphenylether (25 g) after heating for 3 hours at 220 °C and 1 hour at 250 °C. The yield was 4.31 g (25%), pale yellow prisms, mp 282 °C (glacial acetic acid).

Method B: **4i** was obtained from trimethylindole **2a** (1.0 g, 63 mmol) and benzylmalonate **3g** (3.35 g, 65 mmol). The yield was 1.2 g (63%), colorless prisms, mp 280 °C (glacial acetic acid); ir: 3300-2400 m, 1670 m, 1640 s, 1630 m, 1615 w, 1605 m cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.45 (s, 6 H, 2 Me), 3.77 (s, 2 H, benzyl-CH_2), 6.23 (s, 1 H, H-1), 7.11 and 7.21 (2 dd, J = 2 and 8 Hz, H-2 and H-3), 7.24-7.35 (m, 5 H, PhH), 7.54 (dd, J = 2 and 8 Hz, 1 H, 1-H), 8.52 (dd, J = 2 and 8 H, 1 H, H-4), 10.66 (s, b, OH).

Anal. Calcd. for $C_{21}H_{19}NO_2$ (317.39): C, 79.47; H, 6.03; N, 4.41. Found: C, 79.22; H, 6.24; N, 4.65.

7-Benzyl-2-chloro-8-hydroxy-10,10-dimethyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4j**).

Method A: **4j** was obtained from chloro-trimethylindole **2b** (7.14 g, 37 mmol), benzylmalonate **3e** (10.18 g, 41 mmol) and diphenylether (20 g) after heating for 3 hours at 220 °C and 1 hour at 250 °C. The yield was 1.27 g (9.8%), pale yellow prisms, mp 259.8 °C (glacial acetic acid); ir: 3250-2820 m, b, 1660 s, 1610 m, 1585 w cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.47 (s, 6 H, 2 Me), 3.76 (s, 2 H, benzyl-CH_2), 6.23 (s, 1 H, H-9), 7.10 (dd, J = 2 and 8 Hz, H-3), 7.23 (d, J = 2 and 8 Hz, 2 H, ArH), 7.29 (dd, J = 2 and 8 Hz, 2 H, ArH), 7.40 (dd, J = 2 and 8 Hz, 1 H, ArH), 7.71 (d, J = 2 Hz, 1 H, H-1), 8.50 (dd, J = 2 and 7 Hz, 1 H, H-4).

Anal. Calcd. for $C_{21}H_{18}ClNO_2$ (351.84): C, 71.69; H, 5.16; N, 3.98. Found: C, 71.43; H, 5.02; N, 3.77.

7-Chloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-dione (**5a**).

A mixture of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4a**) (0.61 g, 2.0 mmol) and *N*-chlorosuccinimide (0.54 g, 4.0 mmol) in dry dioxane (10 mL) was heated for 10 minutes under reflux. The hot mixture was filtered and the filtrate poured into ice/water (100 mL). An oil separated, which solidified after a short period. The solid product was isolated by suction filtration and washed with water. The yield was 0.54 g (80%) bright yellow prisms, mp 144.5-147 °C (ethanol); ir: 3060 w, 2970 w, 1720 m, 1675 s, 1650 s, 1605 m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.45 and 1.55 (2 s, 6 H, 2 Me), 5.85 (s, 1 H, H-9), 7.10-7.70 (m, 8 H, ArH), 8.25 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{16}ClNO_2$ (337.81): C, 71.11; H, 4.77; N, 4.15. Found: C, 71.34; H, 4.56; N, 4.28.

2,7-Dichloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]-indole-6,8(7*H*)-dione (**5b**).

2-Chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4b**) (0.68 g, 2.0 mmol) were reacted and work up was as described for **5a**. The yield was 0.66 g (89%), yellow prisms, mp 157-158 °C (ethanol); ir: 2980 w, 1720 s, 1670 s, 1640 s, 1595 m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.50 and 1.60 (2 s, 6 H, 2 Me), 5.90 (s, 1 H, H-9), 7.10-7.60 (m, 8 H, ArH), 8.25 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{15}Cl_2NO_2$ (372.25): C, 64.53; H, 4.06; N, 3.76. Found: C, 64.47; H, 4.25; N, 3.70

7,9-Dichloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]-indole-6,8(7*H*)-dione (**6a**).

A suspension of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4a**) (9.10 g, 30 mmol) in chloroform (150 mL) was laced with sulfurylchloride (7.35 mL, 90 mmol). The mixture was stirred at room temperature for 20 minutes; during this time, the reaction products dissolved. Then all volatile parts were distilled under reduced pressure, and the oily residue was digested with methanol and cooled for 12 hours at 4 °C. The precipitate was then isolated by suction filtration and washed with cold methanol. The yield was 10.4 g (93%) yellow prisms, mp 165.5-166.5 °C (ethanol); ir: 2980 w, 1730 m, 1720 m, 1690 s, 1625 s, 1600 s cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.70 and 1.80 (2 s, 6 H, 2 Me), 7.20-7.60 (m, 8 H, ArH), 8.25 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{15}Cl_2NO_2$ (372.25): C, 64.53; H, 4.06; N, 3.76. Found: C, 64.52; H, 4.05; N, 3.71.

2,7,9-Trichloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]-indole-6,8(7*H*)-dione (**6b**).

A mixture of 2-chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4b**) (6.12 g, 18 mmol) and sulfurylchloride (5.9 mL, 72 mmol) in chloroform (90 mL) was reacted and work up was as described for **6a**. The yield was 6.70 g (92%), yellow prisms, mp 207-208 °C (ethanol); ir: 2980 w, 1720 s, 1685 s, 1620 m, 1590 m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.70 and 1.80 (2 s, 6 H, 2 Me), 7.20-7.50 (m, 7 H, ArH), 8.20 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{14}Cl_3NO_2$ (406.70): C, 59.07; H, 3.47; N, 3.44. Found: C, 58.86; H, 3.49; N, 3.34.

7,9-Dibromo-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]-indole-6,8(7*H*)-dione (**6c**).

A mixture of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4a**) (3.03 g, 10 mmol) and bromine (2.5 mL) in dioxane (75 mL) was heated under reflux, until the mixture was dissolved. Then the reaction mixture was poured into ice/water (1000 mL) and allowed to stand for 48 hours. The solid was isolated by suction filtration, and washed with water. The yield was 4.37 g (95%) yellow prisms, mp 182-183.5 °C (glacial acetic acid); ir: 1705 s, 1670 s, 1615 m, 1590 m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.80 and 1.85 (2 s, 6 H, 2 Me), 7.10-7.60 (m, 8 H, ArH), 8.20 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{15}Br_2NO_2$ (461.16): C, 52.09; H, 3.28; N, 3.04. Found: C, 52.28; H, 3.40; N, 3.02.

7,9-Dibromo-2-chloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-dione (**6d**).

2-Chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4b**) (3.38 g, 10 mmol) and bromine (2.5 mL) were reacted and work up was as described for **6c**. The yield was 4.81 g (97%), mp 161-162.5 °C (glacial acetic acid); ir: 1710 s, 1680 s, 1610 m, 1590 s cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.80 and 1.85 (2 s, 6 H, 2 Me), 7.10-7.60 (m, 8 H, ArH), 8.20 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{141}Br_2ClNO_2$ (495.60); C, 48.47; H, 2.85; N, 2.83. Found C, 48.39; H, 2.83; N, 2.75.

9-Chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]-indole-6(7*H*)-one (**7a**).

A refluxing solution of 7,9-dichloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-dione (**6a**) (3.72 g (10 mmol) in glacial acetic acid (180 mL) was laced quickly with zinc-dust (4.1 g) and the reaction mixture stirred until decolorization took place (about 30 seconds). The solution was filtered quickly while still hot to remove excess zinc-dust and the filtrate was taken to dryness under reduced pressure. The residue was treated with ice/water (200 mL) and the precipitate was isolated by filtration after standing for some hours. The yield was 3.14 g (93%) pale yellow prisms, mp 234-236 °C (ethanol); ir: 3250 b, 1635 s, 1610 m, 1545 s cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.70 (s, 6 H, 2 Me), 7.10-1.75 (m, 8 H, ArH), 8.45 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{16}ClNO_2$ (337.81): C, 71.11; H, 4.77; N, 4.15. Found: C, 71.27; H, 4.79; N, 4.10.

2,9-Dichloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6(7*H*)-one (**7b**).

2,7,9-Trichloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-dione (**6b**) (4.07 g, 10 mmol) was reacted and worked up as described for **7a**. The yield was 3.28 g (88%) pale yellow prisms, mp 223-225 °C (ethanol); ir: 3200-2700 b, 1640 s, 1610 m, 1545 s cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.70 (s, 6 H, 2 Me), 7.20-7.50 (m, 6 H, ArH), 7.70 (d, J=2 Hz, H-1), 8.50 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{15}Cl_2NO_2$ (372.25): C, 64.53; H, 4.06; N, 3.76. Found: C, 64.76; H, 4.07; N, 3.66.

9-Bromo-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]-indol-6(7*H*)-one (**7c**).

A suspension of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4a**) (3.03 g, 10 mmol) and bromine (2.5 mL) in chloroform (50 mL) was stirred for 15 minutes at room temperature. The solvent was then removed under reduced pressure and the residue treated with 2-propanol (20 mL) and heated to boiling. The color of the suspension became nearly colorless and the mixture was heated for further 5 minutes, cooled and then kept for 12 hours at 4 °C. The precipitate was isolated by suction filtration and washed with a small amount of cold methanol. The yield was 3.35 g (88%), pale yellow prisms, mp 237.5-239 °C (ethanol); ir: 3200-2400 b, 1630 s, 1610 m, 1545 s cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.80 (s, 6 H, 2 Me), 7.20-7.70 (m, 8 H, ArH), 8.50 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{16}BrNO_2$ (382.27): C, 62.84; H, 4.22; N, 3.66. Found: C, 62.46; H, 4.28; N, 3.60.

9-Bromo-2-chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6(7*H*)-one (**7d**).

2-Chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido-[1,2-*a*]indol-6-one (**4b**) (3.38 g, 10 mmol) was reacted and work up was as described for **7a**. The yield was 3.70 g (89%), pale yellow prisms, mp 218-219.5 °C (glacial acetic acid); ir: 3200 -2500 b, 1630 s, 1610 m, 1545 s cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.75 (s, 6 H, 2 Me), 7.10-7.50 (m, 6 H, ArH), 7.70 (d, J = 2 Hz, 1 H, H-1), 8.50 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{15}BrClNO_2$ (416.71): C, 57.65; H, 3.63; N, 3.36. Found: C, 58.04; H, 3.70; N, 3.35.

8-Chloro-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6(7*H*)-one (**8**).

A solution of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4a**) (3.03 g, 10 mmol) in phosphoryl chloride (9 ml) was heated under reflux for 2.5 hours. The excess of phosphoryl chloride was removed under reduced pressure, and after cooling the mixture was poured onto crushed ice (100 g). After warming to room temperature the mixture was brought to pH~6 and the resulting solid isolated by suction filtration. The yield was 2.18 g (68%), light yellowish prisms, mp 157 °C (acetic acid/water); ir: 3075 w, 2975 w, 1650 sh, 1645 s, 1620 m, 1590 s cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.56 (s, 6 H, 2 Me, 6.97 (s, 1 H, H-9), 7.40-7.44 (m, 7 H, PhH, H-2 and H-3), 7.63 (dd, J = 2 and 8 Hz, 1 H, H-1), 8.49 (dd, J = 2 and 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{16}ClNO$ (321.81): C, 74.65; H, 5.01; N, 4.35. Found: C, 74.40; H, 4.92; N, 4.22.

8-Benzylamino-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]-indol-6(7*H*)-one (**9**).

A solution of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4a**) (3.03 g, 10 mmol) in benzylamine (30 mL) was heated under reflux using a short column as air condenser for about 12 hours. During this time, water was liberated. When the formation of water had stopped, the excess benzylamine was removed under reduced pressure. The residue was dissolved in dimethylformamide (2 mL) and quenched with ethanol (about 10 mL). The precipitate was isolated by suction filtration. The yield was 1.2 g (29 %), yellow prisms, mp 252 °C (ethanol); ^1H nmr (DMSO-d_6): δ = 1.64 (s, 6 H, 2 Me), 3.63 (d, J = 8 Hz, CH_2), 7.32 (s, 1 H, H-9), 7.41-7.86 (m, 9 H, ArH), 8.01-8.09 (m, 2 H, ArH), 8.79 (dd, J = 2 and 8 Hz, 1 H, H-4), 10.17 (t, J = 7 Hz, 1 H, NH).

Anal. Calcd. for $C_{27}H_{24}N_2O$ (392.51): C, 82.62; H, 6.16; N, 7.14. Found: C, 82.40; H, 6.07; N, 7.16.

10,10-Dimethyl-7-nitro-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-dione (**10a**).

A mixture of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4a**) (3.03 g, 10 mmol), concentrated nitric acid (2.5 mL, d = 1.41) and sodium nitrite (0.05 g) in glacial acetic acid (100 mL) was stirred at room temperature for 15 minutes. The reaction mixture was then poured into ice/water (1000 mL), the formed precipitate was isolated by suction filtration, washed several times with water and air dried. The yield was 3.37 g (97%) dark yellow prisms, mp 156 °C dec. (ethanol); ir: 3070 w, 2960 w, 1720 s, 1635 s, 1600 m, 1565 a cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.30 and 1.55 (2 s, 6 H, 2 Me), 6.35 (s, 1 H, H-9), 7.15-7.65 (m, 8 H, ArH), 8.10 (dd, J = 8 and 2 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{16}N_2O_4$ (348.36): C, 68.96; H, 4.63; N, 8.04. Found: C, 69.31; H, 4.69; N, 8.00.

2-Chloro-10,10-dimethyl-7-nitro-7-phenyl-10*H*-pyrido[1,2-*a*]-indole-6,8(7*H*)-dione (**10b**).

2-Chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4b**) (3.38 g, 10 mmol) was reacted and work up was as described for **10a**. The yield was 3.50 g (91%), mp 155 °C dec. (ethanol); ir: 2960 w, 1720 s, 1665 s, 1635 s, 1600 m, 1565 s cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.40 and 1.60 (2 s, 6 H, 2 Me), 5.85 (s, 1 H, H-9), 7.15-7.55 (m, 7 H, ArH), 8.25 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{15}ClN_2O_4$ (382.81): C, 62.75; H, 3.95; N, 7.32. Found: C, 63.05; H, 4.06; N, 7.06.

7-Hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-dione (**11a**).

Method A) A solution of 8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4a**) (3.03 g, 10 mmol) and concentrated nitric acid (2.5 mL, d = 1.41) in glacial acetic acid (100 mL) was heated under reflux for 15 minutes, then concentrated to 10 mL under reduced pressure and poured into ice/water (150 mL). The precipitate was isolated by suction filtration and washed with water. The yield was 3.11 g (97%), light yellow prisms, mp 166-169 °C (toluene).

Method B) A solution of 10,10-dimethyl-7-nitro-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-dione (**10a**) (0.35 g, 1.0 mmol) in glacial acetic acid (10 mL) was heated under reflux for 10 minutes, then concentrated to 1.0 mL under reduced pressure and poured into ice/water (10 mL). The precipitate was isolated by suction filtration and washed with water. The yield was 0.31 g (97%), the mp and tlc was identical with the product of Method A.

Ir: 3450 s, 2970 w, 1730 m, 1655 m, 1635 s, 1605 m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.50 and 1.55 (2 s, 6 H, 2 Me), 4.30 (s, 1 H, OH), 5.85 (s, 1 H, H-9), 7.10-7.60 (m, 8 H, ArH), 8.20 (dd, J = 8 and 2 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{17}NO_3$ (319.36): C, 75.22; H, 5.37; N, 4.39. Found: C, 75.26; H, 5.36; N, 4.39.

2-Chloro-7-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]-indole-6,8(7*H*)-dione (**11b**).

Method A) 2-Chloro-8-hydroxy-10,10-dimethyl-7-phenyl-10*H*-pyrido[1,2-*a*]indol-6-one (**4b**) (3.38 g, 10 mmol) was reacted and work up was as described for **11a**. The yield was 3.45 g (98%), light yellow prisms, mp 206-208 °C (toluene).

Method B) 2-Chloro-10,10-dimethyl-7-nitro-7-phenyl-10*H*-pyrido[1,2-*a*]indole-6,8(7*H*)-dione (**10b**) (0.38 g, 10 mmol) was reacted and work up was as described for **11b**. The yield was 0.35 g (98%); the mp and tlc was identical with the product of Method A.

Ir: 3470 m, 2870 w, 1705 s, 1670 s, 1650 s, 1600 w cm^{-1}; ^1H nmr (DMSO-d_6): δ = 1.55 (s, 6 H, 2 Me), 6.0 (s, 1 H, H-9), 6.50 (s, 1 H, OH), 7.10-7.55 (m, 6 H, ArH), 7.70 (d, J = 2 Hz, 1 H, H-1), 8.10 (d, J = 8 Hz, 1 H, H-4).

Anal. Calcd. for $C_{20}H_{16}ClNO_3$ (353.81): C, 67.90; H, 4.56; N, 3.96. Found: C, 67.85; H, 4.57; N, 4.01.

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