Simple preparation of fused pyrrolo[2,3-*b*]pyrrolidinones and pyrrolo[2,3-*c*]pyridazinones [1]

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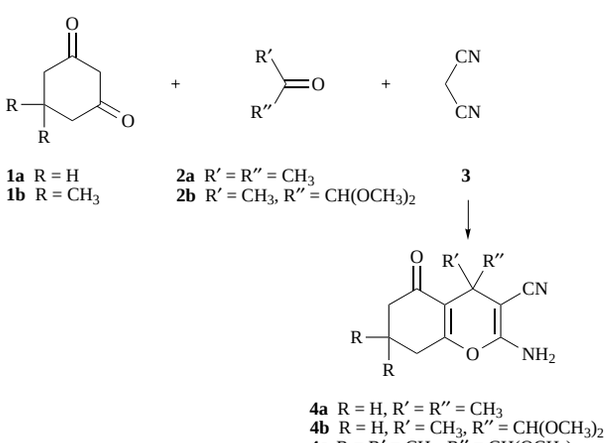
4-Methyl-4-(dimethoxymethyl)pyrans 4b, 4c and 15, prepared from cyclohexane-1,3-diones 1 or 4-hydroxycoumarin 14, pyruvaldehyde dimethyl acetal 2b and malononitrile 3, are subjected to hydrolysis with HCl to give fused furofuranones 5 and 16, which are treated with amines or hydrazines to give fused pyrrolopyrrolidinones 9 and 18 and pyrrolopyridazinones 12.

Introduction

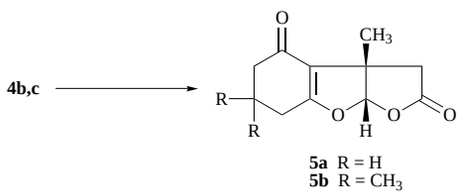
Naturally occurring (−)-physostigmine and its analogues having pyrrolo[2,3-*b*]pyrrolidine as a main structural component have attracted much attention because some of them are inhibitors of acetylcholinesterase [2] and are medically used to treat glaucoma and myasthenia gravis.[3] More importantly, they are candidate agents for the treatment of Alzheimer's disease.[4] Consequently a number of strategies [5] for the synthesis of these and related structures have been reported. However, several steps are required in these methods. Recently, Abdel-Latif *et al.* reported the preparation of fused pyran derivative **4a** from cyclohexane-1,3-dione **1a**, acetone **2a** and malononitrile (Scheme 1).[6] In connection with our work [7] on simple preparations of saturated polyheterocycles using dicarbonyl compounds, we attempted to apply this approach to the preparation of pyrrolopyrrolidine derivatives by replacing acetone **2a** with pyruvaldehyde dimethyl acetal **2b**. Herein we report a simple and unique preparation of pyrrolopyrrolidinone and pyrrolopyridazinone systems.



Scheme 1 *Reagents:* piperidine, benzene

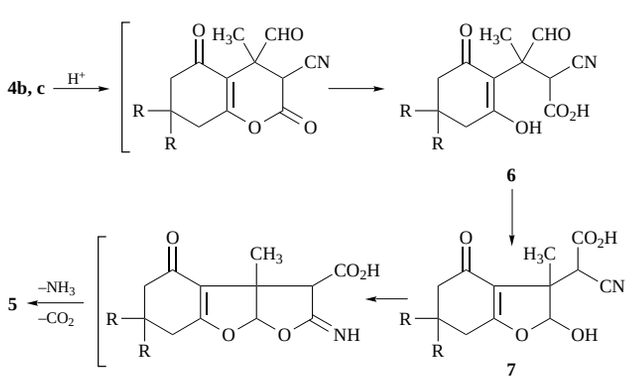
Results and discussion

A solution of a dione **1**, ketone **2b**, and nitrile **3** in benzene was heated under reflux in the presence of piperidine to give 4-methyl-4-(dimethoxymethyl)pyrans **4b** and **4c** in yields of 64 and 85%, respectively (Scheme 1). The structure of product **4c** was based on a characteristic acetal methine carbon at δ_C 108.76 and a C-3 quaternary carbon at δ_C 58.27 in the ^{13}C NMR spectrum and a molecular ion peak at *m/z* 306 in the mass spectrum. Compounds **4b** and **4c** were hydrolysed with 2 M HCl to afford the fused furo[2,3-*b*]furanones **5a** and **5b** in 62 and 64% yield (Scheme 2). The structure of compound **5b** was determined as follows: the ^{1}H NMR spectrum showed the acetal methine proton at δ 6.23 and the ^{13}C NMR spectrum indicated the acetal methine carbon at δ_C 111.97, with three methylene carbons at δ_C 36.15, 37.83 and 50.64, and four quaternary carbons at δ_C 33.92, 47.92, 116.42 and 173.11, respectively. The mass spectrum showed a molecular ion at *m/z* 236. The IR spectrum exhibited carbonyl absorptions at 1650 and 1790 cm^{-1}.



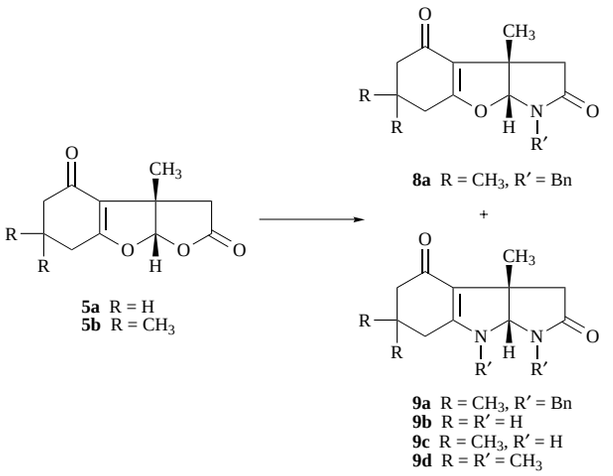
Scheme 2 *Reagent:* 2 M HCl

A possible mechanism for the formation of furofuranones **5** from pyrans **4** was deduced as follows: acid-catalysed hydrolysis of the acetal and ring opening of substrates **4** give the intermediate **6**, which is then recyclized to the hemiacetal **7**. Subsequently, compounds **7** undergo recyclization and decarboxylation to give products **5** (Scheme 3).



Scheme 3

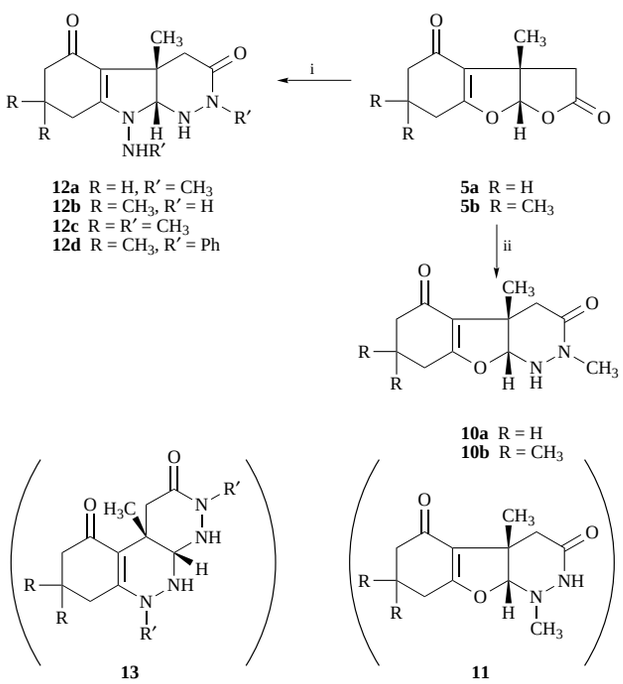
Compounds **5** were easily converted to the fused pyrrolopyrrolidinones **9** in 48–53% yield by heating with primary amines in EtOH or water (Scheme 4). In the case of benzylamine, one mole equivalent of benzylamine reacted with compound **5b** to give the furopyrrolidinone **8a** and the pyrrolopyrrolidinone **9a** in 46 and 12% yield, respectively. On treatment of compound **5b** with two mole equivalents of benzylamine, products **8a** and **9a**



Scheme 4 *Reagents:* $R'NH_2$, EtOH or water

were produced in 3 and 60% yield. These compounds were assigned by mass and ^{1}H and ^{13}C NMR spectroscopy.

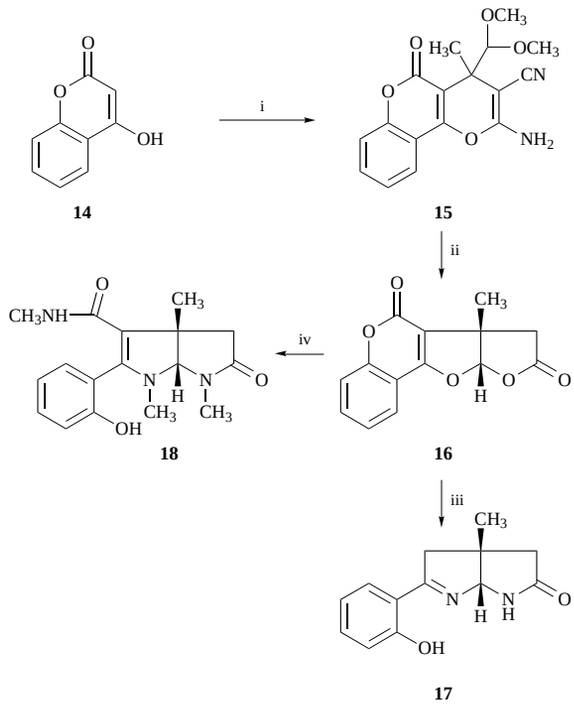
Reaction of compounds **5** with one mole equivalent of methylhydrazine in EtOH gave the furopyridazinones **10a** and **10b** in 68 and 64% yield. Regioisomer **11** was also a possible product, but was disregarded because of the observed spin coupling between the amine and methine protons (*J* 1.98 Hz). When compounds **5** were treated with two mole equivalents of methyl- or phenyl-hydrazine, the pyrrolopyridazinones **12** were produced in 52–68% yield (Scheme 5).



Scheme 5 *Reagents:* i, 2 equiv. $R'NHNH_2$, EtOH; ii, 1 equiv. CH_3NHNH_2, EtOH

Another plausible structure (**13**) was disregarded because the methyl protons at δ 2.49 were seen to undergo spin coupling to the amine proton (*J* 5.61 Hz) in the ^{1}H NMR spectrum of compound **12c**. The spectral data strongly supported the assigned structures. Compound **10b** was readily converted to the pyrrolopyridazinone **12c** by treatment with methylhydrazine in 67% yield.

As an application of this approach, we next examined the reaction involving 4-hydroxycoumarin **14**. Thus, treatment of compound **14** with ketone **2b** and nitrile **3** gave the pyranopyran **15** in 92% yield, which was subjected to hydrolysis with HCl to give the furofuranone **16** in 77% yield (Scheme 6). Treatment of lactone **16** with aq. ammonia in a sealed tube afforded the



Scheme 6 *Reagents:* i, **2b**, **3**, benzene; ii, 2 M HCl; iii, NH_4OH; iv, aq. CH_3NH_2

imino compound **17** in 63% yield after ring opening and decarboxylation of the ensuing β-carboxyenamine (Scheme 6). The structure of product **17** was determined as follows: the ^{1}H NMR spectrum showed the hydroxy group proton of the phenol moiety at δ 13.26 and the ^{13}C NMR spectrum indicated two methylene carbons at δ_C 43.87 and 48.08, respectively. The mass spectrum exhibited a molecular ion at *m/z* 230. The IR spectrum showed carbonyl absorptions at 1690 cm^{-1}. Compound **16** was also heated with methylamine to give the 4-(*N*-methylcarbamoyl)pyrrolopyrrolidinone **18** in 32% yield.

Reduction of pyrrolopyrrolidinones to pyrrolopyrrolidines has already been achieved by Marino *et al.*[8] A short approach to pyrrolopyrrolidinones using three components has now been established. Conversion of these compounds to related pyrrolopyrrolidine derivatives is being investigated.

Experimental

Mps were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded with a JASCO IR A-100 grating IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-EX270 spectrophotometer using tetramethylsilane as internal standard. *J* Values are given in Hz. Mass spectra were obtained with a JEOL JMS-DX 303 mass spectrometer.

5,6,7,8-Tetrahydro-7,7-dialkyl-2-amino-3-cyano-4-methyl-4-(dimethoxymethyl)-5-oxo-4*H*-benzo[*b*]pyran 4b and 4c

A solution of the cyclohexanedione **16** (10 mmol), pyruvaldehyde dimethyl acetal **2b** (1.21 ml, 10 mmol), malononitrile (0.63 ml, 10 mmol) and piperidine (0.49 ml, 5 mmol) in benzene (50 ml) was refluxed for 3 h using a Dean–Stark apparatus. The precipitated solid was collected, washed with EtOH, and recrystallized from EtOH.

Compound **4b**: yield 1.78 g (64%); mp 196–197 °C (Found: C, 60.21; H, 6.52; N, 9.92. $C_{14}H_{18}N_2O_4$ requires C, 60.42; H, 6.52; N, 10.07%); ν_{max}/cm^{-1} 2200 (CN) and 1680 (C=O); δ_H[$(CD_3)_2SO$] 1.41 (3 H, s, CH_3), 1.74–2.08 (2 H, m, CH_2), 2.12–2.63 (4 H, m, CH_2 × 2), 3.26 (3 H, s, CH_3), 3.38 (3 H, s, CH_3), 4.47 (1 H, s, CH) and 6.59 (2 H, s, NH_2); δ_C[$(CD_3)_2SO$] 22.23 and 57.46 (CH_3), 19.83, 27.03 and 37.99 (CH_2), 108.63 (CH), 39.99, 58.23, 114.51, 119.76, 158.81, 164.76 and 197.25 (C); *m/z* 278 (M^+).

Compound **4c**: yield 2.60 g (85%); mp 230–231 °C (Found: C, 62.50; H, 7.37; N, 8.83. $C_{16}H_{22}N_2O_4$ requires C, 62.73; H, 7.24; N, 9.14%); ν_{max}/cm^{-1} 2200 (CN) and 1670 (C=O); δ_H[$(CD_3)_2SO$] 0.98 (3 H, s, CH_3), 1.03 (3 H, s, CH_3), 1.41 (3 H, s, CH_3), 2.09 (1 H, d, *J* 15.18, C*H*H), 2.24 (1 H, d, *J* 17.82, C*H*H), 2.34 (1 H, d, *J* 15.18, CH*H*), 2.50 (1 H, d, *J* 17.82, CH*H*), 3.26 (3 H, s, CH_3), 3.44 (3 H, s, CH_3), 4.51 (1 H, s, CH) and 6.60 (2 H, s, NH_2); δ_C[$(CD_3)_2SO$] 22.21, 25.90, 28.44, 56.58 and 58.41 (CH_3), 40.36 and 51.72 (CH_2), 108.76 (CH), 31.51, 39.85, 58.27, 113.67, 119.74, 158.86, 162.77 and 197.15 (C); *m/z* 306 (M^+).

2,3,3a,4,5,6,7,8a-Octahydro-6,6-dialkyl-3a-methyl-2,4-dioxobenzo[*b*]furo[3,2-*d*]furan 5a and 5b

A suspension of a pyran **4** (2 mmol) in 2 M HCl (20 ml) was refluxed for 12 h. The reaction mixture was extracted with CH_2Cl_2 (4 × 25 ml). The CH_2Cl_2 layer was washed with water (20 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH = 50:1).

Compound **5a**: yield 2.60 g (62%); mp 134–135 °C (Found: C, 63.42; H, 5.90. $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.81%); ν_{max}/cm^{-1} 1790 and 1640 (C=O); δ_H($CDCl_3$) 1.50 (3 H, s, CH_3), 2.03–2.13 (2 H, m, CH_2), 2.33–2.39 (2 H, m, CH_2), 2.51–2.55 (2 H, m, CH_2), 2.62 (1 H, d, *J* 18.48, C*H*H), 3.08 (1 H, d, *J* 18.48, CH*H*) and 5.96 (1 H, s, CH); δ_C($CDCl_3$) 21.86 (CH_3), 38.23, 36.69, 23.25 and 21.25 (CH_2), 112.14 (CH), 48.29, 118.04, 173.51, 174.61 and 194.52 (C); *m/z* 208 (M^+).

Compound **5b**: yield 2.60 g (64%); mp 85–87 °C (Found: C, 65.89; H, 7.05. $C_{13}H_{16}O_4$ requires C, 66.09; H, 6.83%); ν_{max}/cm^{-1} 1790 and 1650 (C=O); δ_H[$(CD_3)_2SO$] 1.02 (3 H, s, CH_3), 1.03 (3 H, s, CH_3), 1.38 (3 H, s, CH_3), 2.12 (1 H, d, *J* 16.17, C*H*H), 2.25 (1 H, d, *J* 16.17, CH*H*), 2.37 (1 H, d, *J* 18.14, C*H*H), 2.48 (1 H, d, *J* 18.14, CH*H*), 2.76 (1 H, d, *J* 18.14, C*H*H), 2.84 (1 H, d, *J* 18.14, CH*H*) and 6.23 (1 H, s, CH); δ_C[$(CD_3)_2SO$] 20.91, 27.25 and 28.25 (CH_3), 36.15, 37.83 and 50.64 (CH_2), 111.97 (CH), 33.92, 47.92, 116.42, 173.11, 173.78 and 193.45 (C); *m/z* 236 (M^+).

Reaction of furobenzofuran 5b with benzylamine

A solution of compound **5b** (2 mmol) and benzylamine (2 mmol) in EtOH (10 ml) was heated under reflux for 12 h. The solvent was evaporated off under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2–MeOH = 20:1).

2,3,3a,4,5,6,7,8a-Octahydro-1-benzyl-3a,6,6-trimethyl-2,4-dioxo-1*H*-benzo[4,5]furo[2,3-*b*]pyrrole 8a. Yield 0.3 g (46%); mp 153–154 °C (Found: C, 74.06; H, 7.17; N, 4.41. $C_{20}H_{23}NO_3$ requires C, 73.82; H, 7.12; N, 4.30%); ν_{max}/cm^{-1} 1680 and 1640 (C=O); δ_H($CDCl_3$) 0.99 (6 H, s, CH_3 × 2), 1.32 (3 H, s, CH_3), 2.10 (1 H, d, *J* 17.82, C*H*H), 2.11 (2 H, s, CH_2), 2.18 (1 H, d, *J* 17.82, CH*H*), 2.42 (1 H, d, *J* 18.15, C*H*H), 2.87 (1 H, d, *J* 18.15, CH*H*), 4.10 (1 H, d, *J* 14.85, C*H*H), 4.84 (1 H, d, *J* 14.85, CH*H*), 5.27 (1 H, s, CH) and 7.22–7.25 (5 H, m, Ph); δ_C($CDCl_3$) 23.34, 28.00 and 28.81 (CH_3), 37.45, 41.66, 44.14 and 51.21 (CH_2), 101.71, 127.78, 128.32 and 128.70 (CH), 33.94, 44.46, 117.90, 135.63, 173.32, 173.43 and 193.80 (C); *m/z* 325 (M^+).

1,2,3,3a,4,5,6,7,8,8a-Decahydro-1,8-dibenzyl-3a,6,6-trimethyl-2,4-dioxopyrrolo[2,3-*b*]indole 9a. Yield 0.1 g (12%); mp 176–177 °C (Found: C, 77.94; H, 7.35; N, 6.84. $C_{27}H_{30}N_2O_2$ requires C, 78.23; H, 7.29; N, 6.76%); ν_{max}/cm^{-1} 1680 and 1620 (C=O); δ_H($CDCl_3$) 1.03 (3 H, s, CH_3), 1.07 (3 H, s, CH_3), 1.29 (3 H, s, CH_3), 2.03–2.17 (4 H, m, CH_2 × 2), 2.56 (1 H, d, *J* 18.15, C*H*H), 3.19 (1 H, d, *J* 18.15, CH*H*), 4.17 (1 H, d, *J* 16.49, C*H*H), 4.29 (1 H, d, *J* 15.83, C*H*H), 4.33 (1 H, d, *J* 16.49, CH*H*), 4.62 (1 H, s, CH), 4.81 (1 H, d, *J* 15.83, CH*H*), 6.96–7.31 (10 H, m, Ph × 2); δ_C($CDCl_3$) 24.20, 28.22 and 28.81 (CH_3), 36.29, 41.41, 44.65, 49.37 and 50.61 (CH_2), 86.39, 126.43, 126.91, 127.56, 127.94, 128.75 and 128.94 (CH), 33.97, 44.49, 115.34, 136.06, 136.52, 163.16, 174.72 and 190.80 (C); *m/z* 414 (M^+).

1,2,3,3a,4,5,6,7,8,8a-Decahydro-6,6,8-trialkyl-3a-methyl-2,4-dioxopyrrolo[2,3-*b*]indoles 9b–9d

A solution of a furofuran **5** (2 mmol) in 28% aq. ammonia (10 ml) [in the case of compound **9d** 40% methylamine solution (10 ml) was used] was heated at 80 °C for 12 h in a sealed tube. The solvent was evaporated off under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2–MeOH = 20:1).

Compound **9b**: yield 0.26 g (52%); mp 251–253 °C (Found: C, 63.72; H, 6.66; N, 13.40. $C_{11}H_{14}N_2O_2$ requires C, 64.06; H, 6.84; N, 13.58%); ν_{max}/cm^{-1} 3250 (NH), 1700 and 1670 (C=O); δ_H[$(CD_3)_2SO$] 1.26 (3 H, s, CH_3), 1.79–1.86 (2 H, m, CH_2), 1.2.05–2.11 (2 H, m, CH_2), 2.21 (1 H, d, *J* 17.15, C*H*H), 2.30–2.35 (2 H, m, CH_2), 2.54 (1 H, d, *J* 17.15, CH*H*), 4.81 (1 H, s, CH), 7.98 (1 H, s, NH) and 8.21 (1 H, s, NH); δ_C[$(CD_3)_2SO$] 24.07 (CH_3), 22.07, 22.97, 36.41 and 41.46 (CH_2), 77.62 (CH), 46.83, 113.69, 165.82, 175.96 and 188.89 (C); *m/z* 206 (M^+).

Compound **9c**: yield 0.31 g (53%); mp 270–272 °C; ν_{max}/cm^{-1} 3150 (NH), 1700 and 1690 (C=O); δ_H[$(CD_3)_2SO$] 0.96 (3 H, s, CH_3), 0.98 (3 H, s, CH_3), 1.26 (3 H, s, CH_3), 1.91 (1 H, d, *J* 15.83, C*H*H), 2.05 (1 H, d, *J* 15.83, CH*H*), 2.14 (1 H, d, *J* 16.83, C*H*H), 2.21 (1 H, d, *J* 17.15, C*H*H), 2.23 (1 H, d, *J* 16.83, CH*H*), 2.53 (1 H, d, *J* 17.15, CH*H*), 4.83 (1 H, s, CH), 7.94 (1 H, s, NH) and 8.21 (1 H, s, NH); δ_C[$(CD_3)_2SO$] 23.74, 27.49 and 28.71 (CH_3), 36.42, 41.36 and 50.62 (CH_2), 77.84 (CH), 33.80, 46.73, 112.05, 164.53, 175.83 and 188.89 (C); *m/z* 234 (M^+) [Found: (EI) M^+, 234.1385. $C_{13}H_{18}N_2O_2$ requires *M*, 234.1368].

Compound **9d**: yield 0.25 g (48%); mp 151–153 °C (Found: C, 68.49; H, 8.61; N, 10.67. $C_{15}H_{22}N_2O_2$ requires C, 68.67; H, 8.45; N, 10.68%); ν_{max}/cm^{-1} 1690 and 1670 (C=O); δ_H($CDCl_3$) 1.07 (3 H, s, CH_3), 1.08 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 2.13–2.21 (4 H, m, CH_2 × 2), 2.23 (1 H, d, *J* 16.83, CH*H*), 2.53 (1 H, d, *J* 17.15, CH*H*), 2.96 (3 H, s, CH_3), 3.12 (3 H, s, CH_3) and 4.58 (1 H, s, CH); δ_C[$(CD_3)_2SO$] 24.66, 28.38, 28.84, 29.00 and 33.29 (CH_3), 36.18, 41.82 and 50.37 (CH_2), 91.44 (CH), 33.70, 43.92, 114.29, 163.88, 174.54 and 190.10 (C); *m/z* 262 (M^+).

1,2,3,4,4a,5,6,7,8,9a-Decahydro-7,7-dialkyl-2,4a-dimethyl-3,5-dioxobenzo[4,5]furo[2,3-*c*]pyridazine 10a and 10b

A solution of a lactone **5** (2 mmol) and methylhydrazine (0.11 ml, 2 mmol) in EtOH (10 ml) was refluxed for 12 h. The EtOH was then evaporated off under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2–MeOH = 8:1).

Compound **10a**: yield 0.32 g (68%); mp 162–164 °C (Found: C, 61.20; H, 7.07; N, 11.91. $C_{12}H_{16}N_2O_3$ requires C, 61.00; H, 6.83; N, 11.86%); ν_{max}/cm^{-1} 3240 (NH) and 1640 (C=O); δ_H($CDCl_3$) 1.43 (3 H, s, CH_3), 1.99–2.05 (2 H, m, CH_2), 2.25–2.31 (2 H, m, CH_2), 2.37 (1 H, d, *J* 14.51, C*H*H), 2.42–2.46 (2 H, m, CH_2), 2.97 (1 H, d, *J* 14.51, CH*H*), 3.06 (3 H, s, CH_3), 5.23 (1 H, d, *J* 1.98, CH) and 5.78 (1 H, d, *J* 1.98, NH); δ_C($CDCl_3$) 24.71 and 36.10 (CH_3), 21.45, 23.16, 36.85 and 38.47 (CH_2), 100.80 (CH), 47.35, 116.04, 171.68, 176.34 and 194.45 (C); *m/z* 236 (M^+).

Compound **10b**: yield 0.34 g (64%); mp 150–151 °C; ν_{max}/cm^{-1} 3210 (NH) 1660 and 1640 (C=O); δ_H($CDCl_3$) 1.05 (3 H, s, CH_3), 1.08 (3 H, s, CH_3), 1.43 (3 H, s, CH_3), 2.16 (2 H, s, CH_2), 2.25 (1 H, d, *J* 17.48, C*H*H), 2.34 (1 H, d, *J* 17.48, CH*H*), 2.38 (1 H, d, *J* 14.51, C*H*H), 2.98 (1 H, d, *J* 14.51, CH*H*), 3.05 (3 H, s, CH_3), 5.26 (1 H, d, *J* 1.98, CH) and 5.86 (1 H, d, *J* 1.98, NH); δ_C($CDCl_3$) 24.47, 27.69, 28.83 and 36.08 (CH_3), 37.54, 38.44 and 51.18 (CH_2), 101.15 (CH), 34.08, 47.36, 114.71, 171.76, 175.26 and 193.66 (C); *m/z* 264 (M^+) [Found: (EI) M^+, 264.1477. $C_{14}H_{20}N_2O_3$ requires *M*, 264.1474].

Reaction of lactones 5 with hydrazines. General procedure

A solution of a lactone **5** (2 mmol) and hydrazine (10 mmol) in

EtOH (10 ml) was refluxed for 12 h. The EtOH was then evaporated off under reduced pressure, and the residue was treated with diethyl ether. The precipitated solid was filtered off, and recrystallized with EtOH.

1,2,3,4,4a,5,6,7,8,9a-Decahydro-2,4a-dimethyl-9-methylamino-3,5-dioxopyridazino[3,4-*b*]indole 12a. Yield 0.36 g (68%); mp 199–201 °C (Found: C, 58.90; H, 7.86; N, 21.04. $C_{13}H_{20}N_4O_2$ requires C, 59.07; H, 7.63; N, 21.20%); ν_{max}/cm^{-1} 3280 and 3250 (NH) and 1660 (C=O); δ_H($CDCl_3$) 1.41 (3 H, s, CH_3), 1.86–1.95 (2 H, m, CH_2), 2.15–2.21 (2 H, m, CH_2), 2.34–2.55 (3 H, m, CH_2 and C*H*H), 2.61 (3 H, s, CH_3), 2.97 (3 H, s, CH_3), 3.12 (1 H, d, *J* 14.18, CH*H*), 4.29 (1 H, br, NH), 4.62 (1 H, d, *J* 1.65, CH) and 5.77 (1 H, d, *J* 1.65, NH); δ_C($CDCl_3$) 24.69, 35.48 and 36.53 (CH_3), 21.83, 36.83 and 38.61 (CH_2), 80.08 (CH), 46.08, 108.81, 168.76, 173.05 and 190.99 (C); *m/z* 264 (M^+).

1,2,3,4,4a,5,6,7,8,9a-Decahydro-9-amino-4a,7,7-trimethyl-3,5-dioxopyridazino[3,4-*b*]indole 12b. Yield 0.26 g (52%); mp 251–253 °C; ν_{max}/cm^{-1} 3300, 3260, 3210 and 3140 (NH), 1660 and 1640 (C=O); δ_H[$(CD_3)_2SO$] 0.92 (3 H, s, CH_3), 0.98 (3 H, s, CH_3), 1.28 (3 H, s, CH_3), 1.81 (1 H, d, *J* 15.84, C*H*H), 1.96 (1 H, d, *J* 15.84, CH*H*), 2.24 (1 H, d, *J* 17.15, C*H*H), 2.25 (1 H, d, *J* 13.52, C*H*H), 2.34 (1 H, d, *J* 17.15, CH*H*), 2.67 (1 H, d, *J* 13.52, CH*H*), 4.26 (1 H, d, *J* 2.31, CH), 4.36 (2 H, s, NH_2), 5.88 (1 H, d, *J* 2.31, NH) and 8.21 (1 H, s, NH); δ_C[$(CD_3)_2SO$] 25.13, 27.69 and 28.99 (CH_3), 35.27, 38.28 and 50.78 (CH_2), 86.21 (CH), 33.19, 45.16, 106.16, 167.73, 174.90 and 187.52 (C); *m/z* 264 (M^+) [Found: (EI) M^+, 264.1567. $C_{13}H_{20}N_4O_2$ requires *M*, 264.1586].

1,2,3,4,4a,5,6,7,8,9a-Decahydro-9-methylamino-2,4a,7,7-tetramethyl-3,5-dioxopyridazinol[3,4-*b*]indole 12c. Yield 0.31 g (53%); mp 215–217 °C (Found: C, 61.69; H, 8.55; N, 19.02. $C_{15}H_{24}N_4O_2$ requires C, 61.62; H, 8.27; N, 19.16%); ν_{max}/cm^{-1} 3260 (NH), 1660 and 1640 (C=O); δ_H($CDCl_3$) 0.88 (3 H, s, CH_3), 0.99 (3 H, s, CH_3), 1.24 (3 H, s, CH_3), 1.80 (1 H, d, *J* 15.84, C*H*H), 1.99 (1 H, d, *J* 15.84, CH*H*), 2.24 (1 H, d, *J* 17.15, C*H*H), 2.33 (1 H, d, *J* 17.15, CH*H*), 2.35 (1 H, d, *J* 13.52, C*H*H), 2.49 (3 H, d, *J* 5.61, CH_3), 2.78 (1 H, d, *J* 13.52, CH*H*), 2.84 (3 H, s, CH_3), 4.57 (1 H, d, *J* 1.98, CH), 4.88 (1 H, q, *J* 5.61, NH) and 6.33 (1 H, d, *J* 1.98, NH); δ_C($CDCl_3$) 24.55, 26.95, 29.09, 35.13 and 36.18 (CH_3), 34.89, 38.18 and 50.67 (CH_2), 80.54 (CH), 33.21, 45.41, 106.25, 166.98, 172.14 and 187.89 (C); *m/z* 292 (M^+).

1,2,3,4,4a,5,6,7,8,9a-Decahydro-9-anilino-4a,7,7-trimethyl-2-phenyl-3,5-dioxopyridazino[3,4-*b*]indole 12d. Yield 0.51 g (61%); mp 235–236 °C (Found: C, 72.33; H, 6.84; N, 13.30. $C_{25}H_{28}N_4O_2$ requires C, 72.09; H, 6.78; N, 13.45%); ν_{max}/cm^{-1} 3320 and 3230 (NH), 1690 and 1620 (C=O); δ_H($CDCl_3$) 0.97 (3 H, s, CH_3), 1.00 (3 H, s, CH_3), 1.45 (3 H, s, CH_3), 2.04–2.17 (4 H, m, CH_2 × 2), 2.49 (1 H, d, *J* 17.82, C*H*H), 3.05 (1 H, d, *J* 17.82, CH*H*), 4.83 (1 H, s, CH), 6.29 (1 H, br, NH), 6.44–6.56 (4 H, m, ArH), 6.77–6.84 (2 H, m, ArH), 6.91 (1 H, br, NH) and 7.06–7.18 (4 H, m, ArH); δ_C($CDCl_3$) 24.19, 27.61 and 29.15 (CH_3), 35.10, 39.94 and 50.94 (CH_2), 83.72, 112.67, 113.36, 121.18, 121.59 and 129.45 (CH), 42.39, 111.53, 145.25, 145.86, 166.18, 173.96 and 191.47 (C); *m/z* 416 (M^+).

Compound 12c from benzofuran 10b and methylhydrazine

A solution of compound **10b** (0.53 g, 2 mmol) and methylhydrazine (0.53 ml, 10 mmol) in EtOH was refluxed for 12 h. The EtOH was evaporated off under reduced pressure and the resulting residue was purified by flash column chromatography (CH_2Cl_2–MeOH = 8:1) to give compound **12c** in 67% yield. The product was identified by comparison of its spectra with the spectral data of an authentic sample of compound **12c**.

2-Amino-3-cyano-4-dimethoxymethyl-4-methyl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene 15

A solution of 4-hydroxycoumarin **14** (1.62 g, 10 mmol), pyruvaldehyde dimethyl acetal **2b** (1.21 ml, 10 mmol), malononitrile **3** (0.63 ml, 10 mmol) and piperidine (0.49 ml, 5 mmol) in benzene (50 ml) was refluxed for 3 h using a Dean–Stark apparatus. The precipitated solid was collected, washed with EtOH and recrystallized from EtOH to give the *title compound* **15** (3.02 g, 92%); mp 239–241 °C (Found: C, 62.33; H, 5.06; N, 8.21. $C_{17}H_{16}N_2O_5$ requires C, 62.19; H, 4.91; N, 8.53%); ν_{max}/cm^{-1} 2200 (CN) and 1710 (C=O); δ_H[$(CD_3)_2SO$] 1.65 (3 H, s, CH_3), 3.26 (3 H, s, CH_3), 3.52 (3 H, s, CH_3), 4.62 (1 H, s, CH), 7.14 (2 H, s, NH_2), 7.44–7.50 (2 H, m, ArH), 7.70–7.76 (1 H, m, ArH) and 7.88–7.92 (1 H, m, ArH); δ_C[$(CD_3)_2SO$] 21.77, 56.96 and 58.44 (CH_3), 108.36, 116.21, 122.68, 124.60 and 132.96 (CH), 40.69, 57.85, 105.06, 112.73, 119.31, 151.98, 154.03, 158.65 and 159.32 (C); *m/z* 328 (M^+).

***cis*-6b,7,8,9a-Tetrahydro-6b-methyl-6,8-dioxofuro[3′,2′:4,5]-furo[3,2-*c*]chromene 16**

A suspension of nitrile **15** (0.66 g, 2 mmol) in 2 M HCl (20 ml) was refluxed for 12 h. The precipitated solid was collected and recrystallized from EtOH to give *title compound* **16** (0.40 g, 77%); mp 193–194 °C (Found: C, 65.27; H, 4.04. $C_{14}H_{10}O_5$ requires C, 65.12; H, 3.90%); ν_{max}/cm^{-1} 1800 and 1715 (C=O); δ_H[$(CD_3)_2SO$] 1.61 (3 H, s, CH_3), 2.97 (1 H, d, *J* 18.14, C*H*H), 3.08 (1 H, d, *J* 18.14, CH*H*), 6.64 (1 H, s, CH), 7.40–7.52 (2 H, m, ArH), 7.71–7.77 (2 H, m, ArH); δ_C[$(CD_3)_2SO$] 20.48 (CH_3), 37.45 (CH_2), 112.94, 116.75, 122.74, 124.57 and 133.37 (CH), 48.73, 107.79, 111.46, 154.60, 158.13, 162.88 and 173.46 (C); *m/z* 258 (M^+).

***cis*-1,2,3,3a,4,6a-Hexahydro-5-(2-hydroxyphenyl)-3a-methyl-2-oxopyrrolo[2,3-*b*]pyrrole 17**

A suspension of lactone **16** (0.52 g, 2 mmol) in 28% aq. ammonia (10 ml) was heated at 80 °C in a sealed tube for 2 h. Then the precipitated solid was filtered off and recrystallized from EtOH to give *title compound* **17** (0.29 g, 63%); mp 218–219 °C (Found: C, 67.75; H, 6.23; N, 12.10. $C_{13}H_{14}N_2O_2$ requires C, 67.81; H, 6.13; N, 12.17%); ν_{max}/cm^{-1} 3180 (OH), 3090 (NH) and 1690 (C=O); δ_H[$(CD_3)_2SO$] 1.34 (3 H, s, CH_3), 2.14 (1 H, d, *J* 17.49, C*H*H), 2.40 (1 H, d, *J* 17.49, CH*H*), 3.02 (1 H, d, *J* 17.82, C*H*H), 3.37 (1 H, d, *J* 17.82, CH*H*), 5.30 (1 H, s, CH), 6.90–6.97 (2 H, m, ArH), 7.37–7.50 (2 H, m, ArH), 8.69 (1 H, s, NH) and 13.26 (1 H, br, OH); δ_C[$(CD_3)_2SO$] 24.74 (CH_3), 43.87 and 48.08 (CH_2), 90.66, 116.58, 118.63, 130.37 and 133.26 (CH), 41.77, 116.29, 160.29, 175.40 and 177.48 (C); *m/z* 230 (M^+).

***cis*-1,2,3,3a,6,6a-Hexahydro-5-(2-hydroxyphenyl)-1,3a,6-trimethyl-4-methylcarbamoyl-2-oxopyrrolo[2,3-*b*]pyrrole 18**

A suspension of lactone **16** (0.52 g, 2 mmol) in 40% aq. methylamine (10 ml) was heated at 80 °C in a sealed tube for 5 h. Water was evaporated off under reduced pressure and the resulting residue was purified by flash column chromatography (CH_2Cl_2–MeOH = 20:1) to give *title compound* **18** (0.2 g, 32%); mp 195–197 °C (Found: C, 65.03; H, 6.64; N, 13.41. $C_{17}H_{21}N_3O_3$ requires C, 64.74; H, 6.71; N, 13.32%); ν_{max}/cm^{-1} 3450 (NH), 3050 (OH), 1690 and 1680 (C=O); δ_H[$(CD_3)_2SO$] 1.44 (3 H, s, CH_3), 2.32 (1 H, d, *J* 17.49, C*H*H), 2.39 (3 H, d, *J* 4.62, CH_3), 2.68 (3 H, s, CH_3), 2.73 (1 H, d, *J* 17.49, CH*H*), 2.82 (3 H, s, CH_3), 4.64 (1 H, s, NCHN), 5.30 (1 H, br, NH), 6.90–7.49 (4 H, m, ArH) and 9.90 (1 H, s, OH); δ_C[$(CD_3)_2SO$] 22.15, 25.57, 27.41 and 34.82 (CH_3), 42.18 (CH_2), 88.73, 116.42, 119.52, 130.47 and 131.12 (CH), 47.52, 110.92, 118.09, 149.52, 155.02, 165.21 and 172.82 (C); *m/z* 315 (M^+).

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