Isomerization of 4-Aminobenzofurans to 4-Hydroxyindoles

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Abstract: 4-Amino-2-methylbenzofurans are quantitatively converted to 4-hydroxy-2-methylindoles in acidic medium. The rearrangement mechanism involves the ring opening of the furan ring to produce an intermediate carbocation, which undergoes ring closure to the indole system. Isomerization takes place only in the presence of a methyl substituent in 2 position.

Key words: aminobenzofurans, hydroxyindoles, synthesis, isomerization

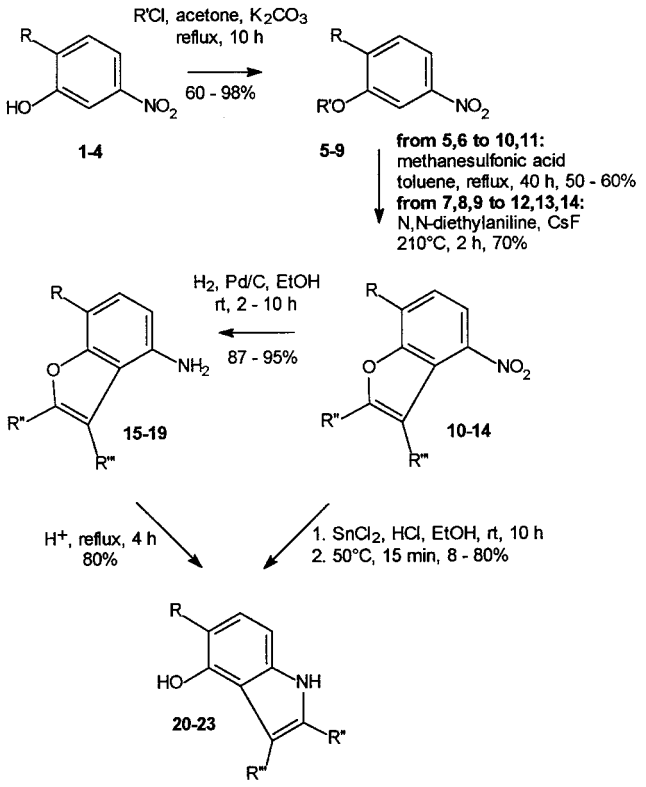
In the last few years we have been interested in synthesizing some derivatives of 4*H*-furo[2,3-*h*]quinolin-4-one,[1] to find out whether they would show antiproliferative activity, similar to 2*H*-furo[2,3-*h*]quinolin-2-ones.[2] During these studies, we often used 4-aminobenzofurans as key intermediates for the synthesis of furoquinolin-4-ones. It immediately appeared that 4-aminobenzofurans are not stable in acidic conditions and that they are easily interconverted to their structural isomers, 4-hydroxyindole derivatives.

This finding must be taken into consideration when handling aminobenzofurans, which are of great interest, both as building blocks in organic and medicinal chemistry and as true pharmacophores.[3–5] In addition, it may be of some importance in preparing hydroxyindole derivatives, since they are very frequently used in the synthesis of several compounds of biological interest.[6–9]

Our studies started from the observation that very different products are formed during the reduction of 4-nitrobenzofurans under varying conditions. Whereas catalytic hydrogenation of 2,7-dimethyl-4-nitrobenzofuran (**12**) gives only 4-amino-2,7-dimethylbenzofuran (**17**) in 87% yield, reduction of **12** with $SnCl_2$ affords 4-hydroxy-2,5-dimethylindole (**21**) in 80% yield (Scheme 1).

Careful investigation of the reaction progress showed that compound **17** was initially formed, but was completely converted into **21** during the subsequent workup of the reaction mixture. Therefore, as soon as the starting compound had disappeared, ethanol was evaporated from the reaction mixture under reduced pressure and the semisolid residue was further heated at 50°C for 15 minutes. In this way, the initially formed aminobenzofuran remained in strong acidic medium (concd HCl survives in the reaction mixture after evaporation of EtOH) and isomerized to hydroxyindole. Further confirmation of this finding was that compound **17**, unequivocally prepared by catalytic reduction, was converted to **21** in refluxing concentrated HCl, in 80% yield.

Various methylated nitrobenzofurans were reacted under the same conditions in order to define the role of methyl substitution on the furan ring. Thus, nitrobenzofurans carrying a methyl group either in the 2 or 3 position or two methyl groups in both the 2 and 3 positions were prepared,



	R	R′	R″	R‴		R	R′	R″	R‴
1	Me	–	–	–	**13**	$NHCO_2Et$	–	Me	H
2	NH_2	–	–	–	**14**	OMe	–	Me	H
3	$NHCO_2Et$	–	–	–	**15**	Me	–	H	Me
4	OMe	–	–	–	**16**	Me	–	Me	Me
5	Me	CH_2COMe	–	–	**17**	Me	–	Me	H
6	Me	CH(Me)COMe	–	–	**18**	$NHCO_2Et$	–	Me	H
7	Me	$CH_2C{\equiv}CH$	–	–	**19**	OMe	–	Me	H
8	$NHCO_2Et$	$CH_2C{\equiv}CH$	–	–	**20**	Me	–	Me	Me
9	OMe	$CH_2C{\equiv}CH$	–	–	**21**	Me	–	Me	H
10	Me	–	H	Me	**22**	$NHCO_2Et$	–	Me	H
11	Me	–	Me	Me	**23**	OMe	–	Me	H
12	Me	–	Me	H					

Scheme 1

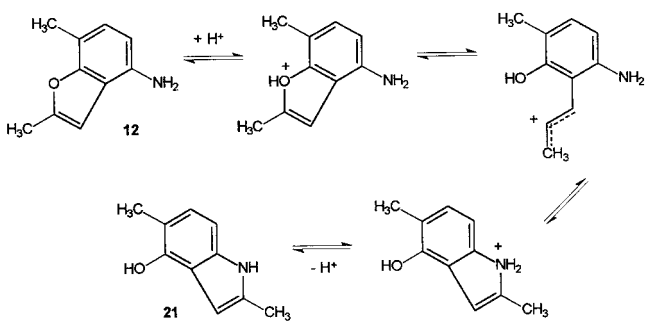
according to Scheme 1, starting from 2-hydroxy-4-nitrotoluene (**1**), 2-ethoxycarbonylamino-5-nitrophenol (**3**), and 2-methoxy-5-nitrophenol (**4**), which were condensed with the appropriate α-halo ketone or propargyl chloride[1] to give ethers **5–9**. These compounds were then cyclized under appropriate conditions to 7-methyl- or 7-ethoxycarbonylamino- or 7-methoxy-4-nitrobenzofurans **10–14.** 2-Substituted nitrophenols were chosen so that only one possibility of cyclization of the ethereal moiety in the *ortho* position could occur. 2-Amino-5-nitrophenol (**2**)

was previously protected as ethyl carbamate to avoid side reactions on the amino group.

The nitrobenzofuran intermediates were then reduced unequivocally to the corresponding aminobenzofurans **15–19** by catalytic hydrogenation and then submitted to isomerization in various acidic media. Compounds **16, 17, 18** and **19**, i.e. those carrying the methyl group in 2 position, were quantitatively converted into the corresponding 5-substituted-4-hydroxyindoles **20, 21, 22** and **23** in all acidic conditions tested, i.e. concd HCl, glacial AcOH, CF_3CO_2H (TFA) or $HClO_4$ in AcOH. On the contrary, compound **15** remained unchanged. Isomerization was also performed in concd H_2SO_4 with the same results, but degradation of reaction products occurred to various extents.

Reduction of nitro groups and concomitant isomerization using $SnCl_2$ and concd HCl was successful only for compounds **12, 13** and **14**. Compound **10** gave only the aminobenzofuran **15**, as expected, and compound **11** afforded the hydroxyindole **20** only in low yield (8%).

These findings reveal that the conversion of the benzofuran system to the indole system does not seem to be a hydrolysis of the system analogous to the one described for the conversion of 4-alkylaminoindoles to 1-alkyl-4-aminoindoles,[8] which requires the presence of water. Instead, the isomerization reported by us here occurs only in the presence of concentrated acids, as shown by the fact that all the attempts to isomerize the aminobenzofurans in dilute acids, such as 6M HCl or 70% $HClO_4$ failed. As shown in Scheme 2, we suggest that the rearrangement mechanism involves the opening of the furan ring to produce a tertiary carbocation intermediate, which undergoes ring closure to the more stable indole system: in the absence of the methyl group in the 2 position, secondary carbocation cannot be generated, or does not survive long enough to undergo isomerization.



Scheme 2

Analytical TLC was performed on precoated 60 F_{254} silica gel plates (0.2 mm, Merck) with an EtOAc/cyclohexane mixture (3:7). Column chromatography was performed using silica gel (0.063–0.100 mm, Merck), eluting with CH_2Cl_2. Melting points were determined using an open-capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian-Gemini 200 MHz spectrometer and refer to the deuterium lock signal from the sample solvent. Microanalyses were performed by the Microanalytical Laboratory of the Department of Pharmaceutical Sciences of University of Padova. All reagents and solvents were of commercial quality and were used without further purification.

Intermediates **5, 7, 10, 12** were prepared according to literature methods,[1] preparation of the other starting materials is not described in the literature.

2-Ethoxycarbonylamino-5-nitrophenol (3):
A suspension of **2** (12.5 g, 81.1 mmol) and ethyl chloroformate (17.6 g, 15.5 mL, 162.2 mmol) in Et_2O (800 mL) was stirred at r.t. until **2** had disappeared (9 d, TLC). The solid was filtered and the solution concentrated under reduce pressure. The residue was crystallized from EtOAc to give **3** (10.1 g, 55%); mp 179 °C.
IR (KBr): ν = 3235, 2990, 1730, 1590, 1560, 1510, 1340, 1200, 1060, 740 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.36 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 4.30 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 7.75 (d, J = 8.9 Hz, 1 H, H-3), 7.78 (d, J = 2.3 Hz, 1 H, H-6), 7.84 (dd, J = 8.9 Hz, 2.3 Hz, 1 H, H-4).
Anal. Calcd ($C_9H_{10}N_2O_5$): C, 47.79; H, 4.46; N, 12.38. Found: C, 47.78; H, 4.55; N, 12.31.

1-Methyl-2-(1-methyl-2-oxoprop-1-yloxy)-4-nitrobenzene (6):
To a solution of **1** (7.5 g, 49.1 mmol) in acetone (150 mL) were added 2-chlorobutan-3-one (7.9 g, 74.3 mmol) and anhyd K_2CO_3 (15 g). The mixture was refluxed until **1** had disappeared (10 h, TLC). After cooling, the solid was filtered and washed with acetone. The solvent was evaporated from the combined filtrate and washings and the residue was crystallized from cyclohexane to give **6** (10.7 g, 98%); mp 86°C.
IR (KBr): ν = 2985, 2925, 1710, 1510, 1345, 1245, 1095, 860, 800, 740 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.58 (d, J = 6.8 Hz, 3 H, $CHCH_3$), 2.25 (s, 3 H, $COCH_3$), 2.38 (s, 3 H, Ar-CH_3), 4.80 (q, J = 6.8 Hz, 1 H, CH), 7.32 (d, J = 8.2 Hz, 1 H, H-6), 7.49 (d, J = 2.1 Hz, 1 H, H-3), 7.80 (dd, J = 8.2 Hz, 2.1 Hz, 1 H, H-5).
Anal. Calcd ($C_{11}H_{13}NO_4$): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.28; H, 5.85; N, 6.21.

1-Carbethoxyamino-4-nitro-2-(prop-2-yn-1-yloxy)benzene (8):
To a solution of **3** (3.8 g, 16.8 mmol) in acetone (150 mL) were added propargyl chloride (3.1 g, 3 mL, 41.7 mmol) and anhyd K_2CO_3 (15 g). The mixture was refluxed until **3** had disappeared (10 h, TLC). After cooling, the solid was filtered and washed with acetone. The solvent was evaporated from the combined filtrate and washings and the residue was crystallized from EtOAc/cyclohexane to give **8** (2.7 g, 60%); mp 135 °C.
IR (KBr): ν = 3410, 3255, 2950, 1730, 1545, 1480, 1340, 1230, 1055, 810, 740 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ = 1.35 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.63 (t, J = 2.4 Hz, 1 H, C≡CH), 4.28 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.88 (d, J = 2.4 Hz, 2 H, CH_2), 7.46 (br s, 1 H, NH), 7.88 (d, J = 2.4 Hz, 1 H, H-3), 7.97 (dd, J = 9.0 Hz, 2.4 Hz, 1 H, H-5), 8.33 (d, J = 9.0 Hz, 1 H, H-6).
Anal. Calcd ($C_{12}H_{12}N_2O_5$): C, 54.55; H, 4.58; N, 10.60. Found: C, 54.38; H, 4.55; N, 10.55.

1-Methoxy-4-nitro-2-(prop-2-yn-1-yloxy)benzene (9):
Compound **4** (5.0 g, 29.6 mmol) was reacted with propargyl chloride (5.2 g, 5.0 mL, 69.1 mmol) in the presence of anhyd K_2CO_3 (15 g) as described for compound **8**. The residue was crystallized from EtOAc/cyclohexane to give **9** (3.7 g, 60%); mp 140°C.
IR (KBr): ν = 3300, 1580, 1520, 1340, 1270, 1140, 1095, 1000, 815, 740 cm^{-1}.
^{1}H NMR (CDC1^3): δ = 2.59 (t, J = 2.4 Hz, 1 H, C≡CH), 3.99 (s, 3 H, OCH_3), 4.85 (d, J = 2.4 Hz, 2 H, CH_2), 6.95 (d, J = 8.8 Hz, 1 H, H-6), 7.93 (d, J = 2.6 Hz, 1 H, H-3), 7.98 (dd, J = 8.8 Hz, 2.6 Hz, 1 H, H-5).
Anal. Calcd ($C_{10}H_9NO_4$): C, 57.97; H, 4,38; N, 6.76. Found: C, 57.88; H, 4.50; N, 6.65.

4-Nitro-2,3,7-trimethylbenzofuran (11):
A solution of **6** (5.0 g, 22.3 mmol) in toluene (500 mL) was refluxed for 40 h, adding portions of $MeSO_3H$ (10.7 g, 111.3 mmol) during intervals. After cooling, the solution was washed with H_2O and the dried (Na_2SO_4) organic phase concentrated under reduced pressure. Column chromatography of the residue yielded **11** (2.7 g, 60%); mp 79 °C.

IR (KBr): ν = 2975, 2925, 1585, 1520, 1440, 1350, 1260, 1160, 1030, 800, 735 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.30 (q, J = 0.7 Hz, 3 H, CH_3 at 2 or 3), 2.46 (q, J = 0.7 Hz, 3 H, CH_3 at 2 or 3), 2.55 (s, 3 H, 7-CH_3), 7,05 (d, J = 8.2 Hz, 1 H, H-6), 7.86 (d, J = 8.2 Hz, 1 H, H-5).
Anal. Calcd ($C_{11}H_{11}NO_3$): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.40; H, 5.56; N, 6.92.

7-Ethoxycarbonylamino-2-methyl-4-uitrobenzofuran (13):
A mixture of **8** (2.7 g, 10.2 mmol), CsF (1.0 g, 6.6 mmol) and *N*,*N*-diethylaniline (15 mL) was heated at 210°C for 2 h. After cooling, the mixture was diluted with EtOAc (100 mL), washed with 1 M HCl (5 × 100 mL) and the dried (Na_2SO_4) organic phase concentrated under reduced pressure. Column chromatography of the residue yielded **13** (1.9 g, 70%); mp 152°C.
IR (KBr): ν = 3380, 2970, 1730, 1590, 1530, 1495, 1310, 1230, 1195, 1030, 810 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.38 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.55 (d, J = 0.9 Hz, 3 H, 2-CH_3), 4.32 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 7.16 (q, J = 0.9 Hz, 1 H, H-3), 7.35 (br s, 1 H, NH), 8.05 (d, J = 9.1 Hz, 1 H, H-5 or 6), 8.17 (d, J = 9.1 Hz, 1 H, H-5 or 6).
Anal. Calcd ($C_{12}H_{12}N_2O_5$): C, 54.55; H, 4.58; N, 10.60. Found: C, 54.40; H, 4.56; N, 10.62.

7-Methoxy-2-methyl-4-nitrobenzofuran (14):
A mixture of **9** (2.4 g, 11.6 mmol), CsF (1.1 g, 7.2 mmol) and *N*,*N*-diethylaniline (10 mL) was reacted as described for compound **13**. Column chromatography of the residue yielded **14** (1.7 g, 70%); mp 153°C.
IR (KBr): ν = 2975, 1590, 1495, 1320, 1280, 1095, 960, 790, 730 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.56 (d, J = 1.2 Hz, 3 H, 2-CH_3), 4.11 (s, 3 H, OCH_3), 6.79 (d, J = 8.8 Hz, 1 H, H-6), 7.15 (q, J = 1.2 Hz, 1 H, H-3), 8.17 (d, J = 8.8 Hz, 1 H, H-5).
Anal. Calcd ($C_{10}H_9NO_4$): C, 57.97; H, 4.38; N, 6.76. Found: C, 57.90; H, 4.36; N, 6.70.

4-Aminobenzofurans 15–19; General Procedure:
To a solution of nitrobenzofuran (20.0 mmol) in absolute EtOH (100 mL) was added a catalytic amount of Pd/C and the mixture was kept at r.t. under a low pressure of H_2. After stirring for 10 h, the catalyst was filtered and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography.

4-Amino-3, 7-dimethylbenzofuran (**15**): yield 95% (3.1 g); gum.
IR (neat): ν = 3485, 3390 (NH_2), 2930, 1630, 1510, 1440, 1230, 1120, 1080, 805, 780 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.38 (s, 3 H, 7-CH_3), 2.43 (d, J = 1.3 Hz, 3 H, 3-CH_3), 3.89 (br s, 2 H, NH_2), 6.37 (d, J = 7.7 Hz, 1 H, H-5 or H-6), 6.84 (d, J = 7.7 Hz, 1 H, H-5 or H-6), 7.27 (q, J = 1.3 Hz, 1 H, H-2).
Anal. Calcd ($C_{10}H_{11}NO$): C, 74.51; H, 6.88; N, 8.69: Found: C, 74.63; H, 6.61; N, 8.71.

4-Amino-2,3, 7-trimethylbenzofuran (**16**): yield 90% (3.2 g); mp 53°C.
IR (KBr): ν = 3415, 3315 (NH_2), 2925, 1630, 1510, 1450, 1225, 1130, 1080, 810, 750 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.36 (s, 6 H, 2- and 3-CH_3), 2.39 (d, J = 0.7 Hz, 3 H, Ar-CH_3), 3.80 (br s, 2 H, NH_2), 6.36 (d, J = 7.7 Hz, 1 H, H-5), 6.79 (dq, J = 7.7 Hz, 0.7 Hz, 1 H, H-6).
Anal. Calcd ($C_{11}H_{13}NO$): C, 75.40; H, 7.48; N, 7.99. Found: C, 75.53 ; H, 7.51; N, 7.91.

4-Amino-2, 7-dimethylbenzofuran (**17**): yield 87% (2.8 g); gum.
IR (neat): ν = 3385 and 3275 (NH_2), 2915, 1635, 1510, 1460, 1225, 1185, 1040, 800 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.38 (d, J = 0.7 Hz, 3 H, 7-CH_3), 2.45 (d, J = 1,1 Hz, 3 H, 2-CH_3), 3.70 (br s, 2 H, NH_2), 6.29 (q, J = 1.1 Hz, 1 H, H-3), 6.41 (d, J = 7.8 Hz, 1 H, H-5), 6.80 (dq, J = 7.8 Hz, 0.7 Hz, 1 H, H-6).
Anal. Calcd ($C_{10}H_{11}NO$): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.41; H, 6.90; N, 8.66.

4-Amino-7-ethoxycarbonylamino-2-methylbenzofuran (**18**): yield 93% (4.3 g); gum.
IR (neat): ν = 3420 and 3355 (NH_2), 2970, 1710, 1525, 1410, 1220, 1090, 795 cm^{-1}.
^1H NMR (DMSO-d_6): δ = 1.21 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.39 (d, J = 0.9 Hz, 3 H, 2-CH_3), 4.07 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 5.34 (br s, 2 H, NH_2), 6.25 (d, J = 8.2 Hz, 1 H, H-5 or H-6), 6.62 (q, J = 1.0 Hz, 1 H, H-3), 6.78 (d, J = 8.2 Hz, 1 H, H-5 or H-6), 8.72 (br s, 1 H, NH).
Anal. Calcd ($C_{12}H_{14}N_2O_3$): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.41; H, 6.00; N, 11.86.

4-Amino-7-methoxy-2-methylbenzofuran (**19**): yield 88% (3.1 g); gum.
IR (neat): ν = 3420 and 3355 (NH_2), 2930, 1510, 1415, 1265, 1085, 970, 790 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.47 (d, J = 1.0 Hz, 3 H, 2-CH_3), 3.05 (br s, 2 H, NH_2), 3.94 (s, 3 H, OCH_3), 6.31 (q, J = 1.0 Hz, 1 H, H-3), 6.40 (d, J = 8.3 Hz, 1 H, H-5 or H-6), 6.58 (d, J = 8.3 Hz, 1 H, H-5 or H-6).
Anal. Calcd ($C_{10}H_{11}NO_2$): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.75; H, 6.20; N, 7.82.

Reduction of Nitrobenzofurans 10–14 with $SnCl_2$; General Procedure for One-Pot Reaction:
To a solution of nitrobenzofuran (10 mmol) in EtOH (100 mL) was added a solution of $SnCl_2 \cdot 2H_2O$ (18.0 g, 80 mmol) in concd HCl (50 mL) and the mixture was kept at r.t. with stirring until all the starting material had disappeared (10 h). The mixture was concentrated under reduced pressure at 50°C and kept under vacuum at this temperature for another 15 min. The residue was diluted with 10% $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 50 ml). The dried (Na_2SO_4) organic phase was concentrated under reduced pressure and the residue was purified by column chromatography.
From **10**: The workup gave only **15** (1.6 g, 98%).
From **11**: The workup gave **16** (1.5 g, 88%) and 4-hydroxy-2,3,5-trimethylindole (**20**; 0.14 g, 8%); mp 174°C.

Compound **20**:
IR (KBr): ν = 3415 (NH), 3320 (OH), 2920, 1570, 1490, 1455, 1325, 1235, 1070, 920, 780 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.30 (q, J = 0.7 Hz, 3 H, 2- or 3-CH_3), 2.31 (s, 3 H, 5-CH_3), 2.45 (q, J = 0.7 Hz, 3 H, 2- or 3-CH_3), 4.88 (br s, 1 H, NH or OH), 6.75 (d, J = 8.2 Hz, 1 H, H-6 or H-7), 6.83 (d, J = 8.2 Hz, 1 H, H-6 or H-7), 7.53 (br s, 1 H, NH or OH).
Anal. Calcd ($C_{11}H_{13}NO$): C, 75.40; H, 7.48; N, 7.99. Found: C, 75.43; H, 7.54; N, 7.90.
From **12**: The workup gave 4-hydroxy-2,5-dimethylindole (**21**; 1.3 g, 79%); mp 88 °C.

Compound **21**:
IR (KBr): ν = 3385 (NH), 3235 (OH), 2925, 1600, 1510, 1325, 1240, 1080, 900, 785 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.20 (s, 3 H, 5-CH_3), 2.41 (d, J = 0.9 Hz, 3 H, 2-CH_3), 4.92 (br s, 1 H, NH or OH), 6.19 (q, J = 0.9 Hz, 1 H, H-3), 6.82 (d, J = 8.2 Hz, 1 H, H-6 or H-7), 6.88 (d, J = 8.2 Hz, 1 H, H-6 or H-7), 7.80 (br s, 1 H, NH or OH).
Anal. Calcd ($C_{10}H_{11}NO$): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.45; H, 6.92; N, 8.61.
From **13**: The workup gave 5-ethoxycarbonylamino-4-hydroxy-2-methylindole (**22**; 1.9 g, 80%) as a gum.

Compound **22**:
IR (neat): ν = 3410 (NH), 3295 (OH), 2975, 1730, 1560, 1510, 1260, 1090, 780 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.39 (d, J = 1.0 Hz, 3 H, 2-CH_3), 4.25 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 6.35 (q, J = 1.0 Hz, 1 H, H-3), 6.73 (d, J = 8.4 Hz, 1 H, H-6 or H-7), 6.77 (d, J = 8.4 Hz, 1 H, H-6 or H-7), 7.95 (br s, 1 H, NH or -OH).
Anal. Calcd ($C_{12}H_{14}N_2O_3$): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.45; H, 6.10; N, 12.00.
From **14**: The workup gave 4-hydroxy-5-methoxy-2-methylindole (**23**; 1.4 g, 80%) as a gum.

Compound **23**:
IR (neat): ν = 3470 (NH), 3390 (OH), 2930, 1510, 1450, 1235, 1090, 915, 770 cm^{-1}.
^1H NMR ($CDCl_3$): δ = 2.39 (br s, 3 H, 2-CH_3), 3.89 (s, 3 H, OCH_3), 6.30 (br s, 1 H, H-3), 6.76 (d, J = 8.6 Hz, 1 H, H-6 or H-7), 6.81 (d, J = 8.6 Hz, 1 H, H-6 or H-7), 7.76 (br s, 1 H, NH or OH).
Anal. Calcd ($C_{10}H_{11}NO_2$): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.64; H, 6.22; N, 7.86.

Methyl Substituted 4-Hydroxyindoles 20–23; General Procedure for Stepwise Reaction:
A solution of 4-aminobenzofuran (2.0 mmol) in concd HCl (20 mL) or glacial AcOH (10 mL) or TFA (2 mL) or $HClO_4$ in AcOH (5 mL) was refluxed under N_2 for 4h. The mixture was neutralized with aq 10% $NaHCO_3$ solution and extracted with EtOAc (3 × 50 mL). The dried (Na_2SO_4) organic phase was concentrated under reduced pressure and the residue was purified by column chromatography.

4-Hydroxy-2,3,7-trimethylindole (**20**): yield 80% (0.27 g); mp, IR and ^1H NMR as above reported.

4-Hydroxy-2,5-dimethylindole (**21**): yield 80% (0.26 g); mp, IR and ^1H NMR as above reported.

5-Ethoxycarbonylamino-4-hydroxy-2-methylindole (**22**): yield 80% (0.37 g); IR and ^1H NMR as above reported.

4-Hydroxy-5-methoxy-2-methylindale (**23**): yield 80% (0.28 g); IR and ^1H NMR as above reported.

(1) Rao, V. S.; Rodighiero, P.; Chilin, A.; Castellin, A.; Manzini, P.; Guiotto, A. *Liebigs Ann.* **1997**, 419.
(2) Rodighiero, P.; Guiotto, A.; Chilin, A.; Bordin, F.; Baccichetti, F.; Carlassare, F.; Vedaldi, D.; Caffieri, S.; Pozzan, A.; Dall'Acqua, F. *J. Med. Chem.* **1996**, *39*, 1293.
(3) Mustafa, A. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A.; Taylor, E. C., Eds.; Wiley: New York, 1974; Vol. 29, p 1.
(4) Cagniant, P.; Cagniant, D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Boulton, A. J., Eds.; Academic: New York, 1975; Vol. 18, p 337.
(5) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon: Oxford, 1984; Vol. 4, p 657.
(6) Sundberg, R. J. *Indoles*; Academic: New York, 1996.
(7) Spande, T. F.; Remers, W. A. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A.; Taylor, E. C., Eds.; Wiley: New York, 1979; Vol. 25, Part I, p 1.
(8) Saxton, J. E. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A.; Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, Part IV, p 1.
(9) Brown. T.; Joule, J. A.; Sammers, P. G. In *Comprehensive Organic Chemistry*; Barton, D. H. R.; Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 4, p 411.
(10) Ley, S. V.; Porter, R. A. *J. Chem. Soc., Chem. Commun.* **1982**, 1356.