A New Route to [*g*]-Fused 5-Methyl-1-functionalized Isoquinolines

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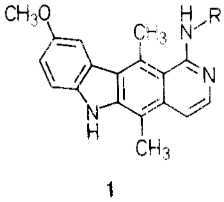
2-(3-Lithio-2-methoxy-4-pyridyl)-4,4-dimethyl-2-oxazoline (**8**) was condensed with aromatic aldehydes. Subsequent hydrolysis gave the corresponding lactones **10**. Reduction by ammoniacal zinc or catalytic hydrogenation of these compounds over palladium yielded 3-arylmethyl-2-pyridone-4-carboxylic acids **11** which were transformed into 3-arylmethyl-4-acetyl-2-pyridones **12** by methyllithium. Acidic ring closure then easily led to (*g*)-fused 5-methyl-2*H*-isoquinoline-1-ones *via* a convergent pathway. This method is more rapid and convenient than former procedures reported for the synthesis of (*g*)-fused 5-methyl-1-functionalized isoquinolines.

The (*g*)-fused 5-methyl-1-functionalized isoquinoline moiety is a part of the pharmacologically relevant ellipticine derivatives and analogues **1** and **2**.[1,2] Compounds **1** and **2** have been obtained by two independent multistep sequences;[3,4] at the present time, however, no general method is available for their synthesis.



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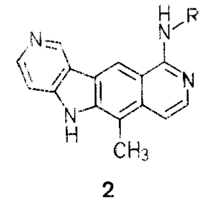
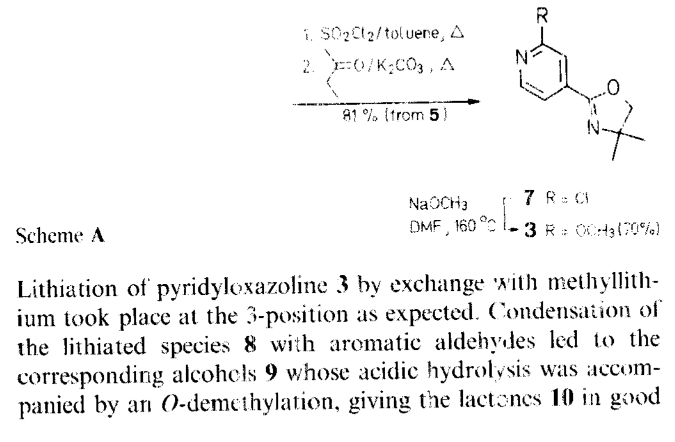


2

R = $-(CH_2)_3N(C_2H_5)_2$

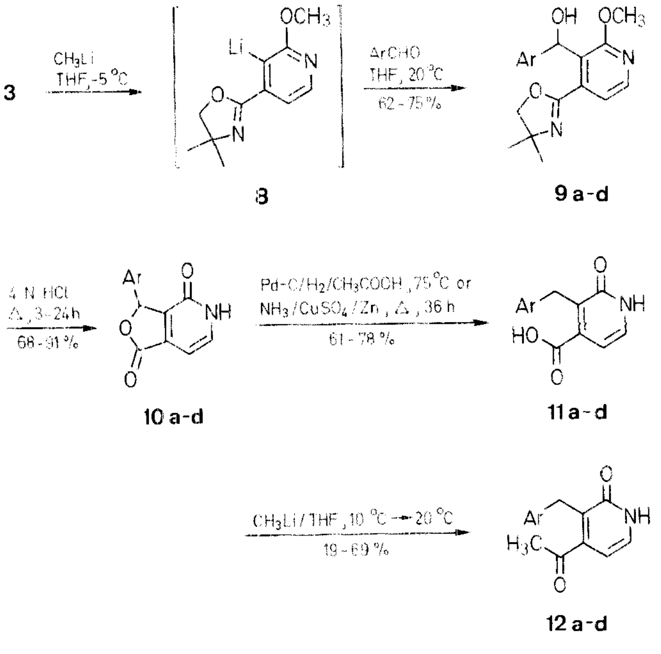
In view of the large number of related polycyclic derivatives bearing the same 5-methyl-1-substituted isoquinoline system fused to various aromatic nuclei that have been programmed for biological screening, we developed a general method for their synthesis resorting to a convergent pathway.

2-(2-Methoxy-4-pyridyl)-4,4-dimethyl-2-oxazoline **3** is the key intermediate in this respect. This compound was obtained according to the transformations summarized in scheme A.



Scheme A

Lithiation of pyridyloxazoline **3** by exchange with methyllithium took place at the 3-position as expected. Condensation of the lithiated species **8** with aromatic aldehydes led to the corresponding alcohols **9** whose acidic hydrolysis was accompanied by an *O*-demethylation, giving the lactones **10** in good yield. Reduction to 3-arylmethyl-2-pyridone-4-carboxylic acids was first performed by catalytic hydrogenation over 10% palladized charcoal in the case of naphthalene derivatives **10a** and **10b**. However, in these conditions, partial reduction of the naphthalene ring was observed for **10a**, and reduction was best achieved by activated zinc in ammonia solution affording the acids **11** in good yields.



9-12	Ar	9-12	Ar
a	1-naphthyl	c	3-methoxyphenyl
b	2-naphthyl	d	3-thienyl

Scheme B

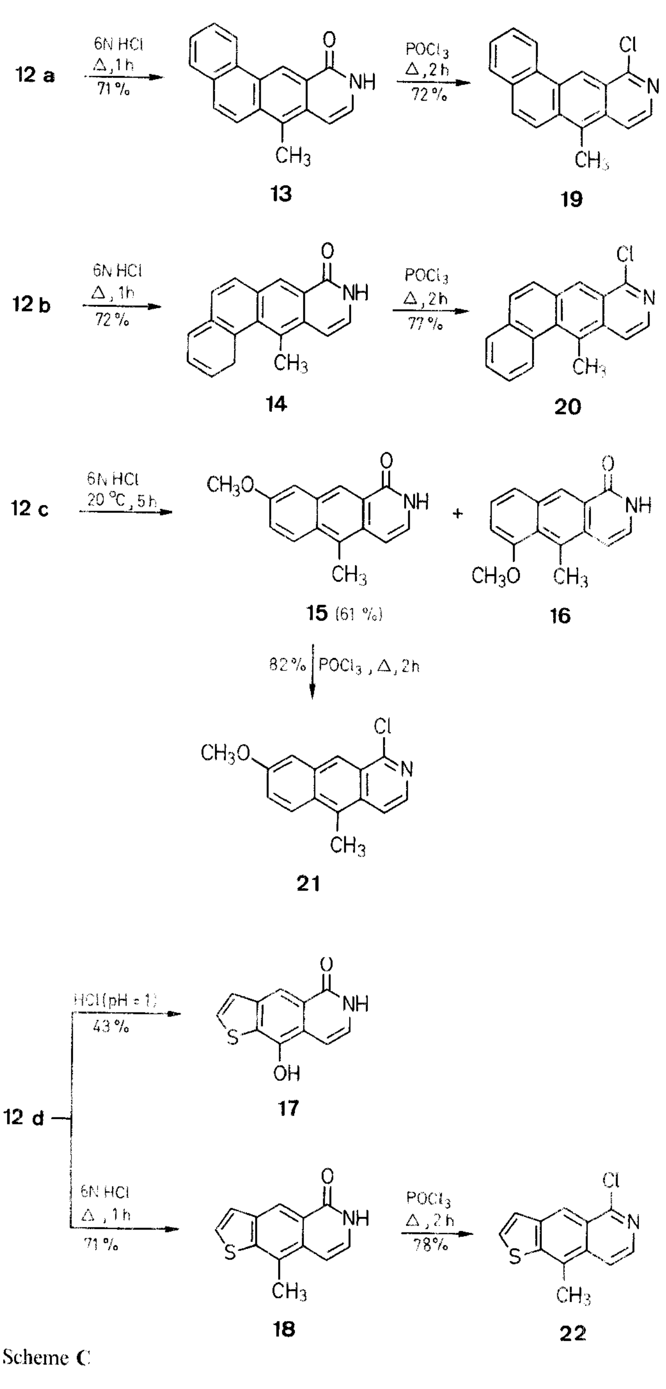
For transformation to methyl ketones **12a–d**, the acids **11** were treated with an excess of methyllithium. The ketones **12a**, **b** and **d** can be isolated as crystalline products. However, ring closure of these ketones to (*g*)-fused 5-methyl-2*H*-isoquinoline-1-ones took place easily and quantitatively in hot 6 normal hydrochloric acid by a Bradsher reaction[5] and with the ketones **12a**, **b** and **c**, the products need not be purified. Consequently we preferred to use crude starting material in order to get a better yield. The situation was not the same with the 3-thienyl ketone **12d**, as discussed below.

Some additional remarks can be made concerning the formation of the ketones **12** and their cyclisation to polycyclic derivatives:

i) In the 1- and 2-naphthyl series **a** and **b**, as well as in the case of 3-methoxyphenyl derivatives **c**, the acids **11** were transformed in good yield into fused isoquinolones **13**, **14** and **15**, respectively, although **15** was contaminated by traces of its isomer **16**.

ii) In contrast, in the 3-thienyl series **d**, the yield of the ketone **12d** was low (ca 20%), and despite attempts to optimize experimental conditions, 5-hydroxy-2*H*-thieno[2,3-g]isoquinoline-1-one (**17**) was always formed competitively. This compound probably results from intramolecular addition of the 2-lithio thiophene derivative generated by exchange with methyllithium to the carboxyl group, explaining the low yield of ketone observed in this series. Moreover, it shows that secondary reactions can limit the applicability of the general scheme, especially with regard to heterocycles with an easily lithiated position near the carboxyl group.

iii) Compound **17** could also be obtained quantitatively by boiling the acid **11d** in 6 normal hydrochloric acid for 4 h. However, this compound was decomposed in boiling xylene giving several new insoluble derivatives (TLC) which have not been identified. They presumably result from oxidation or peroxidation of hydroxy derivative **17** and subsequent decomposition. Therefore in the thiophene series, it is necessary to purify the ketone, as otherwise, treatment of the raw reaction mixture by hot 6 normal hydrochloric acid results in a complex mixture from which it was difficult to obtain the pure compound **18**.



Scheme C

The (*g*)-fused isoquinolones **13**, **14**, **15** and **18** were treated by boiling phosphorous oxychloride to give the corresponding 1-chloro derivatives in good yields (Scheme **C**).

Thus, our results show that 2-(2-methoxy-4-pyridyl)-4,4-dimethyl-2-oxaline (**3**) is a good precursor in the synthesis of various 1-functionalized-5-methyl(*g*)-fused isoquinolines. That the usefulness of this reaction pathway is confined to certain heterocyclic systems is however possible due to the low yield of the methyl ketone **12d**. The preparation of 2-(2-chloro-4-pyridyl)-4,4-dimethyl-2-oxazoline (**7**) has only been mentioned briefly in a recent note from our laboratory.[6] It is described in full below.

2-Chloroisonicotinoyl(2-hydroxy-1,1-dimethylethyl)Amide (5):

To a stirred solution of 2-hydroxy-1,1-dimethylethylamine (102 g, 1.14 mol) in dichloromethane (500 ml) cooled at 0 °C is added dropwise a solution of 2-chloroisonicotinoyl chloride (**4**; 100 g, 0.56 mol) in dichloromethane (500 ml). After the addition is over, the mixture is stirred at ambient temperature for further 2 h and water (500 ml) is added. The aqueous phase is extracted with dichloromethane (3 × 60 ml), washed with water (500 ml) and the combined organic layer is dried with sodium sulfate. Evaporation to dryness leaves a residue which is recrystallized from toluene; yield: 106.5 g (82 %); colorless crystals; m. p. 89 °C.

$C_{10}H_{13}ClN_2O_2$	calc.	C 52.52	H 5.73	N 12.25	Cl 15.50
(228.7)	found	52.49	5.77	12.54	15.78

2-(2-Chloro-4-pyridyl)-4,4-dimethyl-2-oxazoline (7):

Toluene (130 ml) and thionyl chloride (51.5 g, 0.43 mol) are mixed and stirred in a three necked flask and the amide **5** (30 g, 0.131 mol) is added over a 5 min period. The heterogeneous mixture is allowed to stand at room temperature for 1 h and then heated to reflux for 1.5 h and cooled. An aliquot is withdrawn for characterization of the product; evaporation leaves a mixture of the oxazoline **7** and the chloro derivative **6**. The latter is purified by recrystallization from cyclohexane, giving colorless crystals; m. p. 101 °C.

$C_{10}H_{12}Cl_2N_2O_2$	calc.	C 48.60	H 4.90	N 11.34	Cl 28.69
(263.1)	found	48.84	4.96	11.22	27.89

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 1.41$ [s, 6 H, $(CH_3)_2$], 4.38 (s, 2 H, CH_2); 8.07 (q, 1 H, H-5, $J_{5,6} = 5$ Hz, $J_{5,3} = 1.5$ Hz); 8.24 (m, 1 H, H-3); 8.55 (br s, 1 H, NH); 8.7 ppm (d, 1 H, H-6).

The major portion of the toluene solution is evaporated to dryness; the residue is dissolved in 2-butanone (250 ml) and stirred at reflux for 16 h in the presence of potassium carbonate (80 g). The mixture is filtered, the precipitate dissolved in water and the aqueous solution is extracted with dichloromethane (3 × 100 ml). The residue obtained by evaporation of the combined organic layer is distilled to give a pale yellow viscous oil; yield: 22.4 g (81 %); b. p. 138 °C/torr.

$C_{10}H_{11}ClN_2O$	calc.	C 57.02	H 5.26	N 13.30	Cl 16.83
(210.7)	found	57.37	5.47	13.10	16.52

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 1.14$ [s, 6 H, $(CH_3)_2$]; 3.91 (s, 2 H, CH_2); 7.46 (q, 1 H, H-5, $J_{5,6} = 5$ Hz, $J_{5,3} = 1.2$ Hz); 7.56 (m, 1 H, H-3); 8.21 ppm (q, 1 H, H-6, $J_{6,3} = 0.6$ Hz).

2-(2-Methoxy-4-pyridyl)-4,4-dimethyl-2-oxazoline (3):

Sodium (7.67 g, 333 mmol) is dissolved in anhydrous methanol (350 ml) and the excess methanol is evaporated to dryness. The chloropyridyl oxazoline **7** (46.8 g, 222 mmol) in dry dimethylformamide (470 ml) is added and the mixture is heated in an oil bath at 160 °C for 4 h. The cooled mixture is filtered and the precipitate is washed with dichloromethane (200 ml). Evaporation of the filtrate leads to a residue which is taken up in water (250 ml) and extracted with dichloromethane (3 × 150 ml). The combined organic layer is dried with sodium sulfate, evaporated and distilled to give a light yellow viscous oil; yield: 32 g (70 %); b. p. 126–128 °C/8 torr.

$C_{11}H_{14}N_2O_2$	calc.	C 64.06	H 6.84	N 13.58
(206.24)	found	63.89	6.77	13.75

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 1.38$ [s, 6 H, $(CH_3)_2$]; 3.96 (s, 3 H, OCH_3); 4.11 (s, 2 H, CH_2); 7.23 (m, 1 H, H-3); 7.4 (q, 1 H, H-5, $J_{5,6} = 5.2$ Hz, $J_{5,3} = 1.2$ Hz); 8.25 ppm (q, 1 H, H-6, $J_{6,3} = 0.6$ Hz).

2-(2-Methoxy-3-(α-hydroxyarylmethyl)-4-pyridyl)-4,4-dimethyl-2-oxazolines 9a–d; General Procedure:

To a stirred solution of the oxazoline **3** (2.47 g, 12 mmol) in anhydrous tetrahydrofuran (25 ml), is added a 1.18 molar ethereal solution of methyllithium (12.5 ml) under argon at −5 °C. A yellow color quickly develops and after stirring at 0 °C for 1 h, the required aldehyde (10 mmol) dissolved in tetrahydrofuran (10 ml) is added dropwise. The yellow color is discharged, the solution is stirred for 18 h at 20 °C and then poured into water (100 ml). Extraction with dichloromethane (3 × 75 ml) and evaporation of the solvent leaves a residue which is taken up in boiling cyclohexane (25 ml). Except in the case of compound **9c**, which is obtained as an oily residue and hydrolysed without further purification, the cooled mixture slowly crystallizes giving the expected alcohols, which are recrystallized from the same solvent (Table).

3-Aryl-3*H*,5*H*-pyrido[3,4-*d*]furan-1,4-diones 10a–d; General Procedure:

The appropriate alcohol **9** (1 g) and 4 normal hydrochloric acid (50 ml) is refluxed (24 h for **9a**, 3 h for **9b**, 4 h for **9c** and 3.5 h for **9d**) and the resulting mixture is evaporated to dryness under reduced pressure. The solid residue is taken up in water (75 ml), filtered and recrystallized from ethyl alcohol (**10a** and **10c**) or dioxane (**10b** and **10d**) yielding colorless microcrystals (Table).

3-(α-Naphthyl)methyl-2-pyridone-4-carboxylic Acid (11a):

A mixture of the lactone **10a** (3.3 g, 12 mmol), 10% palladized charcoal (0.5 g) and acetic acid (500 ml) is heated at 75 °C and stirred under hydrogen atmosphere at normal pressure till 450 ml of hydrogen is absorbed. The catalyst is filtered, washed with boiling acetic acid (100 ml) and the filtrate evaporated to dryness under reduced pressure. The residue is triturated with boiling ethanol (200 ml), the solid formed is filtered and recrystallized twice from acetic acid to give colorless crystals; yield: 2.03 g (61%); m.p. 295 °C.

$C_{17}H_{13}NO_3 \cdot 0.25H_2O$ (279.3) calc. C 71.95 H 4.76 N 4.93
found 71.68 4.75 4.89

^{1}H-NMR (DMSO-d_6/TMS): δ = 4.24 (s, 2H, CH_2); 6.38 (d, 1H, H-5_{py}, $J_{5,6}$ = 5.5 Hz); 7.38 (d, 1H, H-6_{py}); 7.4–7.86 ppm (m, 7 H_{arom}).

Evaporation of ethanol from the mother liquor gives a solid residue which is recrystallized from ethanol as colorless crystals; yield: 540 mg (16%); m.p. 270–300 °C. This is identified as 3-(1,2,3,4-tetrahydro-5-naphthyl)methyl-2-pyridone-4-carboxylic acid contaminated with traces of **11a** (^{1}H-NMR).

$C_{17}H_{17}NO_3$ (283.3) calc. C 72.06 H 6.05 N 4.94
found 71.75 6.11 4.87

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.8 (m, 2 × 2H, C$\underline{H}_2$–Ar); 2.75 (m, 2 × 2H, C$\underline{H}_2$–Ar); 3.96 (s, 2H, CH_2-3); 6.4 (d, 1H, H-5_{py}, $J_{5,6}$ = 6.4 Hz); 6.52–7.34 (m, 3 H_{arom}); 7.42 ppm (d, 1H, H-6_{py}).

3-(β-Naphthyl)methyl-2-pyridone-4-carboxylic Acid (11b):

A mixture of the lactone **10b** (8.5 g, 31 mmol), 5% palladized charcoal (1.7 g) and acetic acid (300 ml) is stirred under hydrogen atmospheric pressure and ambient temperature till 820 ml of hydrogen is absorbed. The catalyst is filtered, washed with hot acetic acid (100 ml) and the filtrate is evaporated to a solid residue. This is taken up in 1 molar aqueous sodium hydrogen carbonate solution (200 ml) and stirred for 18 h. The insoluble solid which is collected, corresponds to the recovered lactone **10b**; yield: 0.45 g (5.2%). Acidification of the filtrate gives a solid which is recrystallized from acetic acid to give colorless microcrystals of **11b**; yield: 6.71 g (78%); m.p. > 300 °C.

$C_{17}H_{13}NO_3$ (279.3) calc. C 73.11 H 4.69 N 5.02
found 72.83 4.21 5.04

^{1}H-NMR (DMSO-d_6/TMS): δ = 4.24 (s, 2H, CH_2); 6.4 (d, 1H, H-5_{py}, $J_{5,6}$ = 6.7 Hz); 736–7.92 ppm (m, 8H, H-6_{py} + 7 H_{arom}).

3-(*m*-Methoxyphenyl)methyl-2-pyridone-4-carboxylic Acid (11c) and 3-(3-Thienyl)methyl-2-pyridone-4-carboxylic Acid (11d):

A mixture of the lactone **10c** or **10d**, (20 mmol) in 28% ammonia (260 ml) containing cupric sulfate (130 mg) and activated zinc powder (26 g) is heated at reflux for 36 h. with addition of ammonia (4 × 15 ml) after every 8 h. The mixture is then filtered and the insoluble material is washed with water (200 ml). The filtrate is acidified with hydrochloric acid and the resulting precipitate is recrystallized from ethanol giving colorless crystals (Table).

3-Arylmethyl-4-acetyl-2-pyridones 12 (a–d); General Procedure:

To the appropriate acid **11** (10 mmol) in anhydrous tetrahydrofuran (150 ml) cooled at 10 °C, a 1.4 molar ethereal solution of methyllithium (36 ml, 50 mmol) is added at once without further cooling. The temperature increases to 25–30 °C and after stirring for 4 h at 20 °C, the mixture is poured into water (100 ml) and extracted with dichloromethane (4 × 100 ml) Evaporation of the solvent leads to a residue which is recrystallized from toluene giving pale yellow crystals, exept in the case of the *m*-methoxyphenyl derivative **12c**, which remained as an oil. Consequently, cyclization of this compound is performed on the raw

Table. Alcohols **9a**, **9a**, **9d**, Lactones **10a–d** and Acids **11c**, **11d** Prepared

Prod-No.	m.p. (°C)	Yield (%)	Molecular Formula[a]	^{1}H-NMR (Solvent/TMS)[b] δ (ppm)
9a	142	62	$C_{22}H_{22}N_2O_3$ (362.4)	$CDCl_3$: 0.82 (s, 3H, CH_3); 1.28 (s, 3H, CH_3); 3.96 (m, 2H, CH_2); 4.03 (s, 3H, OCH_3); 7.8 (m, 9H, C$\underline{H}$–O$\underline{H}$ + 6 H_{arom} + H-5_{py}); 8.38 (d, 1H, H-6_{py}, $J_{6,5}$ = 5 Hz); 8.7–8.8 (m, 1H, H_{arom})
9b	124	75	$C_{22}H_{22}N_2O_3$ (362.4)	DMSO-d_6: 0.93 (s, 3H, CH_3); 1.29 (s, 3H, CH_3); 3.94 (s, 3H, OCH_3); 3.96 (m, 2H, CH_2); 6.58 (t, 1H, J = 4.9 Hz, C$\underline{H}$OH); 7.29 (d, 1H, H-5_{py}, $J_{5,6}$ = 5.2 Hz); 7.42–7.83 (m, 8H, 7 H_{arom} + OH); 8.32 (d, 1H, J = 5.2 Hz, H-6_{py})
9d	120	71	$C_{16}H_{18}N_2O_3S$ (318.4)	$CDCl_3$: 0.88 (s, 3H, CH_3); 1.30 (s, 3H, CH_3; 3.93 (m, 2H, CH_2); 4.0 (s, 3H, OCH_3); 6.52 (br s, 1H, CH, OH); 6.76 (m, 1H, H-2_{th}); 7.01 (q, 1H, H-5_{th}, $J_{5,4}$ = 5 Hz, $J_{5,2}$ = 1.4 Hz) 7.17 (d, 1H, J = 5 Hz, H-4_{th}); 7.26 (d, 1H, H-5_{py}, $J_{5,6}$ = 5.3 Hz); 7.78 (br s, 1H, OH); 8.23 (d, 1H, H-6_{py})
10a	272	85	$C_{17}H_{11}NO_3$ (277.3)	DMSO-d_6: 6.69 (d, 1H, H-5_{py}, $J_{5,6}$ = 6.5 Hz); 7.20 (q, 1H, H_{arom}); 7.41 (s, 1H, CH); 7.48–8.44 (m, 7H, 6 H_{arom} + H-6_{py}); 11.44 (br s, 1H, NH)
10b	257	91	$C_{17}H_{11}NO_3$ (277.3)	DMSO-d_6: 6.66 (d, 1H, H-5_{py}, $J_{5,6}$ = 6.6 Hz); 6.73 (s, 1H, CH); 7.4 (q, 1H, J = 8.5 Hz, 1.8 Hz, H_{arom}); 7.54–8.07 (m, 7H, 6 H_{arom} + H-6_{py}); 11.36 (br s, 1H, NH)
10c	215	68	$C_{14}H_{11}NO_4$ (257.2)	DMSO-d_6: 3.78 (s, 3H, OCH_3); 6.53 (s, 1H, CH); 6.61 (d, 1H, H-5_{py}, $J_{5,6}$ = 6.5 Hz); 6.85–7.43 (m, 4H, H_{arom}; 7.68 (d, 1H, J = 6.5 Hz, H-6_{py}); 10.21 (br s, 1H, NH)
10d	245	81	$C_{11}H_7NO_3S$ (233.2)	DMSO-d_6: 6.59 (d, 1H, H-5_{py}, $J_{5,6}$ = 6.8 Hz); 6.64 (s, 1H, CH); 7.09 (q, 1H) H-5_{th}, $J_{5,4}$ = 5 Hz, $J_{5,2}$ = 1.1 Hz); 7.53–7.71 (m, 3H, H-6_{py} + H-2_{th} + H-4_{th}); 10.2 (br s, 1H, NH)
11c	255	70	$C_{14}H_{13}NO_4$ (259.3)	DMSO-d_6: 3.72 (s, 3H, OCH_3); 4.05 (s, 2H, CH_2); 6.36 (d, 1H, H-5_{py}, $J_{5,6}$: 6.9 Hz); 6.71–7.24 (m, 4H, H_{arom}); 7.37 (d, 1H, J = 6.9 Hz, H-6_{py})
11d	270	67	$C_{11}H_9NO_3S$ (235.3)	DMSO-d_6: 4.04 (s, 2H, CH_2); 6.35 (d, 1H, H-5_{py}, $J_{5,6}$ = 6.8 Hz); 6.78–7.08 (m. 2H, H-2, H-4, $J_{4,2}$ = 0.9 Hz); 7.34 (d, 1H, J = 6.8 Hz, H-6_{py}); 7.31–7.42 (m. 1H, H-5)

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.2, N ±0.2, S ±0.26.

[b] ^{1}H-NMR spectra were recorded at 100 MHz on a Varian XL 100 spectrometer.

material. In series **a, b** and **c**, acidification of the mother liquor to pH 1 with hydrochloric acid yields traces of starting acids **11a, 11b** and **11c**. For the thienyl series **d**, acidification of the aqueous layer with acetic acid leads to compound **17**.

12a: yield: 69%; m.p. 161 °C.

$C_{18}H_{15}NO_2$	calc.	C 77.96	H 5.45	N 5.05
(271.3)	found	77.98	5.61	4.99

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 2.22$ (s, 3H, CH_3); 4.3 (s, 2H, CH_2); 6.38 (d, 1H, H-5_{py}, $J_{5,6} = 6$ Hz); 6.94 (m, 1H, H-2_{arom}); 7.5 (d, 1H, H-6_{py}); 7.24–8.24 (m, 6H_{arom}); 11.92 ppm (br, s, 1H, NH).

12b: yield: 67%; m.p. 112 °C.

$C_{18}H_{15}NO_2$	calc.	C 77.96	H 5.45	N 5.05
(277.3)	found	78.06	5.81	5.15

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 2.4$ (s, 3H, CH_3); 4.02 (s, 2H, CH_2); 6.37 (d, 1H, H-5_{py}, $J_{5,6} = 6.8$ Hz); 7.45 (d, 1H, H-6_{py}); 7.22–7.85 (m, 7H_{arom}); 11.84 ppm (br, s, 1H, NH).

12d: yield: 19%; m.p. 138 °C.

$C_{12}H_{11}NO_2S$	calc.	C 61.80	H 4.72	N 6.00
(233.3)	found	61.50	4.92	5.76

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 2.38$ (s, 3H, CH_3); 3.8 (s, 2H, CH_2); 6.32 (d, 1H, H-5_{py}, $J_{5,6} = 6.8$ Hz); 6.98 (q, 1H, H-4_{th}, $J_{4,5} = 4.8$ Hz, $J_{4,2} = 1.5$ Hz); 7.08 (m, 1H, H-2_{th}); 7.37 (d, 1H, H-5_{th}); 7.40 (d, 1H, H-6_{py}); 11.8 ppm (br, s, 1H, NH).

5-Hydroxy-2*H*-thieno[2,3-*g*]isoquinoline-2-one (17):

This compound is obtained as mentioned above; yield: 43%. The compound decomposed on recrystallization from boiling xylene, only a minor fraction of the product is obtained. However, it is readily purified from ethyl acetate to give yellow crystals; m.p. 264 °C.

$C_{11}H_7NO_2S$	calc.	C 60.82	H 3.24	N 6.45
(217.2)	found	60.97	3.50	6.67

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 6.91$ (d, 1H, H-4, $J_{4,3} = 7.5$ Hz); 7.12 (q, 1H, H-3, $J_{3,NH\text{-}2} = 5.1$ Hz); 7.60 (d, 1H, H-8, $J_{8,7} = 5.5$ Hz); 7.82 (d, 1H, H-7); 8.36 (s, 1H, H-9); 10.08 (br s, 1H, OH); 11.05 ppm (br s, 1H-NH).

The same compound **17** is also obtained by boiling acid **11d** (250 mg) in 6 normal hydrochloric acid (20 ml) for 4 h. After cooling, water (100 ml) is added and the solid is filtered to give yellow crystals of the hydrate of **17**; yield: 205 mg (82%); m.p. 264 °C.

$C_{11}H_9NO_3S$	calc.	C 56.17	H 3.86	H 5.96
(235.3)	found	56.16	3.53	5.92

Its ^{1}H-NMR, spectrum is identical in all respects with that of the compound described above.

Cyclization of Ketones 12 to 2*H*-(*g*)-fused Isoquinoline-1-ones; General Procedures:

Method A: The pure ketone **12a, 12b** or **12d** (2 mmol) is refluxed with 6 normal hydrochloric acid (70 ml) for 1 h and the mixture is allowed to cool to room temperature. The solid is collected, air dried and recrystallized from toluene to give yellow crystals.

Method B: The raw material resulting from methyllithium addition to the acid **11a, 11b** or **11c** as mentioned in the preparation of **12** is treated as in Method A in cases **a** and **b**, and at 20 °C for a 5h period in the series **c**. The collected solid is washed with 5% aqueous sodium hydrogen carbonate solution (100 ml) and water (150 ml), air dried and recrystallized as mentioned above. For this method, the reported yields are calculated for pure isolated compounds, with regard to the starting acids **11**.

5-Methyl-2H-naphth[2,1-g]isoquinoline-1-one **(13)**; yields: Method A = 71.3%; Method B = 52%; m.p. > 300 °C.

$C_{18}H_{13}NO$	calc.	C 83.37	H 5.05	N 5.40
(259.3)	found	83.17	5.12	5.51

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 2.92$ (s, 3H, CH_3); 6.91 (d, 1H, H-4, $J_{4,3} = 7.6$ Hz); 7.28 (m, 1H, H-3); 7.68–7.84 (m, 2H, H-9 + H-10); 7.94–8.1 (m, 2H, H-7 + H-8); 8.22 (d, 1H, H-6, $J_{6,7} = 9.5$ Hz); 8.84–8.96 (m, 1H, H-11); 9.6 (s, 1H, H-12); 11.25 ppm (br s, 1H, NH).

5-Methyl-2H-naphth[1,2-g]isoquinoline-1-one **(14)**; yields: Method A = 71.5%; Method B = 67%; m.p. 260 °C.

$C_{18}H_{13}NO$	calc.	C 83.37	H 5.05	N 5.40
(259.3)	found	83.19	5.22	5.50

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 3.15$ (s, 3H, CH_3); 6.92 (d, 1H, H-4, $J_{4,3} = 7.4$ Hz); 7.3 (m, 1H, H-3); 7.66–8.08 (m, 5H, H-7 to H-11); 8.73 (s, 1H, H-12); 8.69–8.79 ppm (m, 1H, H-6); 11.3 (br s, 1H, NH).

5-Methyl-8-methoxy-2H-benz[g]isoquinoline-1-one **(15)**; yield: Method B = 61%; m.p. 256 °C.

$C_{15}H_{13}NO_2$	calc.	C 75.30	H 5.48	N 5.85
(239.3)	found	75.33	5.43	5.68

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 2.81$ (s, 3H, CH_3); 3.95 (s, 3H, OCH_3); 6.81 (d, 1H, H-4, $J_{4,3} = 8$ Hz); 7.11 (q, 1H, H-3, $J_{3,NH} = 5.5$ Hz); 7.36 (q, 1H, H-7, $J_{7,6} = 9.5$ Hz, $J_{7,9} = 2.5$ Hz); 7.58 (d, 1H, H-9, $J = 2.5$ Hz); 8.19 (d, 1H, H-6, $J = 9.5$ Hz); 8.72 (s, 1H, H-10); 10.98 ppm (br s, 1H, NH).

The mother liquor from the recrystallization of **15** is evaporated and the residue is chromatographed on silica gel using ethyl acetate as solvent. The first fraction is identified as 5-methyl-6-methoxy-2*H*-benzo[*g*]isoquinoline-1-one **(16)**.

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 3.07$ (s, 3H, CH_3); 3.98 (s, 3H, OCH_3); 6.84 (d, 1H, H-4, $J_{4,3} = 7.6$ Hz); 7.05–7.21 (m, 2H, H-3 + H-7); 7.45 (dd, 1H, H-8, $J = 7.8$ Hz); 7.71 (dd, 1H, H-9, $J_{9,8} = 7.8$ Hz); 8.71 (s, 1H, H-10); 10.9 ppm (br s, 1H, NH).

5-Methyl-2H-thieno[2,3-g]isoquinoline-1-one **(18)**: yield: Method A = 71%; sublimes > 270–280 °C.

$C_{12}H_9NOS$	calc.	C 66.95	H 4.22	N 6.51	S 14.89
(215.3)	found	66.77	4.31	6.60	14.68

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 2.74$ (s, 3H, CH_3); 6.76 (d, 1H, H-4, $J_{4,3} = 7.5$ Hz); 7.21 (q, 1H, H-3); 7.67 (d, 1H, H-8, $J_{8,-} = 5.5$ Hz); 7.88 (d, 1H, H-7, $J = 5.5$ Hz); 8.7 (s, 1H, H-9); 11.19 ppm (br s, 1H, NH).

1-Chloro-5-methyl[*g*]fused Isoquinolines 19–22; General Procedure:

The appropriate isoquinolone (2 mmol) is heated with stirring in boiling phosphorus oxychloride (30 ml) for 2 h and the excess of phosphorus oxychloride is evaporated under reduced pressure. The residue is poured into ice-water (100 ml), made alkaline with ammonia and extracted with dichloromethane (3 × 75 ml). Evaporation of the solvent gives a solid residue which is recrystallized in boiling hexane to afford yellow crystals.

1-Chloro-5-methylnaphth[2,1-g]isoquinoline **(19)**; yield: 72%; m.p. 144 °C.

$C_{18}H_{12}ClN$	calc.	C 77.84	H 4.35	N 5.04	Cl12.77
(277.8)	found	77.57	4.50	5.25	12.99

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.99$ (s, 3H, CH_3); 7.6–7.9 (m, 4H, H-7 to H-10); 7.91 (q, 1H, H-4, $J_{4,3} = 6.2$ Hz, $J_{4,12} = 0.7$ Hz); 8.03 (q, 1H, H-6, $J_{6,7} = 9.4$ Hz, $J_{6,12} = 0.7$ Hz); 8.27 (d, 1H, H-3), 8.83 (m, 1H, H-11), 9.55 ppm (s, 1H, H-12).

1-Chloro-5-methylnaphth[1,2-g]isoquinoline **(20)**; yield: 77%; m.p. 151 °C.

$C_{18}H_{12}ClN$	calc.	C 77.84	H 4.35	N 5.04	Cl 12.77
(277.8)	found	77.51	4.36	5.17	12.84

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 3.22$ (s, 3H, CH_3); 7.6–7.9 (m, 5H, H-7 to H-11); 7.9 (q, 1H, H-4, $J_{4,3} = 6.3$ Hz, $j_{4,12} = 1$ Hz); 8.3 (d, 1H, H-3); 8.5 (m, 1H, H-6); 8.6 ppm (s, 1H, H-12).

1-Chloro-5-methyl-8-methoxybenz[g]isoquinoline **(21)**; yield: 82%; m.p. 150 °C.

$C_{15}H_{12}ClNO$	calc.	C 69.91	H 4.69	N 5.43	Cl 13.76
(257.7)	found	69.83	4.81	5.33	13.54

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 3.02$ (s, 3H, CH_3); 4.01 (s, 3H, OCH_3); 7.31–7.41 (m, 2H, H-7 + H-9); 7.89 (q, 1H, H-4, $J_{4,3} = 6.2$ Hz, $J_{4,10} = 0.9$ Hz); 8.13–8.24 (m, 2H, H-3 + H-6); 8.74 ppm (s, 1H, H-10).

1-Chloro-5-methylthieno[2,3-g]isoquinoline **22**; yield: 78%; m.p. 138 °C.

$C_{12}H_8ClNS$	calc.	C 61.67	H 3.45	N 5.99	Cl 15.17	S 13.72
(233.7)	found	61.64	3.17	5.88	15.57	13.49

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.92$ (s, 3H, CH_3); 7.55 (d, 1H, H-8, $J_{8,7} = 5.7$ Hz); 7.65 (d, 1H, H-7); 7.81 (q, 1H, H-4, $J_{4,3} = 6$ Hz, $J_{4,9} = 1$ Hz); 8.27 (d, 1H, H-3); 8.75 ppm (s, 1H, H-9).

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