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A PREPARATION OF METHYL 2-AMINO-3-FORMYLBENZOATE AND ITS USE IN FRIEDLANDER SYNTHESIS

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Abstract: The title compound has been prepared in four steps from methyl isatin-7-carboxylate. Condensations with 1-indanone and analogs gave 11*H*-indeno[1,2-*b*]quinoline-6-carboxylic acids, and with cyclohexanones gave acridine-4-carboxylic acids.

The Friedlander and Pfitzinger syntheses are classic examples of constructing a fused pyridine ring from an aniline precursor.[1] They involve the condensation of an aromatic *o*-aminoaldehyde or ketone with another aldehyde or ketone which must contain an α-methylene group. The latter synthesis has the advantage of starting with an isatin, generally more readily obtained than the *o*-aminobenzaldehyde required for the former. There is a disadvantage though in that the product necessarily contains a carboxy function *para* to the ring nitrogen, and thermal decarboxylation is required to remove this.

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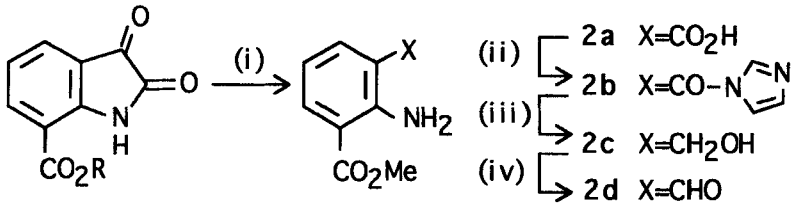
We recently reported the synthesis of the tetracycles exemplified by **4a**, as precursors to antitumor amide derivatives, by Pfitzinger synthesis of **1a** with ketones such as 1-indanone **3a**.[2] Three problems emerged subsequently—decarboxylation of the 10-CO_2H (best done in the solid state with carefully controlled heating) could not be satisfactorily scaled up, certain methoxy substituted compounds underwent concurrent demethylation and decarboxylation, and reactions with substituted benzothiophen-3(2*H*)ones (to give **4** with X = S) were not successful in the strongly basic conditions of the Pfitzinger reaction.

These problems have been solved by using a Friedlander synthesis, which required a source of compound **2d**. The key step in its preparation (Scheme 1) was the successful oxidation of the isatin ring of methyl isatin-7-carboxylate **1b**



1a R=H
1b R=Me

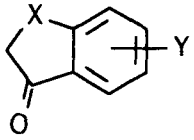
(i) H_2O_2/HO^- (ii) CDI/THF
(iii) $NaBH_4$ (iv) $MnO_2/CHCl_3$

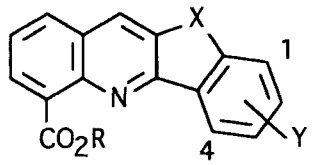
Scheme 1

with alkaline hydrogen peroxide without causing hydrolysis of the ester. The two carboxy functions in **2a** were therefore differentiated, and the acid one was converted to the required aldehyde **2d** by a known sequence.[3] This route to 2-aminobenzene-1,3-dicarboxylic acid is itself an improvement on the standard one (by way of the nitration of *m*-xylene[4]), while **2d** is a stable and useful synthon.

Various examples of the Friedlander reaction of **2d** to give the tetracyclic system of interest to us have been successfully carried out. Dilute potassium

t-butoxide in t-butyl alcohol[5] provided satisfactory conditions for the preparation of **4a** (from 1-indanone **3a**), and the trimethoxy substituted **4e** (from **3e**) (the ester function was hydrolysed during these reactions). Reactions with the more acidic indane-1,3-dione **3b** and the sulfur containing indanone analogs **3d**, **3c**, were better carried out with piperidine in ethanol.

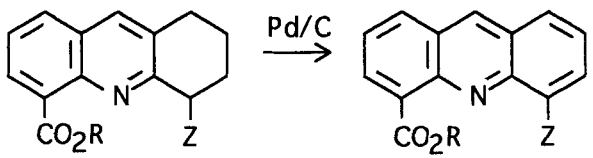




	X	Y
3a	CH_2	H
3b	CO	H
3c	S	5-Cl
3d	S	5-Me
3e	CH_2	5,6,7-$(MeO)_3$

	R	X	Y
4a	H	CH_2	H
4b	Me	CO	H
4c	Me	S	3-Cl
4d	Me	S	3-Me
4e	H	CH_2	2,3,4-$(MeO)_3$

Synthesis of the acridine acids **6** provides a further illustration of the use of **2d**. These compounds again are precursors to potent antitumor amides which are currently in clinical trial.[6] An improved synthesis for larger scale preparation



5a R=Z=H
5b R=Z=Me

6a R=Z=H
6b R=H, Z=Me

of **6a** has been reported recently.[3] The present route provides an alternative, which should also be amenable to scale-up.

Thus, reaction of **2d** with cyclohexanone and t-butoxide in t-butyl alcohol gave **5a**. In an interesting result, reaction with 2-methylcyclohexanone was quite

unsuccessful under these conditions. It appears that Schiff base formation is the first step in the base catalysed reaction and the methyl group provides sufficient bulk to prevent reaction with the hindered amine group. The reaction, to form **5b**, was successful when a switch was made to acid conditions. The initiating step here is presumably condensation of the active methylene function with an activated aldehyde.

Compounds **5** were successfully aromatized to the target acridines **6** by reaction with Pd/carbon at elevated temperatures.[5]

Experimental

Nmr spectra were run on a Bruker AM 300 spectrometer, in $CDCl_3$ unless stated otherwise. Electrospray mass spectra were obtained on a VG Bio-Q triple quadrupole mass spectrometer using a water/methanol/acetic acid (50:50:1) mobile phase. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. 5-Methylbenzothiophen-3(2*H*)-one and 5-chlorobenzothiophen-3(2*H*)-one were kindly supplied by Dr J. Desneves.

Methyl Isatin-7-Carboxylate (**1b**). Isatin-7-carboxylic acid[2] (**1a**) (9.0 g) in 95% methanol (100 mL) was heated under reflux for 3 h. while HCl gas was bubbled through the solution. The methanol was removed at reduced pressure, and the residue was dissolved in $CHCl_3$ (100 mL), washed quickly with 10% $NaHCO_3$ solution, then water, and dried. The product was obtained as a yellow solid (9.1 g, 94%), mp 190-192 °C (lit.[7] mp 192.5-195 °C), after removal of the solvent.

2-Amino-3-methoxycarbonylbenzoic acid (**2a**). A 2.5% NaOH solution (100 mL) was added over 5 min. to a mixture of **1b** (4.10 g, 20 mmol) and 10% H_2O_2 (100 mL). The resulting solution was stirred at room temperature for another 15 min.

and then acidified with concentrated HCl. The precipitate which formed was collected by filtration, washed with water and dried to give an almost colorless solid (3.54 g, 91%), mp 170-172 °C [from light petroleum (bp 60-90 °C)] (Found: C, 55.4; H, 4.5, N, 7.2. $C_9H_9NO_4$ requires C, 55.4; H, 4.6; N, 7.2%). ^1H NMR δ 3.86 (s, CH_3), 6.58 (t, J = 7.8 Hz, H-5), 8.08-8.17 (m, 4H, H-4,6,NH_2). ^{13}C NMR δ 51.7 (CH_3), 110.3 (C), 111.8 (C), 113.8 (CH), 138.4 (2 x CH), 153.6 (C), 168.1 (C), 172.1 (C).

Methyl 2-Amino-3-(hydroxymethyl)benzoate (**2c**). To a solution of **2a** (1.95 g, 10 mmol) in dry THF (75 mL) was added 1,1'-carbonyldiimidazole (2.43 g, 15 mmol) in one portion. The resulting mixture was refluxed for 3.5 h., cooled to room temperature, and a solution of $NaBH_4$ (0.38 g, 10 mmol) in water (15 mL) was added. The solution was stirred at room temperature for 10 min., then partitioned between EtOAc (100 mL) and 10% $NaHCO_3$ solution. The organic layer was washed with warm water (50 mL x 2), brine, dried and the solvent was removed to give the product as a viscous oil (1.60 g, 88%) which was used in this state in the next step. ^1H NMR δ 3.83 (s, OCH_3), 4.63 (s, CH_2), 6.56 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H). ^{13}C NMR δ 51.5 (CH_3), 64.3 (CH_2), 111.2 (C), 115.2 (CH), 125.2 (C), 131.5 (CH), 133.8 (CH), 150.3 (C), 168.6 (C). ESMS: m/z 182 (M+1).

Methyl 2-Amino-3-formylbenzoate (**2d**). A solution of **2c** (1.60 g, 8.8 mmol) in $CHCl_3$ (100 mL) was stirred with MnO_2[8] (7.0 g) at room temperature overnight. The mixture was then filtered and the solvent was evaporated from the filtrate to afford a brown viscous oil (1.30 g, 82%), which gradually solidified and had mp 49-50 °C [from light petroleum (bp 60-90 °C)] (Found: C, 60.6; H, 4.9, N, 7.8. $C_9H_9NO_3$ requires C, 60.3; H, 5.1; N, 7.8%). ^1H NMR δ 3.87 (s, OCH_3), 6.68 (t,

J = 7.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 8.37 (br s, NH_2), 9.86 (s, CHO). ^{13}C NMR δ 51.2 (CH_3), 111.7 (C), 114.1 (CH), 119.6 (C), 138.3 (CH), 142.2 (CH), 152.3 (C), 167.6 (C), 193.4 (C). ESMS: m/z 180 (M+1).

11H-indeno[1,2-b]quinoline-6-carboxylic acid (**4a**). To a solution of aldehyde **2d** (0.18 g, 1.0 mmol) and 1-indanone (0.16 g, 1.2 mmol) in t-BuOH (not dried) (7.5 mL) was added 0.36 M t-BuOK solution (3.3 mL, 1.2 mmol). The resulting mixture was refluxed for 0.5 h., cooled to about 30 °C, light petroleum (bp 60-90 °C) (3 mL) was added and the mixture was cooled on ice. The solid which formed was collected by filtration, dissolved in water (10 mL) and acidified with concentrated HCl to give the tetracycle acid as a yellow solid (0.21 g, 78%), identical with a previous sample.[2]

Methyl 11-Oxo-11H-indeno[1,2-b]quinoline-6-carboxylate (**4b**). To a stirring solution of aldehyde **2d** (0.18 g, 1.0 mmol) and 1,3-indanedione (0.18 g, 1.2 mmol) in ethanol (10 mL) under nitrogen was added piperidine (0.08 g), and the resulting dark brown solution was refluxed for 2 h. The ethanol was removed at reduced pressure and the residue was triturated with light petroleum (bp 60-90 °C). The solid which formed was further purified by column chromatography [silica, ethyl acetate/light petroleum (1:3)] to give the pale yellow methyl ester **4b** (0.21 g, 72%), mp 176-177 °C (after changing form >165 °C). ^1H NMR δ 4.08 (s, CH_3), 7.49-7.57 (m, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.96-8.02 (m, 2H), 8.13 (d, J = 7.5 Hz, 1H), 8.36 (s, H-10). ^{13}C NMR δ 52.6 (CH_3), 122.5 (CH), 124.2 (CH), 126.3 (CH), 127.4 (C), 127.8 (C), 132.0 (CH), 132.3 (CH), 132.4 (CH), 132.5 (C), 133.4 (CH), 135.6 (CH), 137.4 (C), 143.0 (C), 147.7 (C), 162.7 (C), 168.1 (C), 190.6 (C). ESMS: m/z 290 (M+1).

A sample of the crude ester was boiled with 10% NaOH until it disappeared (20 min.), and acidification of the cooled solution gave the acid,

identical to a sample prepared previously.[2]

Methyl 3-Chloro-11H-benzothieno[3,2-b]quinoline-6-carboxylate (**4c**). This was prepared from **2d** and 5-chlorobenzothiophen-3(2*H*)-one as for **4b**, and on the same scale. After the ethanol was removed, the residue was dissolved in $CHCl_3$, and washed with 2% HCl solution, water, brine and then dried. A brown solid was obtained after evaporation of the solvent. This was flash chromatographed (silica, benzene) to give the product as a pale brown solid (64%). For microanalysis, a sample was recrystallized from benzene/light petroleum (bp (60-90 °C), and obtained as a pale yellow solid, mp 211-212 °C (Found: C, 62.4; H, 2.8; N, 4.3. $C_{17}H_{10}ClNO_2S$ requires C, 62.3; H, 3.1; N, 4.3%). ^1H NMR δ 4.14 (s, CH_3), 7.55-7.63 (m, 2H), 7.74 (d, J = 8.8 Hz, 1H), 8.02 (dd, J = 8.3,1.2 Hz, 1H), 8.06 (dd, J = 7.1,1.2 Hz, 1H), 8.57 (d, J = 2.1 Hz, H-4), 8.60 (s, H-10). ^{13}C NMR δ 52.6 (OCH_3), 123.9 (CH), 124.2 (CH), 125.5 (CH), 126.6 (C), 129.5 (CH), 130.0 (CH), 130.4 (CH), 130.5 (CH), 131.6 (C), 131.7 (C), 132.6 (C), 135.3 (C), 139.4 (C), 143.3 (C), 153.2 (C), 168.4 (C). ESMS: m/z 328 (100%), 330 (40%), both (M+1).

Methyl 3-Methyl-11H-benzothieno[3,2-b]quinoline-6-carboxylate (**4d**). This was prepared from **2d** and 5-methylbenzothiophen-3(2*H*)-one as for **4c**, and on the same scale (18 h. reflux). The solid obtained after removal of the ethanol was recrystallized from benzene/light petroleum (bp 60-90 °C) to give **4d** (77%) as a red/brown solid, mp 198-200 °C (Found: C, 70.4; H, 4.5, N, 4.5. $C_{18}H_{13}NO_2S$ requires C, 70.4; H, 4.2; N, 4.6%). ^1H NMR δ 2.56 (s, CH_3), 4.14 (s, OCH_3), 7.45 (d, J = 8.2 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 8.04-8.10 (m, 2H), 8.46 (s, H-4), 8.66 (s, H-10). ^{13}C NMR δ 21.3 (CH_3), 52.6 (OCH_3), 122.7 (CH), 124.8 (CH), 125.3 (CH), 126.5 (C), 130.4 (CH), 130.5

(CH), 131.0 (CH), 132.2 (CH),132.9 (C),133.2 (C), 135.4 (C), 138.8 (C), 142.4 (C), 142.5 (C), 153.6 (C), 168.4(C). ESMS: m/z 308 (M+1).

2,3,4-Trimethoxy-11H-indeno[1,2-b]quinoline-6-carboxylic acid (**4e**). This was prepared from **2d** (2 mmol scale) and 5,6,7-trimethoxy-1-indanone [prepared by hydrogenation of 3,4,5-trimethoxycinnamic acid (Pd/C/EtOH), then cyclization with polyphosphoric acid[9]] as for **4a** (reflux under nitrogen for 15 min.). Light petroleum (bp 60-90 °C) was then added and the mixture was cooled on ice. The solid which separated was washed well with hot light petroleum and then subjected to Soxhlet extraction with $CHCl_3$ to give the soluble potassium salt of the product acid. After the solvent was evaporated, the residue was dissolved in 2% NaOH, washed with ether and acidified with concentrated HCl to give the product as a yellow solid (0.36 g, 54%), mp 257-259 °C (some sublimation >196 °C), which contained trace impurities. ^{1}H NMR (DMSO-d_6) δ 3.84 (s, OCH_3), 3.96 (s, OCH_3), 4.13 (s, CH_2), 4.15 (s, OCH_3), 7.22 (s, H-1), 7.78 (t, J = 7.7 Hz, H-8), 8.35 (d, J = 7.1 Hz, 1H), 8.54 (d, J = 7.3 Hz, 1H), 8.71 (s, H-10). ^{13}C NMR (DMSO-d_6) δ 34.2 (CH_2), 56.7 (OCH_3), 61.1 (OCH_3 x 2), 105.1 (CH), 120.8 (C), 121.8 (C),126.0 (CH), 126.3 (CH), 133.9 (CH), 134.0 (CH), 134.3 (C), 136.3 (C), 140.6 (C), 141.7 (C), 144.6 (C), 150.4 (C), 158.0 (C), 158.8 (C), 167.6 (C). ESMS: m/z 336 (M+1).

Acridine-4-carboxylic acid (**6a**). The reaction of **2d** (2 mmol scale) and cyclohexanone was carried out as for **4a** (18 h. reflux). The organic solvent was removed at reduced pressure and the residue was dissolved in water and filtered. The filtrate was acidified with concentrated HCl and extracted twice with $CHCl_3$. The extracts were washed with 1% $NaHCO_3$ solution, water, brine, dried and the solvent evaporated to give the intermediate *5,6,7,8-tetrahydroacridine-4-*

carboxylic acid (**5a**) as a pale yellow solid (87%), mp 161-163 °C [from EtOAc/light petroleum (bp 60-90 °C)]. ^{1}H NMR δ 1.93-2.06 (m, 4H), 3.05 (t, J = 6.3 Hz, 2H), 3.25 (t, J = 6.3 Hz, 2H), 7.64 (t, J = 7.7 Hz, H-2), 7.98 (dd, J = 7.6,1.2 Hz, 1H), 8.11 (s, H-9), 8.64 (dd, J = 7.4,1.2 Hz, 1H).

A mixture of this compound (0.23 g) and 10% Pd/carbon (0.10 g) in diphenyl ether (10 mL) was refluxed for 4.5 h. The cooled mixture was then filtered through Celite and washed with EtOAc. After removal of the EtOAc at reduced pressure, the remainder was extracted with 10% NaOH (3 x 10 mL). The combined extracts were carefully acidified with HOAc, extracted with EtOAc, and the extract was dried and the solvent was removed. Column chromatography of the residue [silica; EtOAc/light petroleum (bp 60-90 °C), 1:1] gave **6a** as a yellow solid (0.13 g, 58%), mp 197-199 °C (lit.[3] mp 196-197 °C). ^{1}H NMR δ 7.68 (t, J = 7.5 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.95 (t, J = 7.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.26 (d, J = 7.9 Hz, 1H), 8.29 (d, J = 7.6 Hz, 1H), 8.94 (d, J = 7.2 Hz, 1H), 9.05 (s, H-9).

5-Methylacridine-4-carboxylic acid (**6b**). To a stirring and refluxing solution of 2-methylcyclohexanone (0.27 g, 2.4mmol) and concentrated H_2SO_4 (0.1 mL) in HOAc (10 mL) was added dropwise a solution of **2d** (0.36 g, 2.0 mmol) in HOAc (5 mL), and heating was continued under nitrogen for another 4 h. The cooled solution was poured into cold 10% aqueous ammonia and extracted with $CHCl_3$ (2 x 20 mL). The combined extracts were washed with brine, dried, and the solvent was evaporated to give the intermediate *methyl 5-methyl-5,6,7,8-tetrahydroacridine-4-carboxylate* (**5b**) as a pale brown oil (0.49 g). ^{1}H NMR δ 1.48 (d, J = 6.9 Hz, CH_3), 1.6-2.2 (complex m, 4H), 2.94 (t, J = 6.3 Hz, CH_2), 3.10 (m, H-5), 4.02 (s, OCH_3), 7.41 (t, J = 7.6 Hz, H-2), 7.75 (s, H-9), 7.77 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 7.0 Hz, 1H).

A mixture of this compound and 10% Pd/carbon (0.18g) in 1,2-dichlorobenzene[10] (5 mL) was refluxed for 2 h., then cooled and filtered through Celite which was further washed with $CHCl_3$. The $CHCl_3$ was evaporated at reduced pressure and the remainder was then added to a large excess of hexane. The precipitate which separated was filtered off and washed repeatedly with hexane to give **6b** as a pale yellow powder (0.29 g, 61%), mp 296-298 °C (lit.[11] mp 300-302 °C). ^{1}H NMR δ 2.91 (s, CH_3), 7.56 (t, J = 7.6 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.77 (d, J = 6.8 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.90 (d, J = 6.9 Hz, 1H), 9.00 (s, H-9).

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10. Hydrolysis of the ester function occurs. If diphenyl ether is used, decarboxylation also occurs and 4-methylacridine is formed.

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