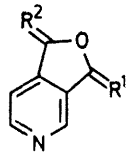
Synthesis of the Pyridine Analogues of Phthalide

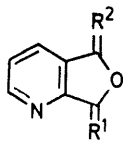
By **William R. Ashcroft, Michael G. Beal,** and **John A. Joule,*** Chemistry Department, Manchester University, Manchester M13 9PL

Routes for the preparation of the four isomeric pyridine analogues of phthalide are described starting from the readily available pyridine 2,3- and 3,4-diacids, or derivatives, and making use of the differential reactivity of substituents at pyridine 2- *versus* 3- and 3- *versus* 4-positions.

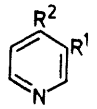
EACH of the four isomeric pyridine analogues of phthalide, furo[3,4-*c*]pyridin-3(1*H*)-one [1-6] (1a), furo[3,4-*c*]pyridine-1(3*H*)-one [1,4,7-10] (1b), furo[3,4-*b*]pyridin-5(7*H*)-one [1,2,4,11-14] (2a), and furo[3,4-*b*]pyridin-7(5*H*)-one [1,7,13-15] (2b) has been described in the literature, but at the commencement of these studies, no way of preparing any of them in quantity had been reported either with sufficient detail or with good enough yield in a convenient sequence, or cleanly enough, as to make it confidently the basis for an assured source of the gram quantities which we required for synthesis of substrates needed in our studies [16] of indole β-nucleophilic substitution.



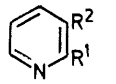
(1)	R^1	R^2
a	O	H_2
b	H_2	O
c	O	O
d	H,Me	O



(2)	R^1	R^2
a	H_2	O
b	O	H_2
c	O	O



(3)	R^1	R^2
a	CN	Me
b	CO_2Me	Me
c	CO_2Me	CH_2OAc
d	CO_2H	CH_2OH
e	CO_2H	CO_2Me
f	Me	CO_2Me
g	CO_2Et	CN
h	CO_2Me	CO_2Me
i	CO_2Me	CO_2H
j	CH_2OH	CO_2H



(4)	R^1	R^2
a	CO_2Me	CO_2H
b	CO_2H	CO_2Me
c	CO_2Me	CO_2Me
d	CH_2OH	CH_2OH
e	CH_2OH	CO_2H

Lactone (1a).—At the time we began our study the best prospect for the preparation of (1a) was the sequence,[5] albeit long, from the nitrile (3a), itself available from an efficient three-step synthesis [17] involving conversion into the *N*-oxide of the ester (3b) (3 steps), acetoxylation of the side chain with acetic anhydride, then alkaline hydrolysis and lactonisation, a further three steps. In re-examining the route we find that it works well up to the point of reaction between *N*-oxide and acetic anhydride. No conditions could be found to achieve this rearrangement cleanly and indeed following the recommended procedure [5] on a 5 g scale, adding the anhydride to refluxing *N*-oxide, led to a violent exotherm: after the addition of a few drops of anhydride the expulsion of black material from the condenser top took place. A modified procedure (see Experimental section) still gave the acetoxy-ester (3c) in only 33% yield. Subsequent conversion into the lactone (1a), for which no yield was quoted,[5] was achieved in only 20% yield.

Recently, Berchtold reported [6] a convenient method for the synthesis of the hydroxy-acid (3d) corresponding to (1a) in two steps based on the differential reactivity [18] of the two carbonyl groups of the anhydride (1c). Our preferred method for the preparation of isomer (1a) utilises these two steps and we here acknowledge receipt of the experimental details in advance of their publication; the description given in the Experimental section is substantially the same as that kindly provided by Professor Berchtold.

Methanolysis of the anhydride (1c) gives a mixture of two ester-acids in which the 4-methoxycarbonyl-3-carboxylic acid (3e) predominates (86 : 14) and can be crystallised pure (74%). Lithium aluminium hydride reduction of (3e) at 0—2 °C gives (3g) (60%) and lactonisation, best achieved using dicyclohexylcarbodiimide in tetrahydrofuran (THF) at room temperature, proceeds in 45% yield. In this case as in later examples it is a simple matter to recycle carboxy-ester residual mixtures by efficient hydrolysis and anhydride-forming reactions.

Lactone (1b).—An attempt [8] to extrapolate a method [19] which works well for the preparation of the methyl homologue (1d), and which it is claimed [11] works for the analogue (2a), by side-chain monobromination of methyl 3-methylisonicotinate (3f) conveniently available *via* the regioselective selenium dioxide oxidation of 3,4-lutidine, gave only a poor yield of lactone owing to further bromination of the side-chain. In attempting [20] to verify the preliminary claim [9] (no yields given) that successive treatment of the 3-cyano-4-ester (3g) with sodium borohydride and then methanolic sulphuric acid gave (1b), we found the formation of very little lactone and further, the preparation of the cyano-ester (3g),

by reaction [21] of the *N*-oxide of methyl isonicotinate with dimethyl sulphate and then potassium cyanide, was far from regioselective in our hands.

Meyers' study [22] of the condensation of a 3-lithiated pyridine carrying a carboxy-group at C-4 in a masked form, as a dimethyloxazoline ring, though reaction with formaldehyde was not recorded,[22] seemed to possess promise for the synthesis of lactone (1b). Several other lactones were recorded as being formed in good yields by reaction with a variety of ketones and aldehydes followed by hydrolysis. A personal communication from Professor Meyers indicated that condensation with formaldehyde did take place and our development of this route has been described [10] but once again only moderate yields were obtained in both the condensation with formaldehyde and subsequent hydrolytic steps.

Carrying forward the theme of greater electrophilicity of a carbonyl group at the pyridine 4- *versus* 3-position we have now shown that hydrolysis of the 3,4-diester (3h) with 1 mol equiv. of 0.44M-aqueous sodium hydroxide gives the 3-methoxycarbonyl 4-acid (3i) together with some of its isomer (3e), in a ratio of 3 : 1. The required ester-acid (3i) can be crystallised pure (35% yield) from the reaction mixture and the residue conveniently recycled by an efficient re-esterification and repeat hydrolysis. Lithium aluminium hydride reduction gave the hydroxy-acid (3j) in 64% yield and lactonisation was achieved, again using dicyclohexylcarbodiimide in THF in 73% yield.

Lactone (2a).—Turning to the 2,3-disubstituted pyridine lactones, (2a) was the major product (2.5 : 1.4) produced,[14] together with (2b), but in only 39% combined yield and after separation of unchanged starting material, by lithium aluminium hydride treatment of the anhydride (2c) at room temperature but although a method for their separation was described [14] involving sublimation of isomer (2a) from the mixture, we were only able to obtain a 15% yield of (2a) in this way. The sublimation residue was considerably charred, still contained (2a), and, further, isomer (2b) could not be crystallised pure directly from this residue as claimed.[14]

We now find that the approach described above for the preparation of (1a) can be adapted for the synthesis of lactone (2a). Thus methanolysis of the anhydride (2c) gives a mixture of carboxy-esters in which, as anticipated, (4a) resulting from attack at the 2-carbonyl group predominates (2 : 1) over its isomer (4b) and can be crystallised pure (42%), the mother-liquor material again being easily recycled. Low-temperature lithium aluminium hydride reduction and dicyclohexylcarbodiimide lactonisation proceeds in 23% yield for the two steps for the preparation of lactone (2a).

Lactone (2b).—Hoping that the method developed for (1b) could be extrapolated, the diester (4c) was hydrolysed [23] with 1 mol equiv. of dilute alkali. A mixture of ester-acids was obtained in which that, (4b), resulting from 2-carbonyl attack, predominated. Unfortunately unlike the analogous 3,4-situation and despite the very comparable ratio (71 : 29) of isomers, the major, desired carboxy-ester (4b) could not be induced to crystallise from the mixture, rendering this route non-viable.

An alternative, depending on the differential pyridine-2- and 3-reactivity but in a different way, was developed. The diester (4c) is first converted [24] into the diol (4d) and this was oxidised with manganese dioxide in chloroform at room temperature. Under these conditions the lactone (2b) is the only product formed (56% yield).

EXPERIMENTAL

Furo[3,4-c]*pyridin*-3(1H)-*one* (1a).—Pyridine-3,4-dicarboxylic acid anhydride [25] (8.4 g, freshly prepared) was dissolved in refluxing dry methanol (100 ml), the solvent was evaporated off, and the residue (10.3 g; m.p. 130—166 °C) was recrystallised from methanol to give the ester-acid (3e) (6.9 g), m.p. 170—172 °C (lit.,[13] 172 °C); $\lambda_{max.}$ (EtOH) 210 and 274 nm (log ε 3.85 and 3.29); $\nu_{max.}$ (Nujol) 2 450br, 1 740s, and 1 610s cm^{-1}; τ([$^2H_6$]DMSO) 1.0 (1 H, s, H-2), 1.15 (1 H, d, *J* 5.5 Hz, H-6), 2.38 (1 H, d, *J* 5.5 Hz, H-5), and 6.10 (3 H, s, CH_3O); δ_C * ([$^2H_6$]DMSO) 167.14 † (s, CO_2Me), 163.33 † (s, CO_2H), 153.31 (d, C-6), 150.46 (d, C-2), 140.65 (s, C-4), 125.50 (s, C-3), 121.85 (d, C-5), and 52.99 (q, CH_3); *m/e* 181 (M^+, 5%), 164 (4), 150 (71), 137 (100), 122 (12), 106 (81), 94 (45), 78 (44), and 50 (78).

To a stirred solution of the carboxy-ester (3e) (6.0 g) in tetrahydrofuran (THF) (250 ml) at 0—2 °C was added lithium aluminium hydride (2.0 g). After a further 4 min, water (6 ml) was added, the resultant mixture was filtered, and the filtrate was discarded. The precipitate was stirred in water (100 ml) for 1 h, refiltered, and the precipitate re-extracted with water (150 ml). The combined aqueous extracts were evaporated *in vacuo* at 30 °C, first to 50 ml and then after acidifying to pH 4 with concentrated hydrochloric acid, to dryness. The resulting *gummy solid* (3d) (5.1 g), $\lambda_{max.}$ (H_2O) 265 nm; $\nu_{max.}$ (Nujol) 3 500br, 3 150br, and 1 620m cm^{-1}; τ(D_2O) 0.85 (1 H, s, H-2), 0.95 (1 H, d, *J* 7 Hz, H-6), 1.5 (1 H, d, *J* 7 Hz, H-5), and 4.65 (2 H, s, CH_2O); *m/e* 153 (M^+, 15%), 135 (100), 123 (33), 106 (96), and 78 (52) (Found: M^+, 153.0426. $C_7H_7NO_3$ requires *M*, 153.0426) could not be further purified ‡ and was utilised for the next stage.

To a solution of hydroxy-acid (3d) ‡ (3.0 g) in water (50 ml) was added a solution of dicyclohexylcarbodi-imide (4.1 g) in THF (50 ml) and the whole was stirred at 20 °C for 2.5 days. The mixture was concentrated *in vacuo* to 50 ml, the precipitate of dicyclohexylurea was filtered off, and the precipitate was washed with water and ether. The combined filtrates were made basic with solid potassium carbonate and extracted with more ether to give the lactone (1a) (1.2 g), m.p. 130—135 °C (lit.,[1] 145 °C) pure enough for further use. The pure lactone (1a) had $\lambda_{max.}$ (EtOH) 222 and 262 nm (log ε 3.92 and 3.19), δ_C([$^2H_6$]DMSO) 167.55 (s, C=O), 154.09 (s, C-7a), 151.53 (d, C-6), 145.53 (d, C-4), 120.29 (s, C-7b), 116.55 (d, C-7), and 68.04 (t, CH_2); *m/e* 135 (M^+, 30%), 106 (52), 78 (31), and 50 (22).

Furo[3,4-c]*pyridin*-1(3H)-*one* (1b).—To dimethyl pyridine-3,4-dicarboxylate [27] [$\lambda_{max.}$ (EtOH) 208 and 270 nm

* ^{13}C Assignments were made by comparison with values calculated using the shift correlation equation [26] for pyridines.

† Assignments may be reversed.

‡ Crude hydroxy-acid materials were analysed quantitatively by u.v. spectroscopy and the amount of organic pyridine thus derived is given as the weight of starting material for the subsequent hydride reduction step.

log ε 3.89 and 3.51); $\delta_C(CDCl_3)$ 165.87 and 164.85 (2 s, 2 × C=O), 152.41 (d, C-6), 149.70 (d, C-2), 139.46 (s, C-4) 124.31 (s, C-3), 121.09 (d, C-5), 52.09 and 51.94 (2 q, 2 × Me); *m/e* 195 (M^+, 5%), 164 (100), 136 (18), 105 (15), and 78 (50)], (16.6 g) suspended in water (160 ml) was added a solution of sodium hydroxide (3.4 g) in water (35 ml) and the mixture was stirred at 20 °C for 1.5 h during which time the mixture became homogeneous. Extraction with chloroform removed unchanged diester (0.21 g) and the aqueous layer was then acidified to pH 1 with concentrated hydrochloric acid and then evaporated to dryness *in vacuo* at 30 °C. Extraction of the residue with boiling THF gave the crude mono-ester (11.3 g), m.p. 130—160 °C which was recrystallised from methanol to give the ester-acid (3i) (5.3 g), m.p. 181—182 °C (lit.,[28] 182 °C); $\lambda_{max.}$ (EtOH) 215 and 269 nm (log ε 4.1 and 3.48); $\nu_{max.}$ (Nujol) 2 500br, 1 730s, and 1 600w cm^{-1}; τ([$^2H_6$]DMSO) 1.0br (1 H, s, H-2), 1.05 (1 H, d, *J* 6 Hz, H-6), 2.25 (1 H, d, *J* Hz, H-5), and 6.10 (3 H, s, CH_3O); δ_C([$^2H_6$]DMSO) 166.91 and 165.68 (2 s, 2 × C=O), 152.83 (d, C-6), 149.33 (d, C-2), 140.58 (s, C-4), 125.19 (s, C-3), 121.91 (d, C-5), and 52.76 (q, CH_3); *m/e* 181 (M^+, 8%), 150 (100), 137 (31), 122 (24), 106 (30), 105 (31), 91 (44), 78 (24), and 50 (29).

To a stirred solution of the carboxy-ester (3i) (6.0 g) in THF (250 ml) was added lithium aluminium hydride (2.0 g) during 2 min at 0—2 °C. After a further 4 min water (6 ml) was added and the mixture filtered. The filtrate was discarded and the solid was stirred in water (100 ml) for 1 h at 20 °C, refiltered, and then extracted with a further portion (150 ml) of water. The combined aqueous extracts were evaporated *in vacuo* at 30 °C, first to 50 ml and then after acidifying to pH 4 with concentrated hydrochloric acid,to dryness. The resulting gummy solid (3j) (4.9 g) [$\lambda_{max.}$ (H_2O) 263 nm; $\nu_{max.}$ (Nujol) 3 500br, 3 250br, and 1 620m cm^{-1}; τ(D_2O) 0.9 (1 H, s, H-2), 1.0 (1 H, d, *J* 6 Hz, H-6), 1.85 (1 H, d, *J* 6 Hz, H-5), and 4.90 (2 H, s, CH_2O); *m/e* 153 (M^+, 0.2%), 135 (100), 106 (98), 78 (63), and 51 (28) (Found: M^+, 153.0423. $C_7H_7NO_3$ requires *M*, 153.0426)] could not be further purified ‡ and was utilised for the next stage.

To a solution of hydroxy-acid (3j) (3.3 g) * in water (50 ml) was added dicyclohexylcarbodi-imide (4.4 g) in THF (50 ml) and the whole was stirred at 20 °C for 19 h. After evaporation *in vacuo* to 50 ml and removal of the dicyclohexylurea by filtration, the filtrate and the water and ether washings of the precipitate were made basic with solid potassium carbonate and extracted with ether. Evaporation gave the lactone (1b) (2.1 g), which after crystallisation (1.1 g) from ether–light petroleum had m.p. 118 °C (lit.,[1] m.p. 118 °C); a further portion (0.49 g) could be obtained by sublimation of the mother-liquor; $\lambda_{max.}$ (EtOH) 217 and 278 nm (log ε 3.64 and 3.52); $\delta_C(CDCl_3)$ 168.86 (s, C=O), 149.60 (d, C-6), 144.79 (d, C-4), 139.97 (s, C-7a), 133.12 (s, C-7b), 118.45 (d, C-7), and 68.45 (t, CH_2); *m/e* 135 (M^+, 73%), 106 (100), 78 (34), and 50 (14).

Furo[3,4-b]*pyridin*-5(7H)-*one* (2a).—Pyridine-2,3-dicarboxylic acid anhydride (19.4 g) was dissolved in refluxing dry methanol (100 ml) and the solvent was evaporated to leave the crude carboxy-ester, m.p. 110—120 °C, which gave pure (4a) (9.9 g) on recrystallisation from methanol, m.p. 120—122 °C (lit.,[28] 123 °C), $\lambda_{max.}$ 209 and 265 nm (log ε 3.93 and 3.50); $\nu_{max.}$ (Nujol) 2 500br, 1 740s, and 1 700w cm^{-1}; τ([$^2H_6$]DMSO) 1.30 (1 H, dd, *J* 1.5 and 6 Hz, H-6), 1.75 (1 H, dd, *J* 1.5 and 8 Hz, H-4), 2.40 (1 H, dd, *J* 6 and 8 Hz, H-5), and 6.18 (3 H, s, CH_3O); δ_C([$^2H_6$]DMSO). 167.21 and 166.33 (2 s, 2 × C=O), 152.14 (d, C-6), 151.69 (s, C-2), 138.24 (d, C-4), 125.94 (s, C-3), 125.43 (d, C-5), and 52.70 (q, CH_3); *m/e* 181 (M^+, 2%), 150 (24), 123 (63), 105 (62), 94 (28), 79 (69), 77 (53), 66 (20), and 50 (41).

Lithium aluminium hydride (2.0 g) was added during 2 min to a stirred solution of the carboxy-ester (4a) (5.0 g) in THF (250 ml) at 0—2 °C. After a further 4 min, water (6 ml) was added, the mixture was filtered and the filtrate was discarded. The precipitate was stirred successively with two portions (100 ml and 150 ml) of water. The aqueous extracts were evaporated *in vacuo* at 30 °C first to 50 ml and then after acidification with concentrated hydrochloric acid to pH 4, to dryness. The resulting gummy solid (4e) (5.3 g) [$\lambda_{max.}$ (H_2O) 267 nm; $\nu_{max.}$ (film) 3 400br and 1 635m cm^{-1}; τ(D_2O) 1.10 (2 H, m, H-4 and H-6), 1.85 (1 H, dd, *J* 5 and 8 Hz, H-5), and 6.60 (2 H, s, CH_2); *m/e* 153 (M^+, 1%), 135 (14), 106 (33), and 78 (25)] could not be further purified * and was utilised for the next stage.

To a solution of the hydroxy-acid (4e) (3.5 g) * in water (50 ml) was added dicyclohexylcarbodi-imide (4.7 g) in THF (50 ml) and the whole was stirred at 20 °C for 15 h. After evaporation *in vacuo* to 50 ml and removal of the dicyclohexylurea by filtration, the filtrate together with water and ether washings of the precipitate were made basic with solid potassium carbonate. The ether extracts were evaporated to give crude lactone (3.6 g), recrystallised from chloroform–ether to give the lactone (2a) (1.0 g), m.p. 139—141 °C (lit.,[1] 142 °C), $\lambda_{max.}$ (EtOH) 222 and 270 nm (log ε 3.96 and 3.65); δ_C([$^2H_6$]DMSO) 168.59 (s, C=O), 166.41 (s, C-7a), 154.95 (d, C-2), 133.51 (d, C-4), 123.81 (d, C-3), 118.62 (s, C-4a), and 70.26 (t, CH_2); *m/e* 135 (M^+, 48%), 106 (100), 78 (53), and 51 (24).

Furo[3,4-b]*pyridin*-7(5H)-*one* (2b).—Dimethyl pyridine-2,3-dicarboxylate [27] (4c) (5.0 g) [$\lambda_{max.}$ (EtOH) 218 and 264 nm (log ε 3.84 and 3.31); $\delta_C(CDCl_3)$ 166.31 (s, C-2), 165.21 (s, C.3), 151.46 (d, C-6), 150.50 (s, C-2), 137.19 (d, C-4), 125.70 (s, C-3), 124.60 (d, C-5), and 52.46 (2 q, 2 × CH_3); *m/e* 195 (M^+, 2%), 166 (58), 164 (92), 138 (76), 136 (100), 107 (85), and 79 (54)] was reduced in ether (150 ml) with lithium aluminium hydride (1.8 g) at reflux for 1 h. Water (5 ml) was added to the cooled mixture, the solid was filtered off, and the filtrate was discarded. Continuous extraction of the precipitate with chloroform gave the diol (4d) (1.87 g), $\lambda_{max.}$ (EtOH) 214 and 263 nm, $\nu_{max.}$ ($CHCl_3$) 3 300br cm^{-1}; δ_C([$^2H_6$]DMSO) 154.78 (s, C-2), 144.28 (d, C-6), 133.27 (s, C-3), 132.97 (d, C-4), 120.35 (d, C-5), 60.76 and 57.62 (2 t, 2 × CH_2); *m/e* 139 (M^+, 0.4%), 121 (38), 109 (42), 108 (52), and 93 (100), which was utilised without further purification.

A solution of the diol (4d) (1.87 g) in chloroform (300 ml) was stirred with manganese dioxide [29] (38 g) for 2.5 h at 20 °C. Filtration through cellulose and evaporation gave the lactone (2b) (1.0 g), m.p. 158—160 °C (lit.,[1] 162 °C), $\lambda_{max.}$ (EtOH) 217 and 272 nm (log ε 3.71 and 3.56); δ_C([$^2H_6$]-DMSO) 166.31 (s, C=O), 149.75 (d, C-2), 141.51 (s, C-7a), 139.47 (s, C-4a), 129.91 (d, C-4), 125.31 (d, C-3), and 66.08 (t, CH_2); *m/e* 135 (M^+, 100%), 106 (70), 91 (99), 78 (64), 64 (57), and 51 (93).

Methyl 4-Acetoxymethylpyridine-3-carboxylate (3c).—The following is a modification of the method previously reported.[5] Methyl 4-methylpyridine-3-carboxylate [5] (32 g) in glacial acetic acid (400 ml) was treated with aqueous hydrogen peroxide (60 ml; 30%) at 80 °C for 2 h with stir-

* Footnote ‡ as on p. 3013.

ring and then with a further portion of oxidant (40 ml; 30%) at 80 °C for 2 h. The solvent was evaporated off and the residue (40 g) was heated on a steam-bath while acetic anhydride (20 ml) was added in drops. After a further 30 min the cooled mixture was poured into water at 0 °C and basified with solid sodium hydrogencarbonate, and the crude product was isolated by extraction with dichloromethane. The black liquid (32 g) resulting was distilled at 140—150 °C and 0.5 mmHg to give the acetoxy-ester (3c) (14.6 g).

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