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Application of Organolithium and Related Reagents in Synthesis. Part 18[1]. Synthetic Strategies Based on Aromatic Metallation. A Conversion of Methyl *ortho*-pyridoylbenzoates into Aza-anthra-5,10-quinones

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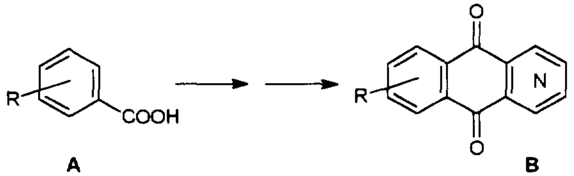
Abstract: The synthesis of the aza-anthraquinones (**16**) and (**17**) *via* metallation (LDA / THF) of the pyridine nucleus at the C^3-carbon atom of the methyl *ortho*-pyridinecarbonyl benzoates (**12**) and (**13**), and then the intramolecular cross addition of the generated lithiated species to the carbomethoxy group is described. Copyright © 1996 Elsevier Science Ltd

The natural occurring 1-aza-anthraquinones[2, 3, 4, 5] (phomazarin and isophomazarin) and 2-aza-anthraquinones[5, 6, 7, 8, 9] (bostrycoidin) and the current interest in these compounds as key starting materials for the preparation of numerous poly-heterocycles including important physiologically active products from marine organisms[10, 11] as well as insect teratogens,[12, 13] anti-microbiological active species,[14, 15, 16] inhibitor of Epstein-Bar virus activation[17] and cytotoxic activity comparable to that of doxorubicin[18] have led us to examine methods for the synthesis of these systems.

The most frequently travelled synthetic route to aza-anthraquinones involves Diels-Alder cyclization in the formation of the heterocyclic ring or terminal carbocyclic ring.[19] This particular methodology in most cases is limited in scope and regioselectivity. Alternative routes of their preparation generally require a total construction of the skeleton *via* multi-step sequence of the condensation and then cyclization reactions,[5, 8, 9, 20] which are in most cases related only to specific instances.

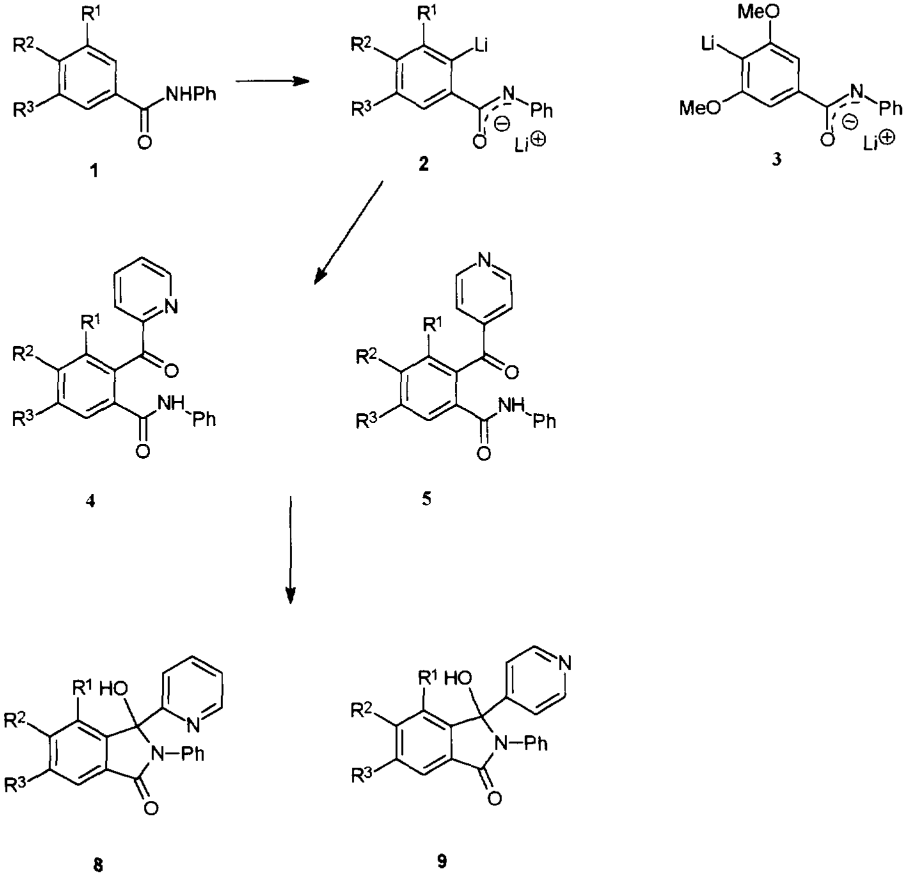
Herein we wish to report a novel efficient and regiospecific synthetic sequence, as a general strategy for the transformation of the aromatic carboxylic acids (**A**) into the corresponding aza-anthraquinones (**B**) in four-step protocol starting from benzoic acids anilides as depicted in the perspective Scheme (**A**) → (**B**).



A **B**

Our route leading to the aza-anthraquinones (**16**) and (**17**) is outlined in Schemes I and II. The process is based upon regiospecific lithiation with lithium diisopropylamide (LDA) of the pyridine ring at the C^3-carbon atom of the *ortho*-pyridoylated methyl benzoates (**12**) and (**13**) and subsequently cyclization *via* intramolecular

Scheme I



For compounds **1**, **2**, **4**, **5**, **8**, **9**

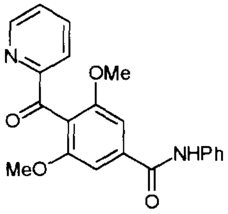
a, R^1 = OMe, R^2 = R^3 = H ; **b**, R^1 = R^3 = OMe, R^2 = H; **c**, R^1 = R^2 = R^3 = OMe addition of the generated lithiated species across of the carbomethoxy carbonyl group. The generation of the required lithiation at the pyridine nuclei was most probably achieved by combined activating effects of two different methods. From one side directed *ortho*-metallation effected by the carbonyl group[21] and on the other hand the remote aromatic metallation[22, 23] caused by the carbomethoxy group.[24] This route begins with a successive *ortho* pyridoylation of the benzoic acids.

In a series of recent studies we have reported that the *N*-substituted carboxyamide moiety and especially *N*-phenylamides (anilides) provide an effective possibility for the regiospecific *ortho*-lithiation and subsequent electrophilic substitution (benzoylation or pyridoylation included) of the aromatic ring.[25, 26, 27, 28]

To this end, the anilides (**1**) were reacted in tetrahydrofuran (THF) with 2.1 mol equivalents of *n*-butyllithium (*n*-BuLi) (amide / -78°C / *n*-BuLi / 0.5 h → 0°C / 2 h) and converted into the bis (*N*- and *C*-*ortho*) lithiated anilides (**2**). In the case of 3,5-dimethoxybenzanilide (**1b**) the formed bis (*N*- and *C*-*ortho*) lithiated anilide (**2b**) was accompanied by (*N*- and 4-) lithiated anilide (**3**) as was indicated by the reaction with an electrophile. The treatment of the solution of the lithiated species with methyl picolinic or isonicotinic esters afforded the corresponding pyridoylated (**4**), (**5**), (**6**) and (**7**) derivatives. The compounds (**4**) and (**5**) upon hydrolytic workup spontaneously cyclized into the 3-hydroxyisoindolin-1-ones (**8**) and (**9**).

The resulted isoindolin-1-ones (**8**) and (**9**) upon reaction with boiling sulphuric acid (50% - H_2SO_4) gave the *ortho*-pyridoylbenzoic acids (**10**) and (**11**) whose sodium salts reacted with iodomethane in DMF at 0°C producing the corresponding methyl esters (**12**) and (**13**). In all cases, MeI appeared to be inert towards *N*-alkylation of the pyridine nucleus (under the conditions used).

In the final step in order to achieve progress in the construction of the aza-anthraquinones (**16**) and (**17**) the cyclization of the pyridoylated benzoic methyl esters (**12**) and (**13**) was undertaken. It was revealed that the ketoesters (**12**) and (**13**) exposed to react with LDA in the presence of hexamethylphosphore triamide generated at the pyridine ring lithiated species of the C^3-position (**14**) and (**15**) which instantly cyclised by intramolecular attack at the carbomethoxy group and then furnished the desired aza-anthraquinones (**16**) and (**17**).



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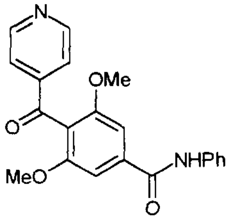

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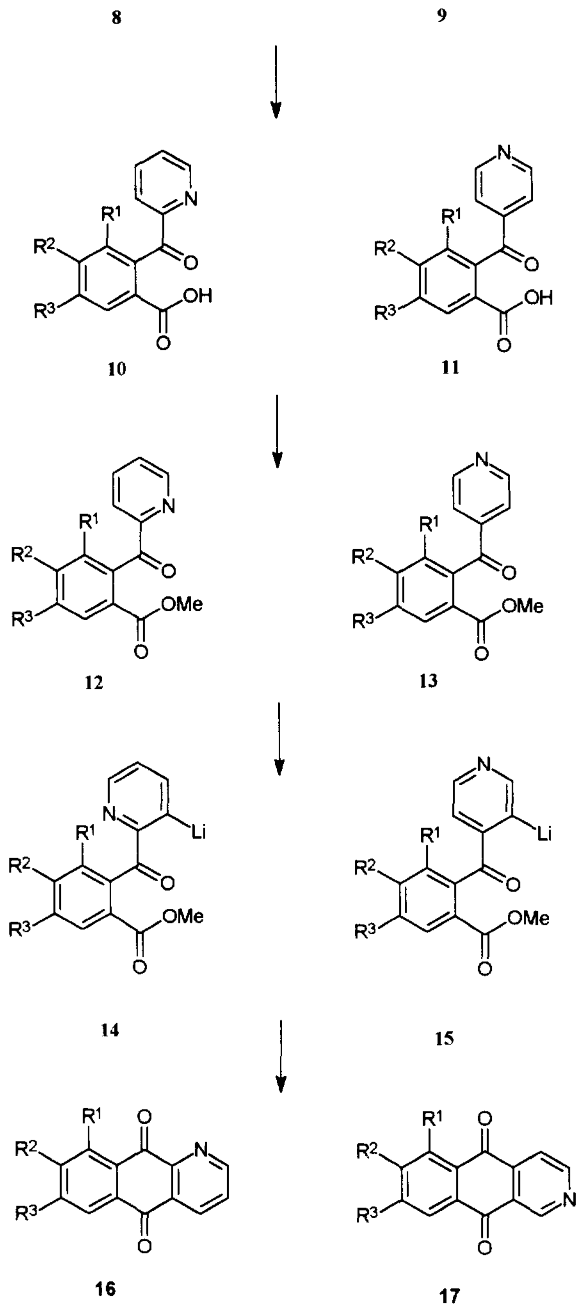
Scheme II



a, R^1 = OMe, R^2 = R^3 = H ; **b**, R^1 = R^3 = OMe, R^2 = H; **c**, R^1 = R^2 = R^3 = OMe

In summary, we have shown a synthetic method for the preparation of aza-anthraquinones (**16**) and (**17**) with an economy of steps which involves: (i) successive conversion of the benzanilides (**1**) into the 3-hydroxy-isoindolin-1-ones (**8**) and (**9**), and then (ii) direct formation of the methyl *ortho*-pyridoylbenzoates (**12**) and (**13**) as precursors of (**16**) and (**17**).

Experimental Section

Melting points were determined using a Boetius hot-stage apparatus and they are uncorrected. IR spectra were recorded on a Zeiss-Jena Specord 71-IR. The ^{1}H NMR spectra were determined on a Varian-Gemini-200 (200 MHz) or on a Tesla BS-467 (60 MHz) spectrometer. When the solvent applied was DMSO-d_6 and the spectra were recorded on a Tesla BS-467 spectrometer, TMS was used as an external reference, while in the remaining cases TMS was used as an internal standard. Ascending thin layer chromatography was performed on precoated of silica gel 60 F 254 (Merck) and the spots were visualised using UV lamp or iodine vapour. Macherey Nagel & Co. silica gel (100-200 mesh ATSM) was used for column chromatography. *n*-Butyllithium in hexane (Aldrich) was used without further purification. Tetrahydrofuran was dried over calcium hydride and used directly after distillation. Benzanilides (**1**) were prepared by the standard methods.

Preparation of 3-hydroxy-2-phenyl-2,3-dihydro-1*H*-isoindolin-1-ones (8) and (9)

To the anilide (0.01 mole) stirred in THF (40 ml) at -78°C *n*-BuLi (0.022 mole) was added. The solution was held at -78°C for 0.1 h, then allowed to rise to 0°C and kept at 0°C for 0.1 h. The whole lot were cooled to -78°C and methyl picolinate or methyl isonicotinate (0.01 mole) in THF (10 ml) was added respectively. The reaction after 0.2 h at -78°C was warmed up to room temperature, and kept for 24 h. Then in the case of compounds (**8**) water (25 ml) was added and the whole lot was neutralised by addition of hydrochloric acid, the products were partially precipitated. The precipitates and the organic layer were separated and the water layer was extracted with a mixture of chloroform and THF - 1:1 (2 x 30 ml). The combined organic solution was dried with magnesium sulphate. After evaporation of organic solvents, the residue and the precipitate were collected. Compounds (**8b**) and (**6**) were isolated by column chromatography and then were purified by crystallisation. The crude products (**8a**) and (**8c**) were washed with ethyl acetate (15 ml) and purified by crystallisation. In the case of compounds (**9**) methanol (20 ml) was added and the solvents were removed under reduced pressure. To the residue water (100 ml) was added and the whole lot was neutralised by addition of hydrochloric acid. The insoluble crude products were separated, washed with water and purified by crystallisation.

3-Hydroxy-4-methoxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1H-isondol-1-one (**8a**), (72%), m.p. 225-227°C (ethanol), (lit.[28] m.p. 226-227°C).

3-Hydroxy-4,6-dimethoxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**8b**), (27%), (eluent chloroform : ethyl acetate - 10:2, R_f 0.4), m.p. 200-202°C (DMSO : water - 5:3, and dried under reduced pressure at 110°C); (Found: C, 69.4; H, 5.0; N, 7.7. Calc. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73%); IR (KBr) 1700 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 60 MHz) 8.3 (1H, d J 5 Hz, 6Py-H), 7.9-7.6 (2H, m, 3Py and 4Py-H), 7.5 (1H, s, exchanges with D_2O, OH-H), 7.4-7.0 (6H, m, Ph and 5Py-H), 6.9 (1H, d J 2Hz, 6-H), 6.7 (1H, d J 2 Hz, 4-H), 3.8 (3H, s, OMe), 3.6 (3H, s, OMe).

3-Hydroxy-4,5,6-trimethoxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**8c**), (62%), m.p. 179-181°C (ethanol); (Found: C, 67.2; H, 5.3; N, 7.3. Calc. for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14%), IR (KBr) 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 8.47 (1H, dd J 4.5 and 1.6 Hz, 6Py-H), 7.67 (1H, td J 7.7 and 1.6 Hz, 4Py-H), 7.32-7.10 (9H, m Ph, 3Py, 5Py, OH and 6-H), 3.97 (3H, s, OMe), 3.87 (3H, s, OMe), 3.49 (3H, s, OMe).

3-Hydroxy-4-methoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**9a**), (70%), m.p. 288-289°C (ethanol), (lit.[28] m.p. 288-289°C).

3-Hydroxy-4,6-dimethoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**9b**), (25%), m.p. 284-286°C (decompose), (ethanol); (Found: C, 69.9; H, 5.0; N, 7.8. Calc. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73%); IR (KBr) 1700 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 60 MHz) 8.7 (2H, dd J 5 and 2 Hz, 2Py and 6Py-H), 7.9 (1H, s, exchanges with D_2O, OH-H), 7.8-7.3 (7H, m, 3Py, 5Py and Ph-H), 7.2 (1H, d J 2 Hz, 5-H), 7.0 (1H, d J 2 Hz, 7-H), 4.2 (3H, s, OMe), 3.9 (3H, s, OMe).

3-Hydroxy-4,5,6-trimethoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1H-isoindol-1-one (**9c**), (57%), m. p. 225-227°C (decompose), (methanol); (Found: C, 67.0; H, 5.0; N, 6.9. Calc. for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14%); IR (KBr) 1690 cm^{-1} (C=O); ^1H NMR (DMSO-d_6, 200 MHz) 8.45 (2H, dd J 4.6 and 1.6 Hz, 2Py and 6Py-H), 7.79 (1H, s, exchanges with D_2O, OH-H), 7.46-7.09 (8H, m, 3Py, 5Py, Ph and 7-H), 3.94 (3H, s, OMe), 3.77 (3H, s, OMe), 3.41 (3H, s, OMe).

3,5-dimethoxy-4-(2-pyridinecarbonyl)benzanilide (**6**), (48%), (eluent chloroform : ethyl acetate - 10:2, R_f 0.2), m.p. 245-248° (acetone : 2-propanol - 1:1); (Found: C, 69.6; H, 5.0; N, 7.6. Calc. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73%); IR ($CHCl_3$) 1680 cm^{-1} (C=O);

^{1}H NMR (DMSO-d$_6$, 60 MHz) 10.7 (1H, s, NH-H), 9.1-8.8 (1H, m, 6Py-H), 8.5-7.2 (10H, m, 3Py, 4Py, 5Py,Ph, 2-H and 6-H), 4.0 (6H, s, OMe).

3,5-dimethoxy-4-(4-pyridinecarbonyl)benzanilide (**7**),
(44%) m.p. 217-219°C (ethyl acetate : toluene - 1:1); (Found: C, 69.8; H, 5.0; N, 7.7. Calc. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73%); IR (KBr) 1690 cm^{-1} and 1650 cm^{-1} (C=O); ^{1}H NMR (DMSO-d$_6$, 60 MHz) 10.7 (1H, s, NH-H), 9.2 (2H, dd J 5 and 2 Hz, 2Py and 6Py-H), 8.3-7.3 (9H, m, 3Py, 5Py, Ph, 2-H and 6-H), 4.1 (6H, s, OMe).

Hydrolysis of the Compounds (8) and (9). Synthesis of the (10) and (11) Acids

The mixture of the compounds (**8**) or (**9**) (0.006 mole) in 50% sulphuric acid (20 ml) was heated till boiling for 1 h. Then the whole lot was poured into water (20 ml) and after cooling the solution was adjusted ($NaHCO_3$) to pH≈4 to precipitate acids (**10**) and (**11**). The crude products were separated, washed with water and purified by crystallisation.

3-Methoxy-2-(2-pyridinecarbonyl)benzoic acid (**10a**),
(92%), m.p. 212-214°C (ethanol), (lit.[28] m.p. 211-213°C).

3,5-Dimethoxy-2-(2-pyridinecarbonyl)benzoic acid (**10b**),
(83%), m.p. 210-214°C (decompose), (ethyl acetate); (Found: C, 62.5; H, 4.6; N, 5.0. Calc. for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.56; N, 4.88%); IR (KBr) 1690 cm^{-1} (C=O); ^{1}H NMR (DMSO-d$_6$, 60 MHz) 13.6-12.8 (br. s, OH-H), 8.6 (1H, d, J 5 Hz, 6Py-H), 8.2-7.2 (3H, m, 3Py, 4Py and 5Py-H), 7.0 (1H, d J 2Hz, 6-H), 6.9 (1H, d J 2 Hz, 4-H), 3.8 (3H, s, OMe), 3.6 (3H, s, OMe)

3,4,5-Trimethoxy-2-(2-pyridinecarbonyl)benzoic acid (**10c**),
(82%), m. p. 188-191°C (ethanol); (Found: C, 60.4; H, 4.9; N, 4.5. Calc. for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.76; N, 4.41%); IR (KBr) 1690 cm^{-1} (C=O); ^{1}H NMR (DMSO-d$_6$, 200 MHz) 13.4-12.8 (br. s, OH-H), 8.6 (1H, d, J 5 Hz, 6Py-H), 8.2-7.4 (3H, m, 3Py, 4Py and 5Py-H), 7.3 (1H, d J 2Hz, 6-H), 3.9 (3H, s, OMe), 3.8 (3H, s, OMe), 3.5 (3H, s OMe).

3-Methoxy-2-(4-pyridinecarbonyl)benzoic acid (**11a**),
(94%), m.p. 227-229°C (ethanol), (lit.[28] m.p. 226-228°C).

3,5-Dimethoxy-2-(4-pyridinecarbonyl)benzoic acid (**11b**),
(81%), m.p. 212-214°C (methanol); (Found: C, 62.7; H, 4.7; N, 4.8. Calc. for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.56; N, 4.88%); IR (KBr) 1690 cm^{-1} (C=O); ^{1}H NMR (DMSO-d$_6$, 60 MHz) 13.6-12.4 (br. s, OH-H), 9.1 (2H, dd J 5 and 2 Hz, 2Py and 6Py-H), 7.8 (2H, dd J 5 and 2 Hz, 3Py and 5Py-H), 7.4 (1H, d J 2Hz, 6-H), 7.3 (1H, d J 2Hz, 4-H), 4.2 (3H, s, OMe), 4.0 (3H, s, OMe).

3,4,5-Trimethoxy-2-(4-pyridinecarbonyl)benzoic acid (**11c**),
(73%), m. p. 209-212°C (ethanol : water - 1:5); (Found: C, 60.4; H, 4.9; N, 4.4. Calc. for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.76; N, 4.41%); IR (KBr) 1690 cm^{-1} (C=O); ^{1}H NMR (DMSO-d$_6$, 200 MHz) 13.90-12.80 (br. s, OH-H), 8.77 (2H, d J 4.4 Hz, 2Py and 6Py-H), 7.54 (2H, d J 4.4 Hz, 3Py and 5Py-H), 7.42 (1H, s, 6 -H), 3.96 (3H, s OMe), 3.89 (3H, s, OMe), 3,63 (3H, s, OMe).

Conversion of Acids (10) and (11) into the Corresponding Methyl Esters (12) and (13)

To the suspension of the acid (**10**) or (**11**) (0.004 mole) in water (30 ml), $NaHCO_3$ (0.005 mole) was added, and stirred until dissolved, then the solvent was removed under reduced pressure and the residue was dried under vacuum. The residue (sodium salt of the corresponding acid) was then subjected to react on with iodomethane (0.004 mole) in DMF (15 ml) at 0°C for 0.8 h in the case of compound (**10**) or for 4 h in the case of compound (**11**). Then the solvent was removed under reduced pressure to give solid residue. The product was extracted with $CHCl_3$ (4 x 15 ml) and separated by column chromatography and then purified by crystallisation.

Methyl 3-methoxy-2-(2-pyridinecarbonyl)benzoate (**12a**),
(90%), (eluent ethyl acetate, R$_f$ 0.5), m.p. 152-154°C (benzene : hexane - 1:1), (lit.[28] m.p. 153-154°C).

Methyl 3,5-dimethoxy-2-(2-pyridinecarbonyl)benzoate (**12b**),
(78%), (eluent chloroform : ethyl acetate - 1:1, R$_f$ 0.3), m.p. 157-160°C (ethyl acetate : heptane - 4:1); (Found: C, 64.1; H, 5.3; N, 4.7. Calc. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65%); IR (KBr) 1720 cm^{-1} and 1690 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$, 60 MHz) 8.5 (1H, dd J 5 and 2 Hz, 6Py-H), 8.2 (1H, d J 8 Hz, 3Py-H), 7.8 (1H, dd J 8 and 2 Hz, 4Py-H), 7.3 (1H, dd J 8 and 5 Hz, 5Py-H), 7.1 (1H, d J 2Hz, 6-H), 6.7 (1H, d J 2Hz, 4-H), 3.8 (3H, s, OMe), 3.6 (3H, s, OMe), 3.5 (3H, s, OMe).

Methyl 3,4,5-trimethoxy-2-(2-pyridinecarbonyl)benzoate (**12c**),
(73%), (eluent acetone : chloroform - 1:1, R$_f$ 0.7), m. p. 109-111°C (ethyl acetate : heptane - 2:3); (Found: C, 61.7; H, 5.4; N, 4.4. Calc. for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.32%); IR (KBr) 1720 cm^{-1} and 1700 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$, 200 MHz) 8.61 (1H, dd J 4.8 and 1.7 Hz, 6-Py-H), 8.24 (1H, dd J 7.8 and 1.3 Hz,

3Py-H), 7.89 (1H, td J 7.7 and 1.7 Hz, 4Py-H), 7.48-7.34 (2H, m, 5Py-H and 6-H), 3.96 and 3.95 (6H, two overlapping s, OMe), 3.74 (3H, s, OMe), 3.63 (3H, s, OMe).

Methyl 3-methoxy-2-(4-pyridinecarbonyl)benzoate (**13a**),
(68%), (eluent ethyl acetate, R_f 0.4), m.p. 102-104°C (hexane : toluene - 1:1), (lit.[28] m.p. 104-105°C).

Methyl 3,5-dimethoxy-2-(4-pyridinecarbonyl)benzoate (**13b**),
(72%), (eluent ethyl acetate, R_f 0.3), m.p. 130-132°C (ethyl acetate : heptane - 1:1); (Found: C, 63.6; H, 4.9; N, 4.9. Calc. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65%); IR (KBr) 1770 cm^{-1} and 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) 8.7 (2H, dd J 5 and 2 Hz, 2Py and 6Py-H), 7.5 (2H, dd J 5 and 2 Hz, 3Py and 5Py-H), 7.1 (1H, d J 2Hz, 6-H), 6.7 (1H, d J 2Hz, 4-H), 3.8 (3H, s, OMe), 3.6 (6H, s, OMe).

Methyl 3,4,5-trimethoxy-2-(4-pyridinecarbonyl)benzoate (**13c**),
(64%), (eluent ethyl acetate, R_f 0.3), m. p. 133-135°C (heptane); (Found: C, 61.4; H, 5.4; N, 4.3. Calc. for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.32%); IR (KBr) 1710 cm^{-1} and 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 8.78 (2H, dd J 4.4 and 1.6 Hz, 2Py and 6Py-H), 7.59 (2H, dd J 4.4 and 1.6 Hz, 3Py and 5Py-H), 7.41 (1H, s, 6-H), 3.98 (6H, s, OMe), 3,74 (3H, s, OMe), 3.68 (3H, s, OMe).

Conversion of Methyl Esters (12) and (13) into the Corresponding Azaanthra-5,10-quinones (16) and (17)

To diisopropylamine (0.0038 mole) stirred in THF (30 ml) at -78°C *n*-BuLi (0.0035 mole) was dropped and after 0.2 h hexamethylphosphoric triamide (0.0035 mole) was added. The whole lot was warmed up to 0°C and kept at 0°C for 0.5 h. To the obtained solution of LDA at -78°C methyl ester (**12**) or (**13**) (0.0012 mole) in THF (20 ml) was added. The reaction after 1 h at -78°C was allowed to reach an ambient temperature, and kept for 24 h, and then water (10 ml) was added. The organic layer was separated and the water layer was extracted with $CHCl_3$ (3 x 10 ml). The combined organic solutions were dried with magnesium sulphate and the solvents were evaporated to give a brown-orange residue. The product (**16**) or (**17**) was separated from the residue by column chromatography and purified by crystallisation.

9-Methoxybenz[g]quinoline-5,10-dione (**16a**),
(55%), (eluent acetone : chloroform - 1:1, R_f 0.3), m.p. 200-201°C (ethanol), (lit.[19a] m.p. 198-199°C); IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$,) 9.11 (1H, dd J 4.6 and 1.6 Hz, 2-H), 8.57 (1H, dd J 7.8 and 1.6 Hz, 4-H), 7.97 (1H, d J 8.4 Hz, 7-H), 7.82-7.64 (2H, m, 3-H and 7-H), 7.41 (1H, d J 8.4 Hz, 8-H), 4.08 (3H, s, OMe).

7,9-Dimethoxybenz[g]quinoline-5,10-dione (**16b**),

(26%), (eluent acetone : chloroform - 1:1, R_f 0.3), m.p. 259-261°C (DMSO and washed acetone : water - 1:1); (Found: C, 66.8; H, 4.4; N, 5.2. Calc. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20%); IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 9.09 (1H, dd J 4.6 and 1.5 Hz, 2-H), 8.54 (1H, dd J 7.9 and 1.5 Hz, 4-H), 7.65 (1H, dd J 7.9 and 4.6 Hz, 3-H), 7.45 (1H, d J 2.1 Hz, 5-H), 6.83 (1H, d J 2 Hz, 7-H), 4.03-4.00 (6H, two overlapping s, OMe).

7,8,9-Trimethoxybenz[g]quinoline-5,10-dione (**16c**),

(39%), (eluent acetone : chloroform - 1:1, R_f 0.5), m. p. 220-221°C (DMSO and washed ethyl acetate); (Found: C, 63.9; H, 4.5; N, 4.7. Calc. for $C_{16}H_{13}NO_5$: C, 64.20; H, 4.38; N, 4.68%); IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 9.09 (1H, dd J 4.5 and 1.5 Hz, 2-H), 8.56 (1H, dd J 7.9 and 1.5 Hz, 4-H), 7.72-7.63 (2H, m, 3-H and 6-H), 4.07 (3H, s, OMe), 4.03 and 4.01 (6H, two overlapping s, OMe).

6-Methoxybenz[g]isoquinoline-5,10-dione (**17a**),

(38%), (eluent chloroform, R_f 0.2), m.p. 206-208°C (DMSO and washed acetone : water - 1:1), (lit.[19a] m.p. 203-205°C); IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 9.49 (1H, s, 1-H), 9.08 (1H, d J 4.8 Hz, 3-H), 8.05 (1H, d J 4.8 Hz, 4-H), 7.97 (1H, d J 7.5 Hz, 9-H), 7.40 (1H, d J 8.3 Hz, 7-H), 7.80 (1H, overlapping dd J 8.3 and 7.5 Hz, 8-H), 4.08 (3H, s, OMe).

6,8-Dimethoxybenz[g]isoquinoline-5,10-dione (**17b**),

(40%), (eluent chloroform, R_f 0.2) m.p. 245-246°C (DMSO and washed acetone : water - 1:1); (Found: C, 66.8; H, 4.0; N, 5.3. Calc. for $C_{15}H_{11}NO_4$: C, 66.90; H, 4.12; N, 5.10%); IR (KBr) 1680 cm^{-1} and 1650 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 9.46 (1H, s, 1-H), 9.06 (1H, d J 4.9 Hz, 3-H), 8.06 (1H, d J 4.9 Hz, 4-H), 7.46 (1H, d J 2.1 Hz, 7-H), 6.82 (1H, d J 2.1 Hz, 9-H), 4.03 and 4.01 (6H, two overlapping s, OMe).

6,7,8-Triimethoxybenz[g]isoquinoline-5,10-dione (**17c**),

(37%), (eluent ethyl acetate, R_f 0.4), m. p. 167-168°C (ethyl acetate); (Found: C, 63.9; H, 4.4; N, 5.0. Calc. for $C_{16}H_{13}NO_5$: C, 64.20; H, 4.38; N, 4.68%); IR (KBr) 1670 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 200 MHz) 9.48 (1H, s, 1-H), 9.07 (1H, d J 4.9 Hz, 3-H), 8.04 (1H, d J 4.9 Hz, 4-H), 7.70 (1H, s, 9-H), 4.08 (3H, s, OMe), 4.02 (6H, s, OMe).

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References

1. Part 17; Epsztajn, J.; Grzelak, R.; Jóźwiak A. *Synthesis*, in press.
2. Cameron, D. W.; Crossley, M. J.; Feutrill, G. I.; Griffits, P. G. *Aust. J. Chem.*,**1978**, *31*, 1335.
3. Birch, A. J.; Butler, D. N.; Effenberger, R.; Rrickards, R. W.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 807.
4. Effenberger, R.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 823.
5. Cameron, D. W.; Deutscher, K. R.; Feutrill, G. I.; Hunt, D. E. *Aust. J. Chem.*,**1982**, *35*, 1451.
6. Cajori, F. A.; Otani, T. T.; Hamilton, M. A. *J. Biol. Chem.*, **1957**, *208*, 107.
7. Arsenault, G. P. *Tetrahedron Lett.*, **1965**, *6*, 4033; Arsenault, G. P. *Tetrahedron*, **1968**, *24*, 4745.
8. Cameron, D. W.; Deutscher, K. R.; Feutrill, G. I. *Aust. J. Chem.*, **1982**, *35*, 1439.
9. Watanabe, M.; Shinoda, E.; Shimizu, Y.; Furukawa, S.; Iwao, M.; Kuraishi, T. *Tetrahedron*, **1987**, *43*, 5281.
10. Schmitz, F. J.; DeGuzman, F. S.; Choi, Y.-H.; Hassain, M. B.; Rizvi, S. K.; van der Helm, D. *Pure Appl. Chem.*, **1999**, *62*, 1393.
11. Molinsky, T. F. *Chem. Rev.*, **1993**, *93*, 1825.
12. Walton, B. T.; Ho, C.-H.; Ma, C. Y.; O'Neill, E. G.; Kao, G. L. *Science*, **1983**, *222*, 422.
13. Ma, C. Y.; Ho, C.-H.; Walton, B. T.; Kao, G. L.; Guerin, M. R. *Environ.Sci. Technol.*, **1984**, *18*, 362.
14. Clark, A. M.; Huddleston, D. L.; Ma, C. Y.; Ho, C.-H. *Pharm. Res.*, **1984**, 269.
15. Koyama, J.; Okatani, T.; Tagahara, K.; Irie, H. *Heterocycles*, **1989**, *29*, 1649.
16. Koyama, J.; Tagahara, K.; Konoshima, T.; Kozuka, M.; Yano, Y.; Taniguchi, M. *Chem. Express*, **1990**, 557.
17. Konoshima, T.; Kozuka, M.; Koyama, J.; Okatani, T.; Tagahara, K.; Tokuda, H. *J. Nat. Prod.*, **1989**, *52*, 987.
18. Lee, H.; Hong, S.-S.; Kim, Y.-H. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 933.
19. For leading recent references see *inter alia*:
    a) Potts, K. T.; Bhattacharjee, D.; Walsh, E. B. *J. Org. Chem.*, **1986**, *51*, 2011.
    b) Khanapure, S. P.; Biehl, E. R. *Heterocycles*, **1988**, *27*, 2643.
    c) Ohgaki, E.; Motoyoshiya, J.; Narita, S.; Kakurai, T.; Hayashi, S.; Hirakawa, K. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 3109.
    d) Bouammali, B.; Pautet, F.; Fillion, H. *Heterocycles*, **1991**, *32*, 915.
    e) Kitahara, Y.; Kubo A. *Heterocycles*, **1992**, *34*, 1089.
    f) Bouammali, B.; Pautet, F.; Fillion, H.; Soufiaoui, M. *Tetrahedron*, **1993**, *49*, 3125.
    g) Nebois, P.; Fillion, H.; Benameur, L.; Fenet, B.; Luche J.-L. *Tetrahedron*, **1993**, *49*, 9767.
    h) Pérez, J. M.; Vidal, L.; Grande M. T.; Menéndez, J. C.; Avendano, C. *Tetrahedron*, **1994**, *50*, 7923.

  i) Carneiro do Nascimento, S.; Bouammali, B.; Boitard, M.; Pautet, F.; Soufiaoui, M.; Fillion, H. *Pharmazie*, **1994**, *49*, 702.
  j) Kitahara, Y.; Tamura, F.; Kubo, A. *Chem. Pharm. Bull.*, **1994**, *42*, 1363.
  k) Nebois, P.; Carneiro do Nascimento, S.; Boitard, M.; Bartoli, M.-H.; Fillion, H. *Pharmazie*, **1994**, *49*, 829.

20. For leading recent references see *inter alia*:
  a) Prager, R. H.; Tsopelas, Ch.; Heisler ,T. *Aust. J. Chem.*, **1991**, *44*, 277.
  b) Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.*, **1991**, *56*, 2289.
  c) Gomez-Bengoe, E.; Echavarren, A. M. *J. Org. Chem.*, **1991**, *56*, 3497.
  d) Bracher, F. *Liebigs Ann. Chem.*, **1992**, 1205.
  e) Bracher, F. *J. Heterocyclic Chem.*, **1993**, *30*, 157.
  f) Marcos, A.; Pedregal, C.; Avendano, G. *Tetrahedron*, **1994**, *50*, 12941.
  g) Echavarren, A. M.; Tamayo, N.; Cardenas, D. T. *J. Org. Chem.*, **1994**, *59*, 6075.
  h) Alvares, M.; Ajana, W.; Lopes-Calahorra, F.; Joule, J. A. *J. Chem. Soc.,Perkin Trans. 1*, **1994**, 917.
  i) Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Queguiner, G.; Sidoliqui, M. A.; Snieckus, V. *J. Org. Chem.*, **1995**, *60*, 292.
  j) Cochennec, C.; Rocca, P.; Marsais, F.;Gordard, A.; Queguiner, G. *Synthesis*, **1995**, 321.

21. Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.*, **1991**, 52, 187.
22 Fu, T.-M.; Zhao, B.-P.; Sharp, M. T.; Snieckus, V. *J. Org. Chem.*, **1991**, *56*, 1683.
23 Wang, W.; Snieckus, V. *J. Org. Chem.*, **1992**, *57*, 424.
24. Ferles, M.; Silhanova, A. *Collect. Czech. Chem. Commun.*, **1979**, *44*, 3137.
25. Epsztajn, J.; Jóźwiak, A.; Czech, K.; Szcześniak, A. K. *Monatsh. Chem.*, **1990**, *121*, 909.
26. Epsztajn, J.; Bieniek, A.; Kowalska, J. A. *Tetrahedron*, **1991**, *47*, 1697.
27. Epsztajn, J.; Bieniek, A.; Kowalska, J. A.; Ścianowski, J. *Monatsh. Chem.*, **1992**, *123*, 1125.
28. Epsztajn, J.; Jóźwiak, A.; Krysiak, J. K. *Tetrahedron*, **1994**, *50*, 2907.

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