Synthesis of 2-Aza-anthraquinone and 2-Azanaphthacenequinone 1-Chloro-derivatives as Key Intermediates for the Preparation of Antitumour Anthraquinone Analogues

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Lithiation of 2-(2-chloro-4-pyridyl)-4,4-dimethyl-4,5-dihydro-oxazole and subsequent condensation with aromatic aldehydes provides a four-step synthesis of both 1-chloro-2-aza-anthraquinone and 1-chloro-2-azanaphthacenequinone derivatives which are key intermediates in the preparation of mitoxanthrone analogues.

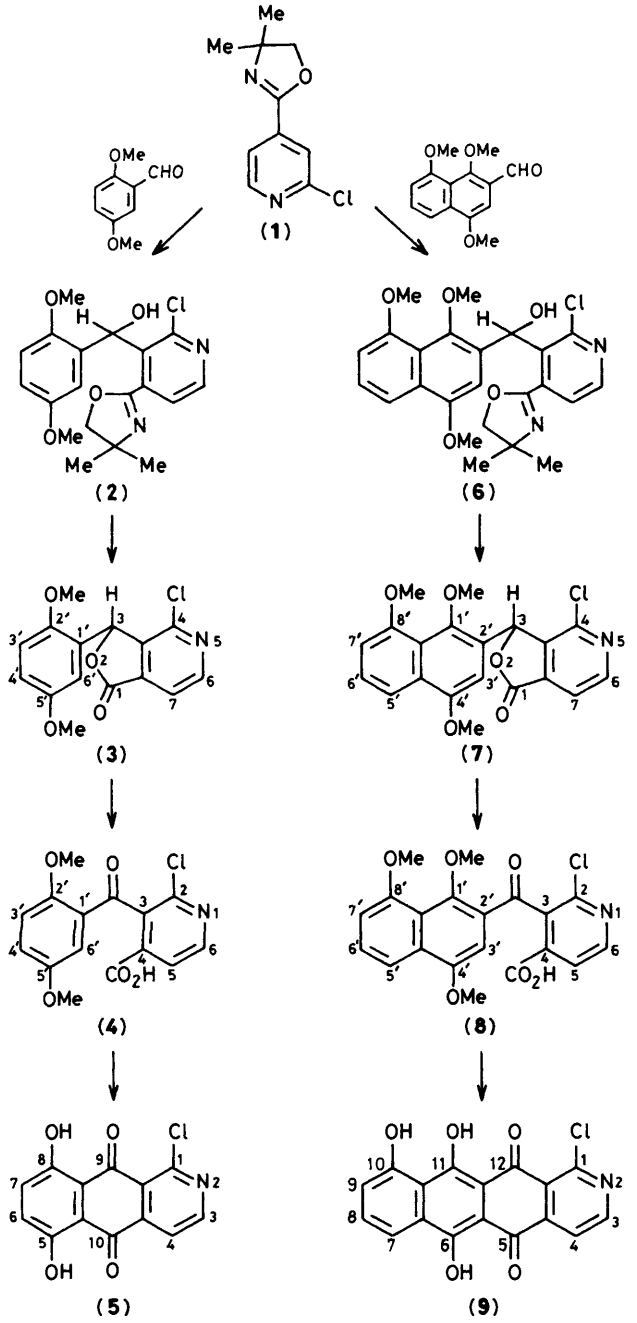
For the last few years workers in our laboratory have studied the synthesis of antitumour drugs bearing an aminoalkyl group attached to an aromatic DNA intercalating system.[1] Furthermore, the introduction of a nitrogen atom in place of a CH group in such molecules, *e.g.* in aminoalkyl ellipticine derivatives, has been shown to increase strongly the antitumour properties as demonstrated by the high activity of 10-(γ-diethylaminopropylamino)-6-methyl-5*H*-pyrido-[3′,4′:4,5]pyrrolo[2,3-*g*]isoquinoline (BD40) on numerous experimental tumours,[2] as well as in various human cancers during phase 1 clinical trials.[3]

On the other hand, various anthraquinone derivatives either synthetic, *e.g.* 1,4-dihydroxy-5,8-bis[2-(2-hydroxyethyl)amino]ethylaminoanthracene-9,10-dione (mitoxanthrone),[4] or natural, *e.g.* adriamycin,[5] are well known as very active anticancer drugs and recent publications have focused interest on aza analogues of such drugs.[6] This note deals with the synthesis of 1-chloro-2-aza-polycyclic quinones as key intermediates in the preparation of new analogues of these antitumoural quinone derivatives.

Lithiation of 2-(2-chloro-4-pyridyl)-4,4-dimethyl-4,5-dihydro-oxazole† (**1**) by means of methyl-lithium (tetrahydrofuran, −70 °C, 1 h under N_2) and subsequent condensation either with 2,5-dimethoxybenzaldehyde or with 1,4,8-trimethoxy-2-naphthaldehyde[7] afforded the 4*H*-1,3-oxazolines (**2**) and (**6**) respectively. Attempts to purify these intermediates led to partial opening of the 4*H*-1,3-oxazoline ring as shown by n.m.r. spectroscopy‡ with the appearance of an OH signal highfield, with a triplet configuration, characteristic of a CH_2OH group.

† Compound (**1**) was prepared from 2-chloroisonicotinoyl chloride and 2-amino-2-methylpropan-1-ol in toluene solution. After conventional treatment the amide was then successively treated by thionyl chloride and by potassium carbonate in methyl ethyl ketone in order to complete cyclization (colourless oil, b.p./7 mmHg 147 °C, 50% overall yield).

‡ ^{1}H N.m.r. spectra were recorded on a Varian XL100/100 MHz spectrometer.



Hydrolysis of (**2**) and (**6**) with HCl led to the phthalides (**3**) and (**7**),§ [(**3**), white crystalline powder from methanol, m.p. 134 °C; ^{1}H n.m.r. ($CDCl_3$) δ 3.66 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 6.63 (m, 1 H, H-6′), 6.66 (s, 1 H, H-3), 6.93 (m, 2 H, H-3′, H-4′), 7.83 (d, 1 H, H-6, J_{6-7} 5 Hz), 8.66 (d, 1 H, H-7); (**7**), white crystalline powder from methanol, m.p. 195 °C; ^{1}H n.m.r. ($CDCl_3$) δ 3.78 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 6.05 (s, 1 H, H-3), 6.99 (q, 1 H, H-7′), 7.13 (s, 1 H, H-3′), 7.47 (t, 1 H, H-6′), 7.88 (m, 1 H, H-5′), 7.85 (d, 1 H, H-6, J_{6-7} 5 Hz), 8.71 (d, 1 H, H-7)]. However, in the HCl hydrolysis of (**6**), partial demethylation occurred and so sodium hypochlorite–acetic acid was used for preparative purposes. The overall yields were 61.5% for (**1**) to (**3**) and 40% for (**1**) to (**7**).

Bromination of phthalides (**3**) and (**7**) with *N*-bromosuccinimide[8] (in refluxing CCl_4, 5 h) and further hydrolysis with sodium hydroxide afforded 2-chloro-3-(2,5-dimethoxybenzoyl)- and 2-chloro-3-(1,4,8-trimethoxy-2-naphthoyl)-isonicotinic acids, (**4**) and (**8**), [(**4**), yellow needles from methanol, m.p. 211 °C, 57% yield; ^{1}H n.m.r. ([$^2H_6$]Me_2SO) δ 3.42 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 7.10 (d, 1 H, H-3′), 7.28 (m, 1 H, H-4′), 7.48 (q, 1 H, H-6′), 7.94 (d, 1 H, H-5, J_{5-6} 5 Hz), 8.65 (d, 1 H, H-6); (**8**), yellow needles from methanol, m.p. 232 °C, 30% yield; ^{1}H n.m.r. ([$^2H_6$]Me_2SO) δ 3.19 (s, 1 H, OMe), 3.36 (br. s, 1 H exchangeable, OH), 3.94 (s, 3 H, OMe), 4.06 (s, 3 H, OMe), 7.17 (q, 1 H, H-7′), 7.41 (s, 1 H, H-3′), 7.65 (t, 1 H, H-6′), 7.85 (m, 1 H, H-5′), 7.96 (d, 1 H, H-5, J_{5-6} 5 Hz), 8.68 (d, 1 H, H-6)].

Cyclizations of (**4**) and (**8**) were performed at first in sulphuric acid as previously described for the synthesis of various anthraquinones.[9] However this procedure required heating and afforded cyclization products in poor yield. Thus methanesulphonic acid (3 h, 120 °C under N_2) was preferred. In both cases almost complete demethylation occurred, leading to 1-chloro-5,8-dihydroxy-2-aza-anthracene-9,10-dione (**5**), and 1-chloro-6,10,11-trihydroxy-2-azanaphthacene-5,12-dione (**9**), [(**5**), red needles from toluene, m.p. 243 °C, 57% yield; ^{1}H n.m.r. ($CDCl_3$) δ 7.34 (d, 1 H, H-6 or H-7, J_{6-7} 9.5 Hz), 7.46 (d, 1 H, H-7 or H-6), 8.21 (d, 1 H, H-4 or H-3, J_{4-3} 5 Hz), 8.88 (d, 1 H, H-3 or H-4), 12.57 (s, 1 H, OH), 12.40 (s, 1 H, OH); (**9**), bright red plates from xylene, m.p. 295 °C, 20% yield; ^{1}H n.m.r. ($CDCl_3$) δ 7.32 (q, 1 H, H-8), 7.76 (t, 1 H, H-9), 7.98 (m, 1 H, H-7), 8.28 (d, 1 H, H-4 or H-3, J_{4-3} 5 Hz), 8.65 (d, 1 H, H-3 or H-4), 12.19 (s, 1 H, OH), 14.26 (s, 1 H, OH-11 or 6), 14.72 (s, 1 H, OH-6 or 11)].

Studies, in order to substitute compounds (**5**) and (**9**) by various amines, are presently under investigation and new compounds will be evaluated for cytotoxicity and antineoplastic activity in this institute.

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§ All new compounds gave satisfactory analytical data (±0.4% C, H, N, Cl).

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