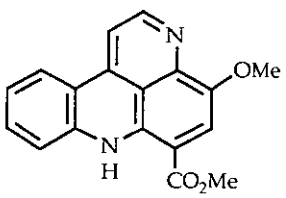
SYNTHESIS OF PYRIDOACRIDINES

Mercedes Alvarez*
Laboratory of Organic Chemistry, Faculty of Pharmacy,
University of Barcelona, Barcelona 08028, Spain
John A. Joule*
Chemistry Department, University of Manchester,
Manchester M13 9PL, U. K.

Abstract - The synthesis of pyridoacridines is reviewed.

A review[1] of quinoline/isoquinoline-containing sea alkaloids revealed that more than 30 compounds, reported thus far, have as a common structural feature a pyrido[2,3,4-*kl*]acridine (dibenzo[*f,ij*][2,7]naphthyridine) nucleus.[2] This group contains substances with a variety of biological activities: Ca-releasing, antiviral, antimicrobial activity, and cytotoxicity to L1210 murine leukemia cells. Norsegoline[3] is representative of the structurally simplest of the group; amongst pentacyclic examples, amphimedine,[4] ascididemine,[5] and meridine[6] include an additional pyridine (pyridone) ring, dercitine[7] has an additional thiazole, the kuanoniamines[8] an isomerically fused thiazole, and shermilamine A[9] an additional thiazine. The segolines[10,11] incorporate an isoprene unit, generating hexacyclic molecules, and eilatine[12] is a 'dimer' of the nucleus.



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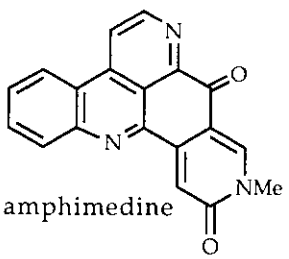

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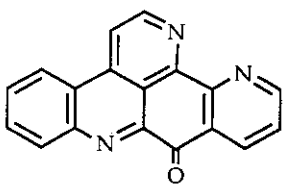
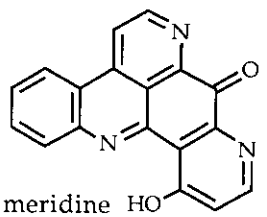
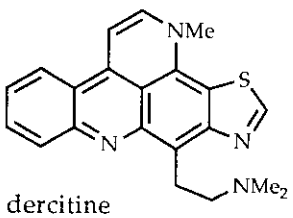


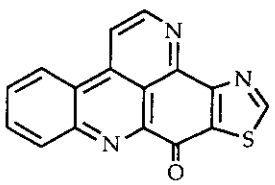
ascididemine



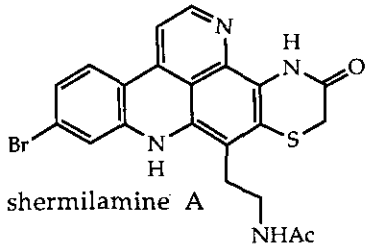
meridine



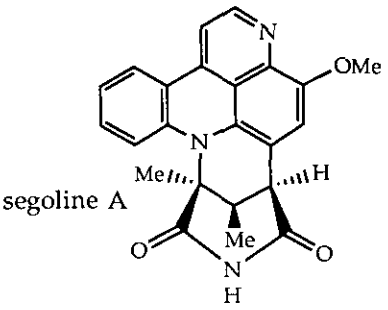
dercitine



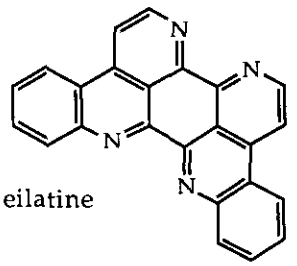
kuanoniamine A



shermilamine A



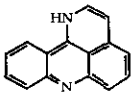
segoline A



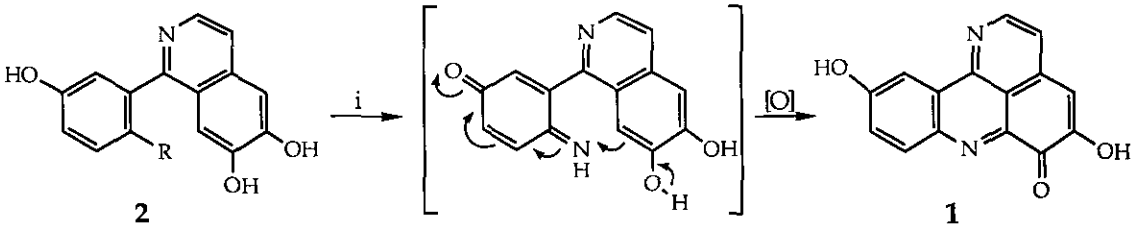
eilatine

In view of the considerable interest in such polyheterocyclic substances, the range of biological activities displayed, and the expectation that further natural, polyheterocyclic, poly-nitrogen-containing substances will be uncovered having variations on the structural types already known,[13] we review here the available methods for the construction of pyrido[2,3,4-*kl*]acridines and, in addition, of all the other, currently known, isomeric pyridoacridines. The review concentrates on the methods which have been used to generate the pyridoacridine nuclei, and generally does not give complete natural product syntheses, even where these have been reported.

1*H*-Pyrido[2,3,4-*kl*]acridines

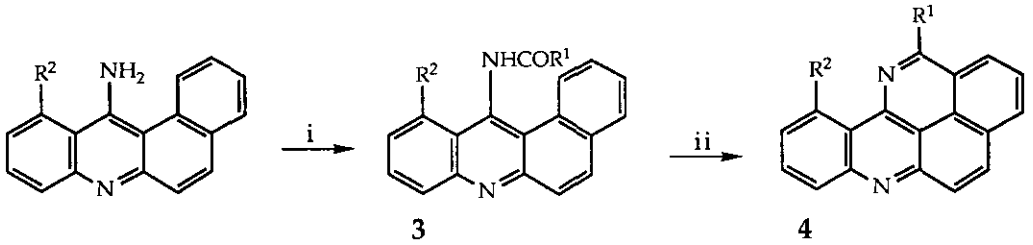


Necatorone (**1**), which has considerable mutagenic activity in the Ames test, has been synthesised.[14] The tetracyclic ring system was established in an interesting oxidative process (Scheme 1), believed to involve a quinone imine: isoquinoline (**2**, R=NH_2), assembled in routine manner, was exposed to air in alkaline solution, however the ring closure could only be achieved at all efficiently on a 10 mg scale. An attempt to close the nitro compound, (**2**, R=NO_2) with triethyl phosphite, resulted in cyclisation of nitrene onto the isoquinoline ring nitrogen atom.

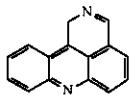


Scheme 1 Reagent : i, O_2, 5% aq. NaOH (67%).

Cyclisation of 9-acetamido- (R^1=Me) and 9-formamido- (R^1=H) -benzo[*a*]acridines (R^1=H) (**3**) in a melt of $AlCl_3$/NaCl was employed in the synthesis (Scheme 2) of pentacyclic benzo-pyrido[2,3,4-*kl*]acridines (R^1= H or Me, R^2=H or Me) (**4**).[15]

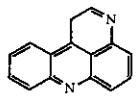


Scheme 2 Reagents : i, Ac_2O, 100°C (92%) or DMF, NaOMe, reflux (52%); ii, $AlCl_3$, NaCl, 220°C (58-64%).



1*H*-Pyrido[3,4,5-*kl*]acridines

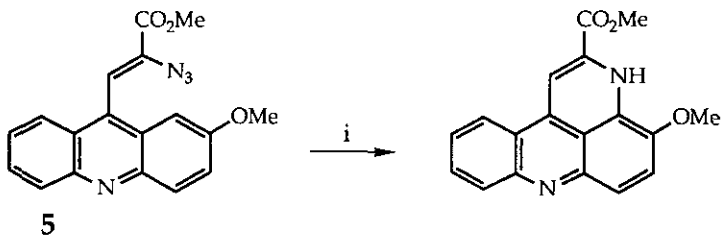
There are no reported examples of this ring system, either natural or synthetic.



1*H*-Pyrido[2,3,4-*kl*]acridines

This, the ring system common to more than 35 marine alkaloids, has been the subject of considerable synthetic effort, and five distinct routes to the nucleus have been described.

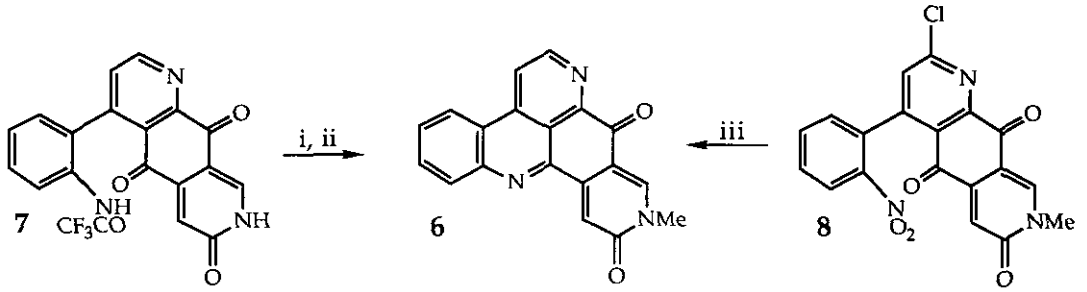
Oxidation of the methyl group in 2-methoxy-9-methylacridine and condensation with methyl azidoacetate gave an azide, (**5**), which on thermolysis generated a nitrene for an insertion (Scheme 3) producing the tetracyclic nucleus.[16]



Scheme 3 Reagent : i, xylene, 140°C (97%).

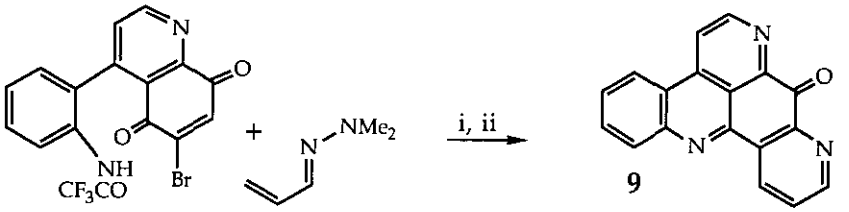
In two total syntheses of amphimedine, (**6**), a simple N/C bonding from advanced *para*-quinonoid intermediates completed the nucleus (Scheme 4). Quinone (**7**)[17] was

prepared by coupling 5,8-dimethoxyquinolin-4-yl triflate with a 2-trifluoroacetylaminophenyltrimethyltin, and the pyridone added using a Diels-Alder cycloaddition with Ghosez' diene; quinone (**8**) was generated using a standard quinolone ring synthesis producing a 4-(2-nitrophenyl)quinolin-2-one, the pyridone again being added later using Ghosez' diene.[18]



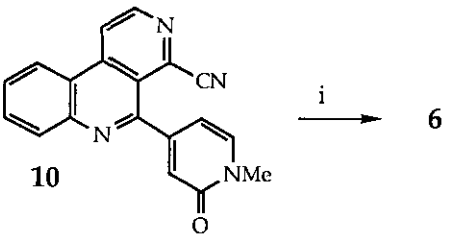
Scheme 4 Reagents : i, HCl, THF, 80°C (86%); ii, Me_2SO_4, K_2CO_3, DMF, 23°C (96%); iii, H_2, 10% Pd-C, Et_3N, MeOH, room temperature (13%).

In a synthesis of 'isoascididemine', (**9**), cycloaddition between a quinoline-5,8-dione and the dimethylhydrazone of acrolein added a pyridine in an orientation isomeric with both ascididemine and amphimedine; again the final ring closure involved a straightforward amine/carbonyl condensation (Scheme 5).[19]



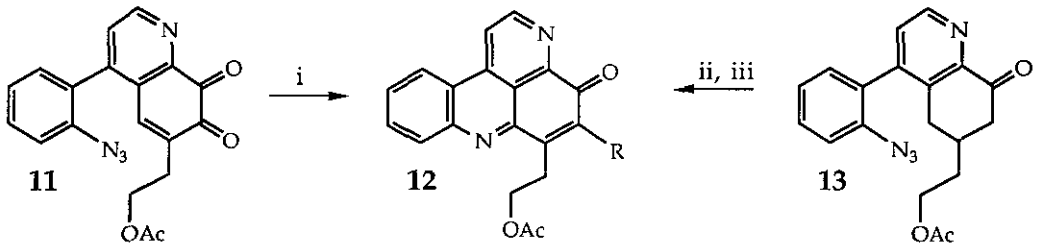
Scheme 5 Reagents : i, CH_3CN, Et_2O, 23 → 80°C; ii, 6M HCl, 80°C (92%).

Intramolecular Friedel-Crafts type acylation of the 2-pyridone, at its C-3, in intermediate (**10**), in a third total synthesis of amphimedine, is a quite different method for the generation of a pyrido[2,3,4-*kl*]acridine (Scheme 6).[20] Substrate (**10**) was produced in a short route which neatly utilised the Schmidt reaction of a pyridyl-aza-fluorenol with migration of the most electron-rich ring.



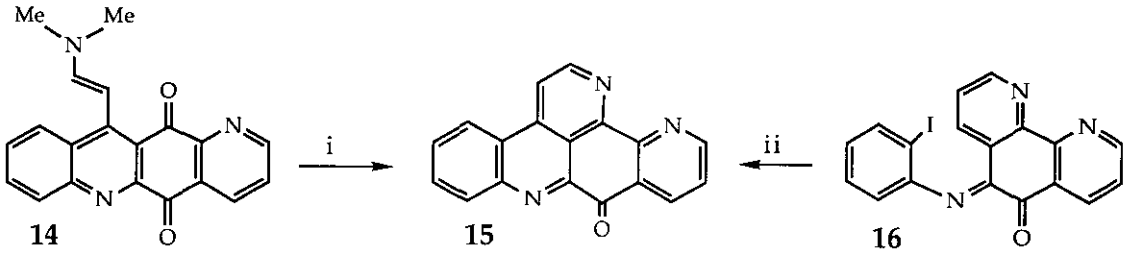
Scheme 6 Reagent : i, PPA, 90°C, 5 h (35%).

Nitrene insertion was also central to a route (Scheme 7) by which cystodytines A and B were synthesised, thus thermolysis of the *ortho*-quinone (**11**) produced **12** (R=OH); a better route involved cyclisation at lower oxidation level, for example in the conversion of **13** into **12** (R=H).[21]



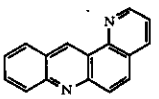
Scheme 7 Reagents : i, PhMe, reflux (74%); ii, hν, PhCl, 110°C; iii, DDQ, 25°C (31%).

The pyrido[2,3-*b*]acridine (**14**) was cyclised to afford ascididemine, (**15**), using the side-chain enamine, formed by reaction of a precursor methyl group with dimethylformamide dimethyl acetal (DMFDMA), as an acetaldehyde synthon (Scheme 8).[22]

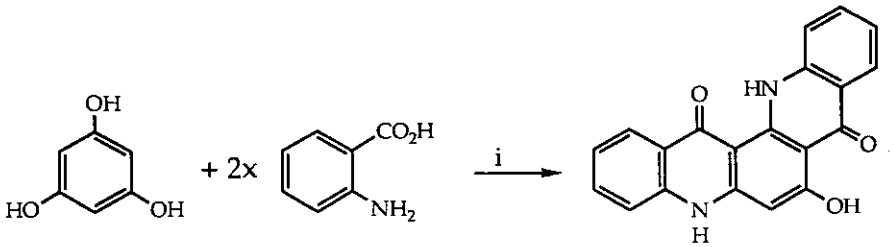


Scheme 8 Reagents : i, NH_4Cl, AcOH, reflux, 1 h (59%); ii, hν, conc. H_2SO_4 (32%).

The same alkaloid has also been constructed[23] in a quite different manner, by the photo-catalysed cyclisation of the iodo-quinone imine (**16**) (Scheme 8), produced in only three steps from phenanthroline.

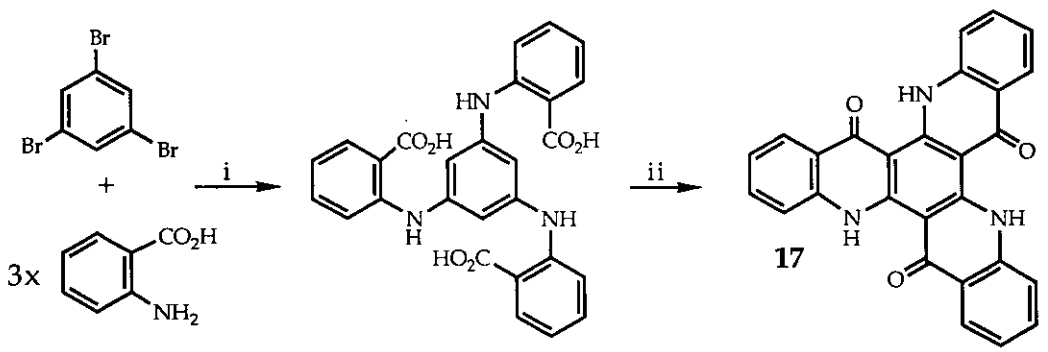
Benzo[*j*][1,7]phenanthroline (Pyrido[2,3-*b*]acridine) 

The reaction of phloroglucinol with anthranilic acid, *via* three Bucherer-type reactions, leads to a dibenzo[1,7]phenanthroline (Scheme 9).[24]



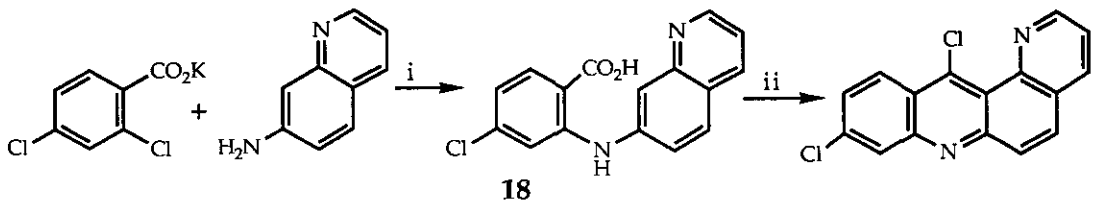
Scheme 9 Reagent : i, heat.

A triple Ullman-amine coupling of 1,3,5-tribromobenzene, then three intramolecular Friedel-Crafts cyclising acylations generated 'triquinolonobenzene', (**17**) (Scheme 10). The compound was prepared for comparison with linear 'quinacridone' (see later) systems, organic pigments with outstanding light fastness, believed to be associated with a high degree of intermolecular hydrogen bonding. Heptacycle (**17**) is only weakly coloured.[25]



Scheme 10 Reagents : i, K_2CO_3, spongy Cu, CuCl, $Cu(OAc)_2.H_2O$, *n*-$C_5H_{11}OH$, reflux (92%); ii, PPA, 140-150°C, 4.5 h (98%).

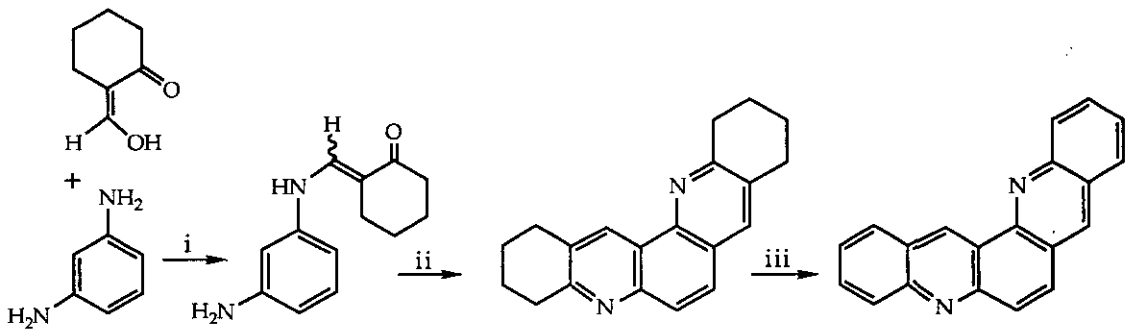
Ullmann-amine coupling with 7-aminoquinoline provided the carboxylic acid (**18**), which was converted into acid chloride, cyclised selectively to the quinoline 8-position, and acridone thus produced converted into the corresponding halo-heterocycle, all in one pot (Scheme 11).[26] This type of approach has been used to produce several isomeric pyridoacridines: Schemes 14, 27 and compound **37**.



18

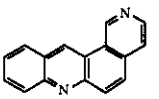
Scheme 11 Reagents : i, Cu-bronze, $EtC(Me)_2OH$, 150°C, 6 h; ii, $POCl_3$, PCl_5, 150°C.

The dibenzo[1,7]phenanthroline, (**19**), was constructed (Scheme 12) from *meta*-phenylenediamine, which on reaction with 2-formylcyclohexanone gave **20**, and this, on strong acid treatment, cyclised to give **21**.[27]

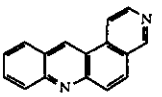


20 **21** **19**

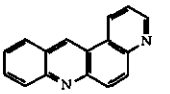
Scheme 12 Reagents : i, EtOH, room temperature (65%); ii, PPA, 160-170 °C (40%); iii, Se, 300°C (58%).

Benzo[*j*][2,7]phenanthroline (Pyrido[3,4-*a*]acridine) 

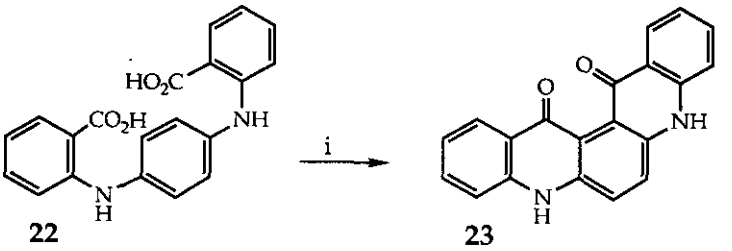
There are no reported examples of this ring system, either natural or synthetic.

Benzo[*j*][3,7]phenanthroline (Pyrido[4,3-*a*]acridine) 

There are no reported examples of this ring system, either natural or synthetic.

Benzo[*b*][4,7]phenanthroline (Pyrido[3,2-*a*]acridine) 

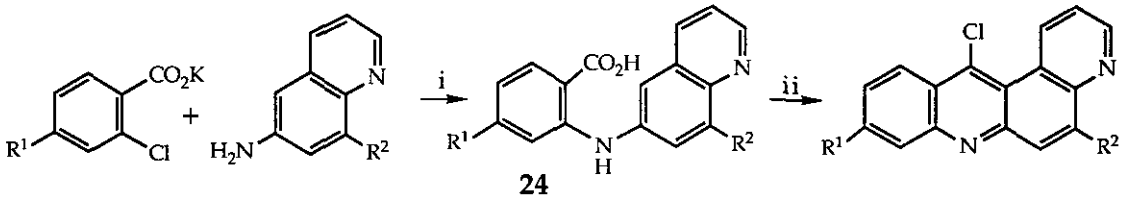
In what appears to be an extraordinary regiochemical preference, the diacid (**22**) closes to the dibenzo[4,7]phenanthroline (**23**) *via* two acid-catalysed Friedel-Crafts intramolecular acylations (Scheme 13).[28]



22 **23**

Scheme 13 Reagent : i, c. H_2SO_4, 100°C (59%).

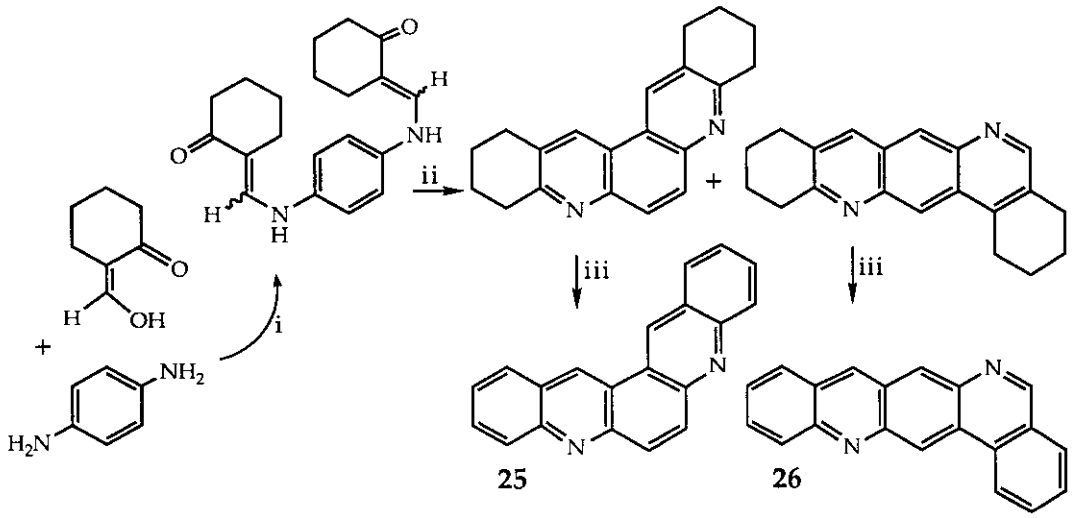
Acids, (**24**) (R^1=H or Cl and R^2=H or Cl), produced *via* Ullmann-amine couplings with 6-aminoquinolines, were cyclised (Scheme 14), in one preparative step involving conversion of acid to acid chloride, intramolecular Friedel-Crafts closure, selective for the quinoline 5-position, and conversion of initial acridone into halo-heterocycle.[26,29,30]



24

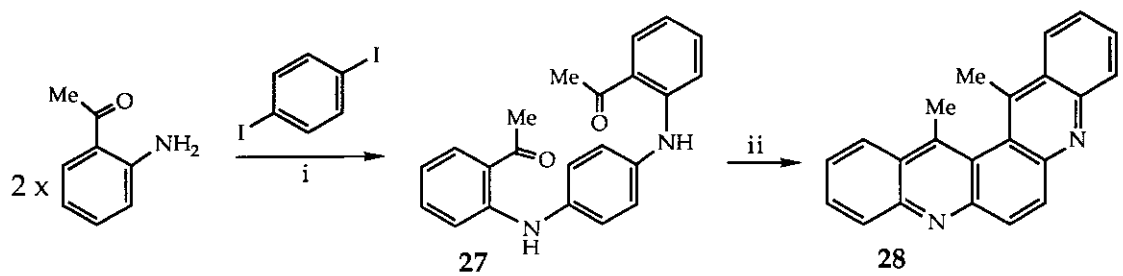
Scheme 14 Reagents : i, Cu-bronze, reflux, $EtC(Me)_2OH$ (50-60%); ii, $POCl_3$, 150°C (70-80%).

The interaction of *para*-phenylenediamine with 2-formylcyclohexanone to generate a bis-enamine, followed by acid-catalysed closure to a mixture of isomers, separate dehydrogenation of which produced (Scheme 15) the dibenzo[4,7]phenanthroline, (**25**) and the dibenzopyrido[2,3-*b*]acridine (**26**).[31] As in Scheme 12, interchange of amino-aromatic, and net transfer of nitrogen to the ring carbonyl carbon must be involved.[32]



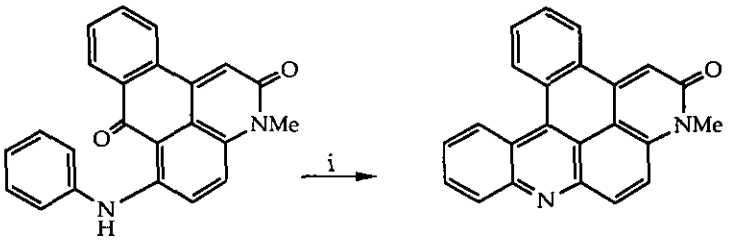
Scheme 15 Reagents : i, EtOH, room temperature (77%); ii, PPA, 180°C (14 and 51%); iii, Se, 300°C (38 and 25%).

1,4-Diiodobenzene reacted in a double Ullmann-amine coupling with 2-aminoacetophenone to give a diketone, (**27**) which underwent acid-catalysed cyclisation with what would have appeared to be an unlikely regioselectivity, for the hindered dibenzo[4,7]phenanthroline, (**28**), was obtained (Scheme 16).[33] It is significant that the bis-benzoyl analogue of **27** only underwent one cyclisation, giving an acridine. This synthetic approach has been used to produce several isomeric pyridoacridines (Schemes 25 and 32).

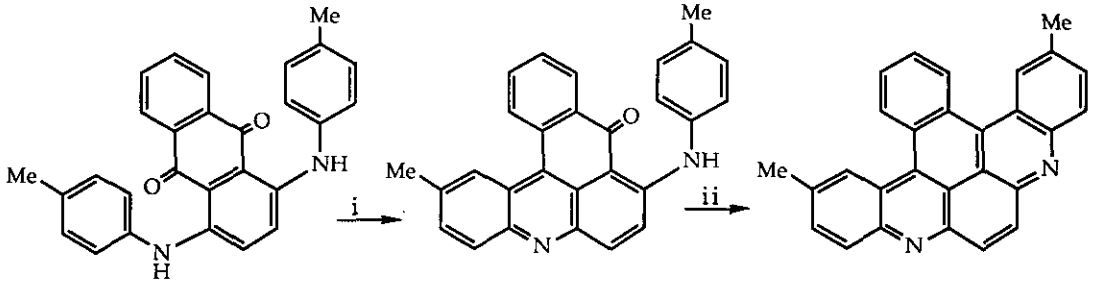


Scheme 16 Reagents : i, Cu, $(n\text{-Bu})_2O$, K_2CO_3, reflux (48%); ii, AcOH, H_2SO_4, 95°C (52%).

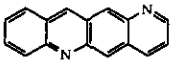
Hexa- and heptacyclic molecules containing a pyrido[3,2-*a*]acridine nucleus were generated (Schemes 17 and 18) by ring closures of anthraquinone-derived precursors.[34]



Scheme 17 Reagent : i, PPA, 170°C (96%).



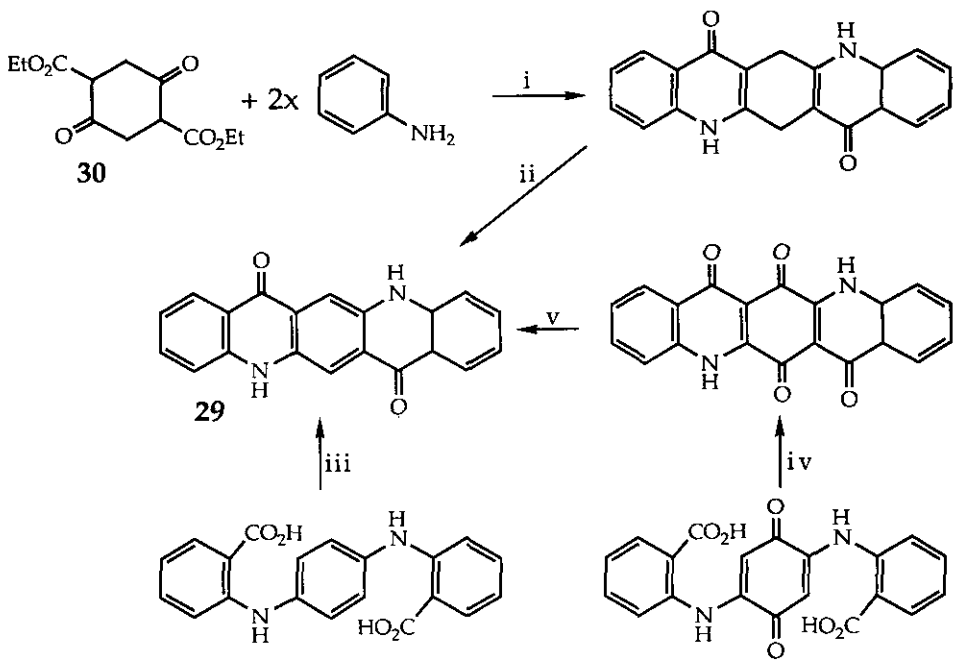
Scheme 18 Reagents : i, PPA, 180°C; ii, PPA, 180°C (79%).

Pyrido[2,3-*b*]acridine 

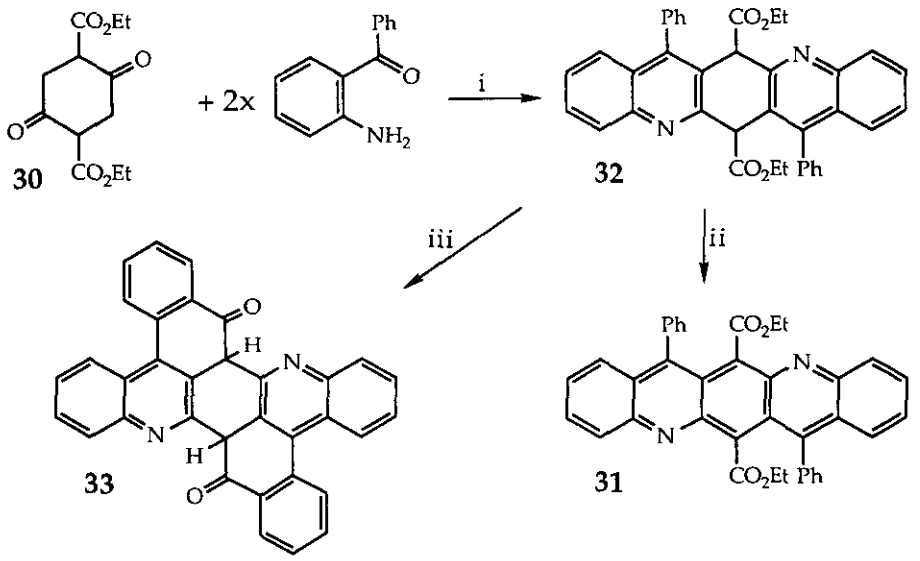
The organic pigment, quinacridone (**29**) can be synthesised from diethyl 2,5-dioxo-1,4-cyclohexanedicarboxylate (**30**) and aniline then dehydrogenation (Scheme 19)[35]; many analogues have been synthesised, and the large field has been reviewed[36] and is accordingly only briefly summarised here. Alternative routes to such systems include cyclisations of 2,4-diarylaminoterephthalic acids which give the fully aromatic systems directly, or cyclisation of 2,4-di-(2-carboxyphenylamino)-1,4-benzoquinones, which give quinones, reducible to the parent system.

Interaction of diketone (**30**) with 2-aminobenzophenone in a double quinoline Friedländer synthesis, and dehydrogenation, provided (**31**) (Scheme 20).[37] Simply heating **32** in 1-chloronaphthalene brought about double intramolecular acylation and the formation of **33**.

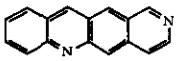
The synthesis of compound (**26**) has already been discussed.[31]



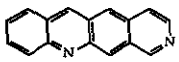
Scheme 19 Reagents : i, heat; ii, *e.g.* chloranil; iii, *e.g.* PPA; iv, *e.g.* c. H_2SO_4, v, *e.g.* Zn dust, 70% H_2SO_4.



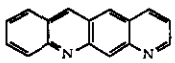
Scheme 20 Reagents : i, 6N HCl, EtOH, reflux (72%); ii, chloranil, methylcellosolve, reflux (92%); iii, $C_{10}H_7Cl$, reflux (83%).

Pyrido[3,4-*b*]acridine 

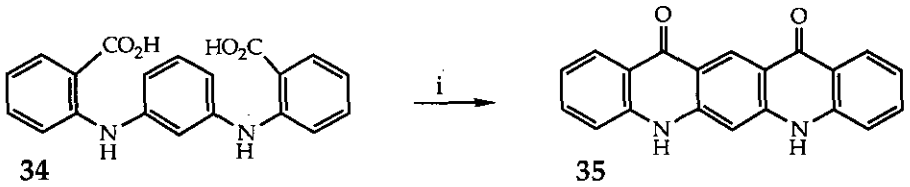
There are no reported examples of this ring system, either natural or synthetic.

Pyrido[4,3-*b*]acridine 

There are no reported examples of this ring system, either natural or synthetic.

Pyrido[3,2-*b*]acridine 

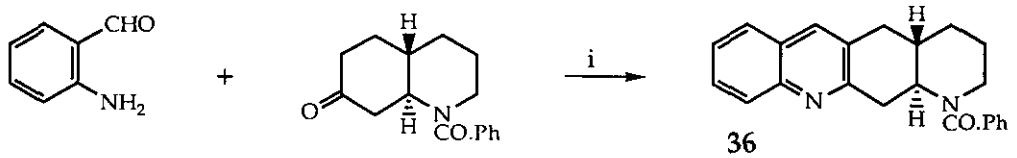
Strong acid-catalysed cyclisation of symmetrical diacid-diarylamine (**34**) affords the linear benzopyrido[3,2-*b*]acridine (**35**) (Scheme 21).[38]



34 35

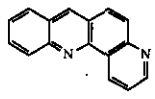
Scheme 21 Reagent : i, PPA, 120-160°C.

The use of a decahydroquinolone-amide in a Friedländer synthesis provided **36**.[39]



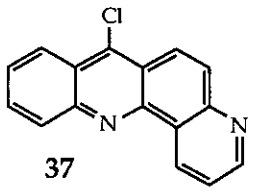
36

Scheme 22 Reagent : i, NaOH, EtOH (85%).

Benzo[*b*][1,7]phenanthroline (Pyrido[2,3-*c*]acridine) 

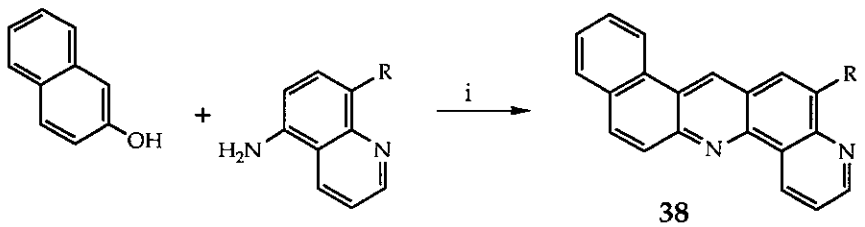
The syntheses of compound (**17**)[25] and of isoascididemine (**9**)[19] have already been discussed.

The route described in Scheme 11 has been utilised, but with 5-aminoquinoline instead of 7-aminoquinoline, to prepare **37**.[40]



37

β-Naphthol condenses (Scheme 23) with 5-aminoquinolines and paraformaldehyde generating naphthaleno[1,7]phenanthrolines (**38**, R = H and Me).[41]

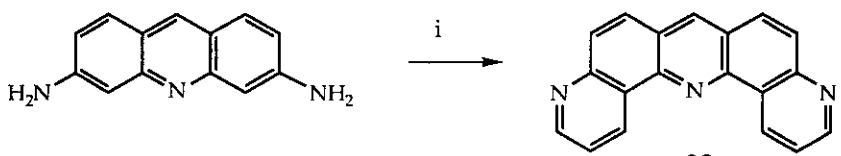


R = H, Me

38

Scheme 23 Reagent : i, paraformaldehyde, 250°C, (15%).

In a double Skraup synthesis (Scheme 24), 3,6-diaminoacridine produced the dipyridoacridine (**39**); the direction of ring closures, both adjacent to the acridine nitrogen, is notable.[42]

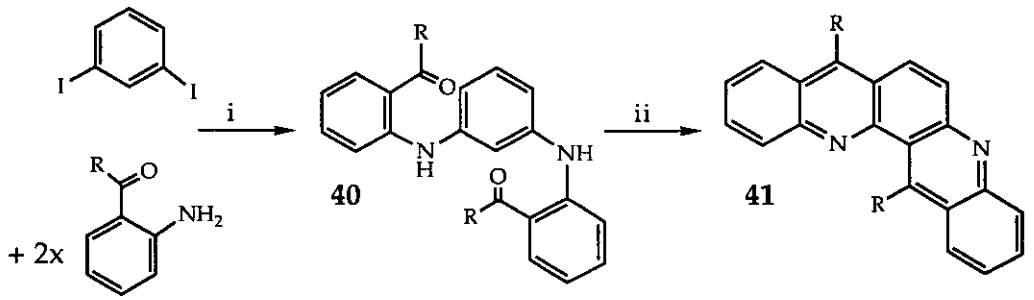


39

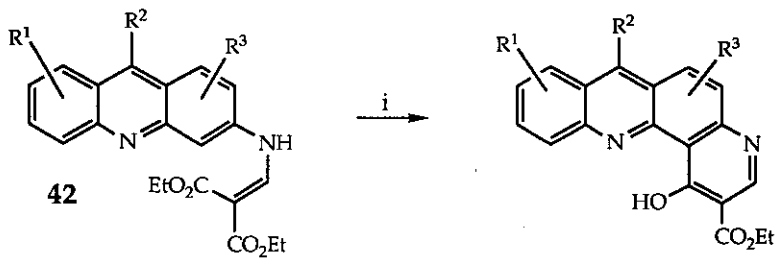
Scheme 24 Reagent : i, $HOCH_2CH(OH)CH_2OH$, H_3AsO_4, H_2SO_4, reflux.

Scheme 25 shows how the condensation of 2-aminoacetophenone and 2-aminobenzophenone with 1,3-diiodobenzene produces **40**, double ring closures of which give the angular systems (**41** R= Me or Ph).[33]

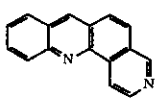
A large number of benzo[*b*][1,7]phenanthrolines have been synthesised by the route shown in Scheme 26, in which an aminoacridine is converted into a aminomethylenemalonate, (**42**, R^1, R^2, and R^3=H, and alkyl (C_{1-10}), Ar, alkylamino, alkylthio, nitro, cyano, alkylsulphonyl, *etc.*) and this cyclised in acid; again, the regioselectivity of cyclisation is interesting.[43]



Scheme 25 Reagents : i, K_2CO_3, Cu, *n*-Bu_2O, reflux (75%); ii, H_2SO_4, AcOH (66%).



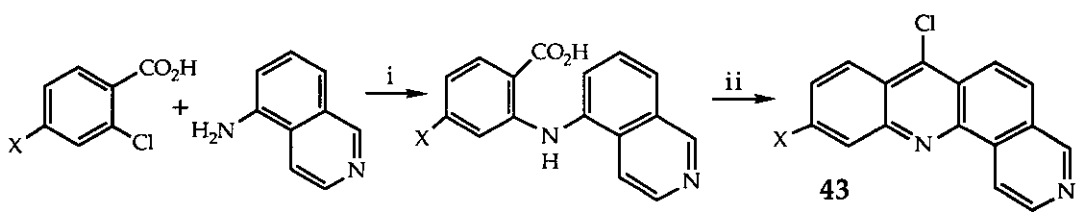
Scheme 26 Reagents : i, Ph_2O, 260°C.



Benzo[*b*][1,8]phenanthroline (Pyrido[3,4-*c*]acridine)

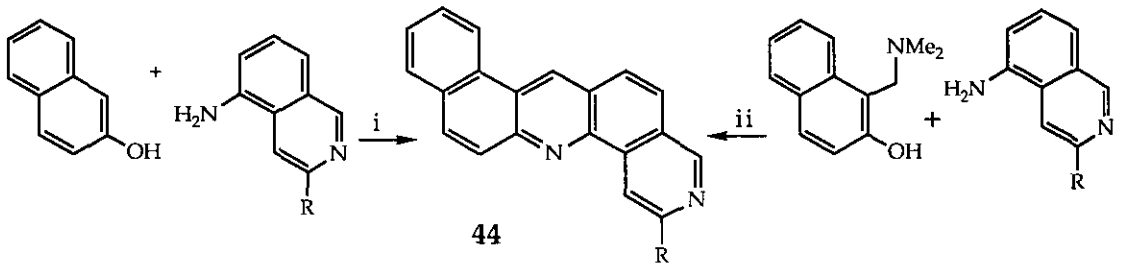
The synthesis of amphimedine, (6) has already been discussed (Schemes 4, 5, and 6)

A sequence of the type encountered before (Schemes 11 and 14) allowed the assembly of **43** (X = H or Cl) from 5-aminoisoquinoline (Scheme 27).[40,44-47]



Scheme 27 Reagents : i, K_2CO_3, Cu, $EtC(Me)_2OH$, reflux (X=H (22%) and X=Cl (15%));
ii, $POCl_3$, reflux, (X=H (39%) and X=Cl (85%)).

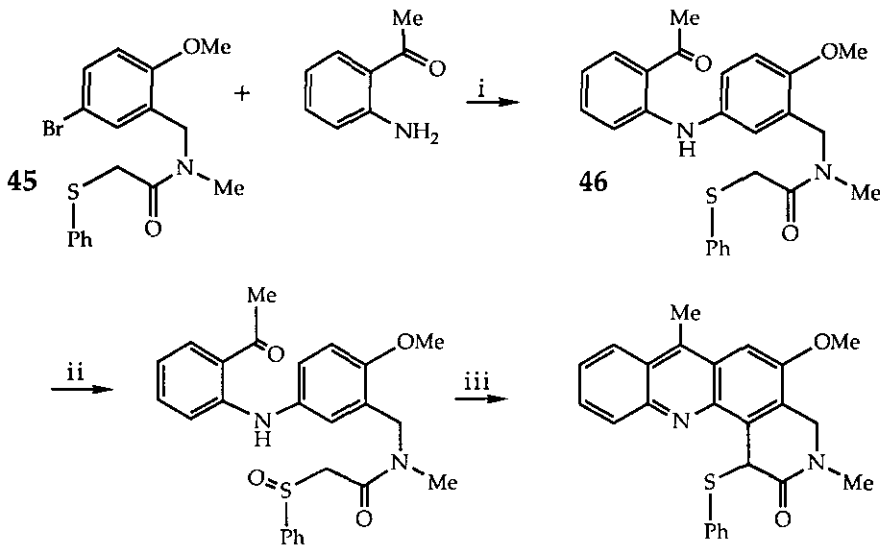
In a manner similar to that described above for 5-aminoquinoline, β-naphthol combines (Scheme 28) with paraformaldehyde and 5-aminoisoquinolines giving naphthaleno[1,8]phenanthrolines (**44**, R=H or Me).[41]



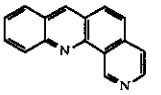
Scheme 28 Reagent : i, paraformaldehyde, 250°C (40%), ii, Ph_2O, reflux (68%).

In a variation of this approach, the Mannich base derived from β-naphthol was used.[48]

In work (Scheme 29) relevant to the development of pyridone-fused acridines of the type found in amphimedine, coupling of 2-aminoacetophenone with **45** gave **46**, then double cyclisation was achieved in one pot, in which one of the closures involved a Pummerer process.[49]

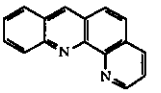


Scheme 29 Reagents : i, Na_2CO_3, Cu (cat.), $PhNO_2$, reflux (68%); ii, MCPBA, CH_2Cl_2, 0°C → room temperature (87%); iii, c. H_2SO_4, AcOH, 130°C (79%).



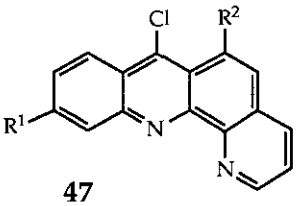
Benzo[*b*][1,9]phenanthroline (Pyrido[4,3-*c*]acridine)

There are no reported examples of this ring system, either natural or synthetic.



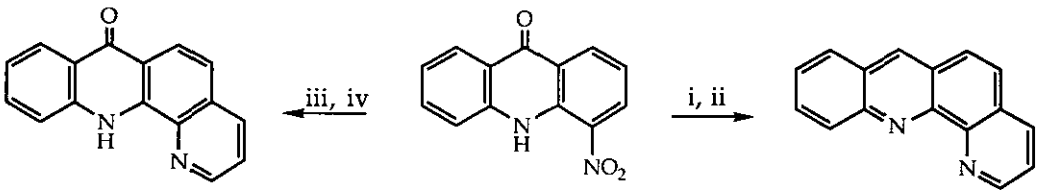
Benzo[*b*][1,10]phenanthroline (Pyrido[3,2-*c*]acridine)

The chloro compounds (**47**, R^1=H or Cl and R^2=H or F or OMe) were prepared by routes totally analogous to those shown in Scheme 11, but starting with an 8-aminoquinoline as the amine component.[30,40,44,47,50-54]



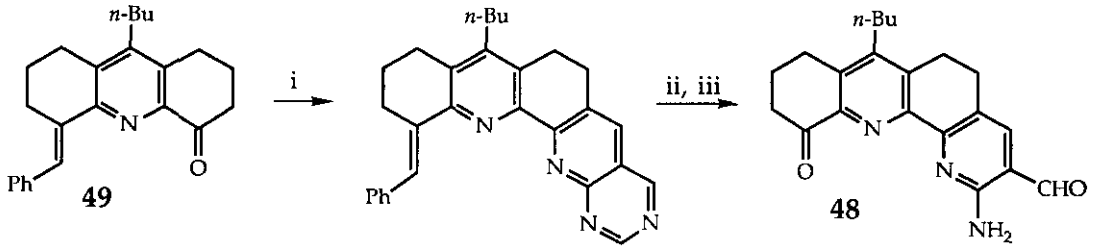
47

Skraup cyclisations (Scheme 30) were successful with 4-aminoacridine and with 4-aminoacridin-9-one.[54]



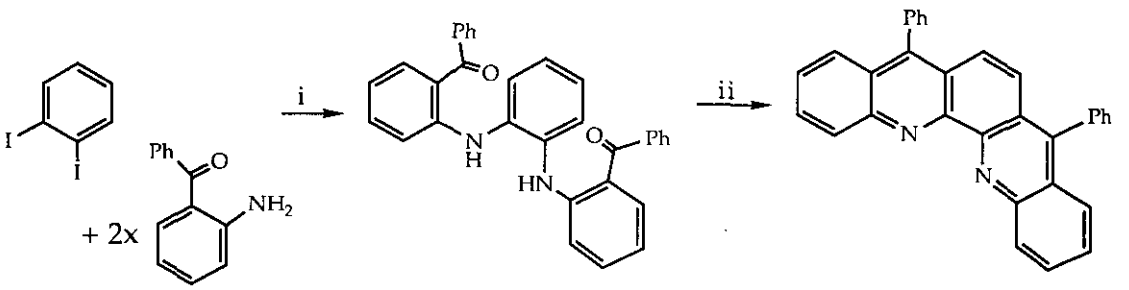
Scheme 30 Reagents : i, Na-Hg, EtOH, H_2O, $NaHCO_3$ reflux (45%); ii, H_2C=CHCHO, $H_3AsO_4.0.5H_2O$, H_3PO_4, 100°C (55%); iii, $SnCl_2$, c. HCl, heat (76%); iv, $HOCH_2CH(OH)CH_2OH$, $H_3AsO_4.0.5H_2O$, H_2SO_4, 100°C (53%)

The amino-aldehyde (**48**) was prepared by condensation of 4-aminopyrimidine-5-carboxaldehyde with ketone (**49**) followed by release of the required functional groups by hydrolysis of the pyrimidine unit; the ketone and the *ortho*-amino-aldehyde groups were then utilised to add two more pyridine rings.[55]



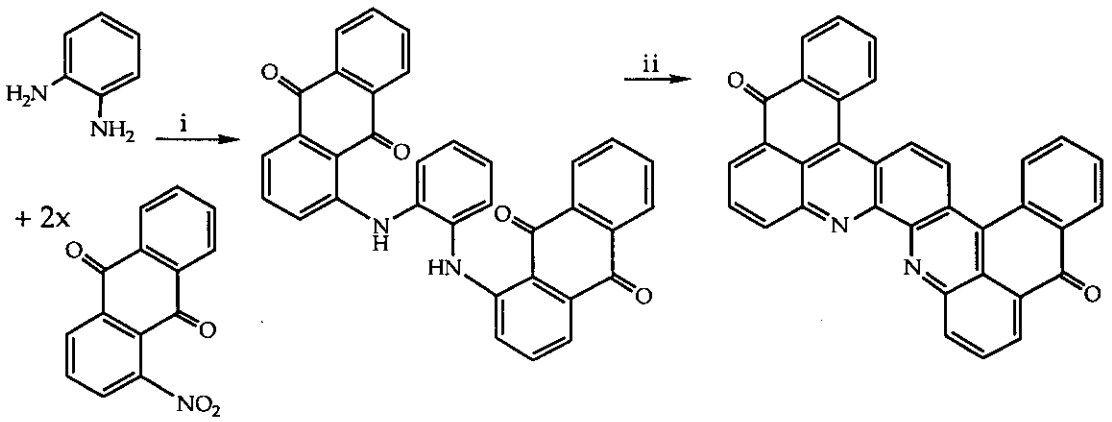
Scheme 31 Reagents : i, 4-aminopyrimidine-5-carboxaldehyde, KOH, MeOH, reflux (93%); ii, 2N HCl, reflux (97%); ii, O_3, MeOH, CH_2Cl_2, -78°C then Me_2S (100%, 2 steps)

2-Aminobenzophenone and 1,2-diiodobenzene underwent a double Ullmann-amine coupling and now, in contrast to the isomeric *para* situation, double ring closure could be brought about (Scheme 32) with strong acid.[33]



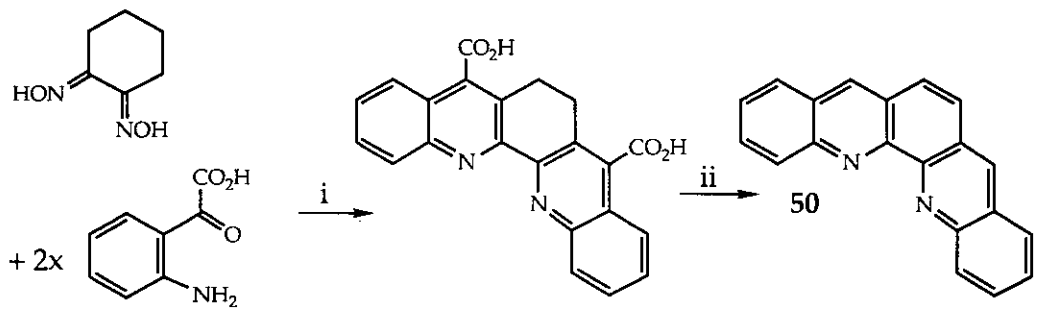
Scheme 32 Reagents : i, K_2CO_3, Cu, *n*-Bu_2O, reflux (67%); ii, H_2SO_4, AcOH, (48%).

In a search for dyestuffs, each of the phenylenediamines was reacted with 1-nitroanthraquinone and 1-amino-4-chloroanthraquinone as Ullmann partners, and the resulting bisquinone cyclised with acid.[56] No details of structure are given, so that the direction of cyclisation of the *meta*- and *para*-phenylenediamines is not described; the *ortho*-isomer can of course close in only one way, and it is the cyclisation of the product of condensation of this isomer with the former quinone which is shown in Scheme 33.



Scheme 33 Reagents : i, Na_2CO_3, Cu bronze, $PhNO_2$; ii, c. 70% H_2SO_4, 160°C (73%).

The final step in the synthesis of **50** involves high temperature decarboxylation with concomitant dehydrogenation (Scheme 34); the skeleton was built up using two quinoline-type synthesies, the *ortho*-aminocarbonyl component being hydrolysed isatin and the other component cyclohexane-1,2-dione dioxime.[57]



Scheme 34 Reagents : i, H_2O, 108°C (22%); ii, paraffin oil, N_2, 320°C (93%).

ACKNOWLEDGEMENT

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