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Heterocycle-Fused Acridines

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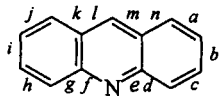
I. Introduction

This review covers the following groups of heterocycle-fused acridines: pyridoacridines, pyranoacridines, pyrroloacridines, thienoacridines, and furoacridines.

Heterocycle-fused acridines possess a variety of biological activities, including Ca^{2+} releasing, antiviral (e.g., anti-HIV), antimicrobial (e.g., antiamebic and antiplasmodium) and antitumor properties. They are also enzyme inhibitors (e.g., topoisomerase II inhibitors and protein tyrosine kinase inhibitors) and have DNA-intercalation and metal-chelating properties.

II. Pyridoacridines

Depending on the ring fusion, pyridoacridines can be classified into the following main classes: pyrido[*a*]acridines (benzo[*j*]phenanthrolines), pyrido[*b*]acridines, pyrido[*c*]acridines (benzo[*b*]phenanthrolines), and pyrido[*kl*]acridines (dibenzo[*f,ij*][2,7]naphthyridines).

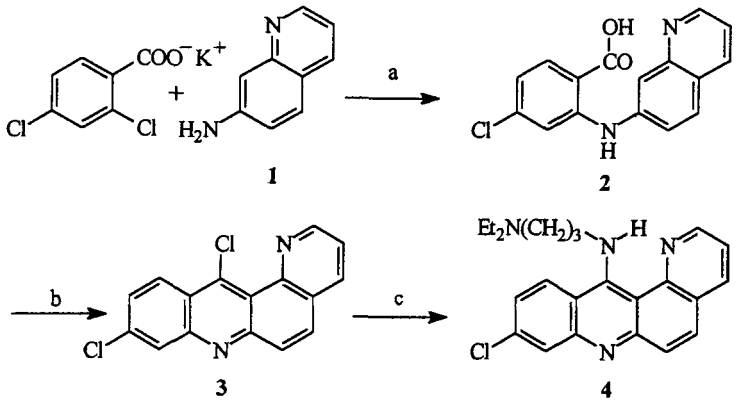


A. Pyrido[*a*]acridines (Benzo[*j*]phenanthrolines)

The pyridine ring is fused at bond *a* of the acridine. Depending on the position of the nitrogen in the fused pyridine ring, four different types of pyrido[*a*]acridines are possible.

1. *Pyrido[2,3-a]acridines (Benzo[j][1,7]phenanthrolines)*

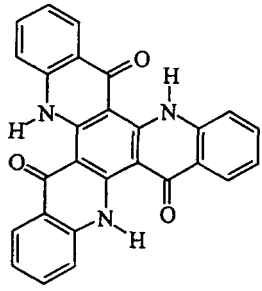
Dobson *et al.* (48JCS123) constructed this ring system by using the Ullmann-amine coupling reaction between 7-aminoquinoline **1** and potassium 2,4-dichlorobenzoate, followed by cyclization of the resultant diaryl-



SCHEME 1. (a) Cu bronze, amyl alcohol, 150°C, 6 h; (b) $POCl_3/PCl_5$, 150°C, 6 h; (c) diethylaminopropylamine, phenol, 100°C, 2 h.

amine **2** with a mixture of $POCl_3$ and PCl_5 (Scheme 1). The pyridoacridine **3** was then converted to a potential antimalarial compound **4,** but poor activity was observed.

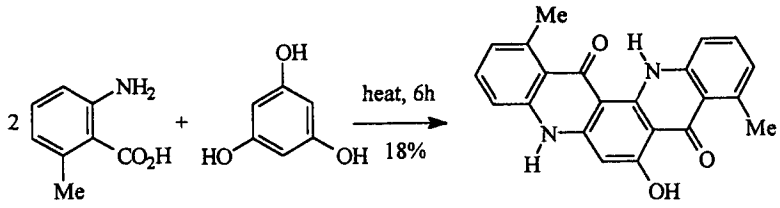
Gordon *et al.* (90MI1) obtained a triquinobenzene **5** from a two-step reaction between 1,3,5-tribromobenzene and anthranilic acid. The reaction involved three Ullmann-amine couplings followed by intramolecular acylations.



5

Reisch *et al.* (93JHC1469) obtained quino[*a*]acridone **6** as the main product from the condensation of phloroglucinol and 6-methylanthranilic acid (Scheme 2). The synthesis of similar quino[*a*]acridones from phloroglucinol and anthranilic acids has been reported in patents (35FRP771486).

The condensation product **7** of *m*-phenylenediamine and 2-formylcyclohexanone, on treatment with polyphosphoric acid (PPA), gave the octahydrobenzophenanthroline **8,** which, on dehydrogenation, afforded



6

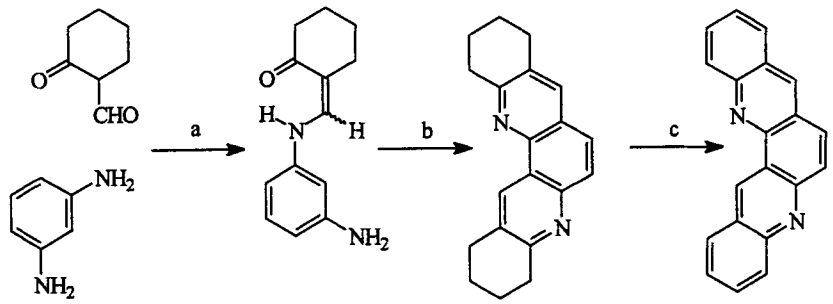
SCHEME 2

quino[*a*]acridine **9** (Scheme 3) (74IJC1230). A rearrangement prior to cyclodehydration is involved. The synthesis of similar compounds from 1,3-diiodobenzene and 2-acylanilines, using the Ullmann-amine coupling reaction followed by cyclization, has been reported by Hellwinkel and Ittemann (85LA1501).

In an attempted reaction toward a pyrido[2,3,4-*kl*]acridine, Gellerman *et al.* (92TL5577) isolated a pyrido[2,3-*a*]acridine **11** from an acid-catalyzed reaction between 1-amino-4-methylacridin-9(10*H*)one **10** and acetylacetone (Scheme 4).

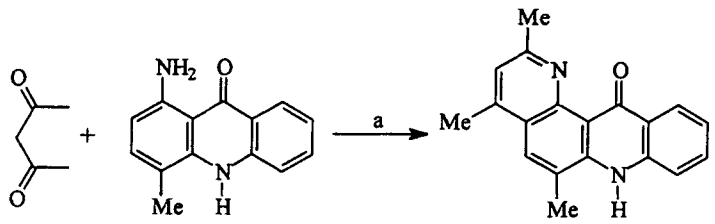
2. *Pyrido[3,2-a]acridines (Benzo[j][4,7]phenanthrolines)*

12-Chloropyrido[3,2-*a*]acridines **12** were prepared by the route described in Scheme 1, but with 6-aminoquinolines instead of 7-aminoquinoline (46JCS151; 47JCS678). The chloroderivatives **12** were then converted to potent antimalarial agents with dialkylaminoalkylamines or alkylaminoalkylamines in phenol at 100°C.



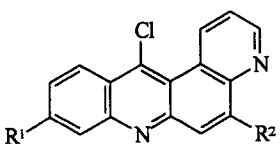
7 8 9

SCHEME 3. (a) EtOH, rt, 65%; (b) PPA, 160–170°C, 2 h, 40%; (c) Se, 300°C, 6 h, 58%.



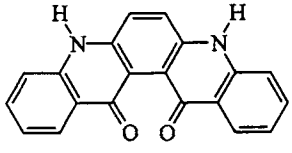
10 **11**

SCHEME 4. (a) AmOH, H^+, 130°C, 1.5 h, 40%.



R^1 = H, Cl R^2 = H, Cl, Me

12



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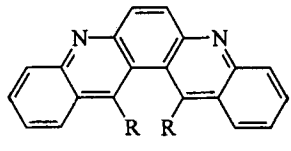
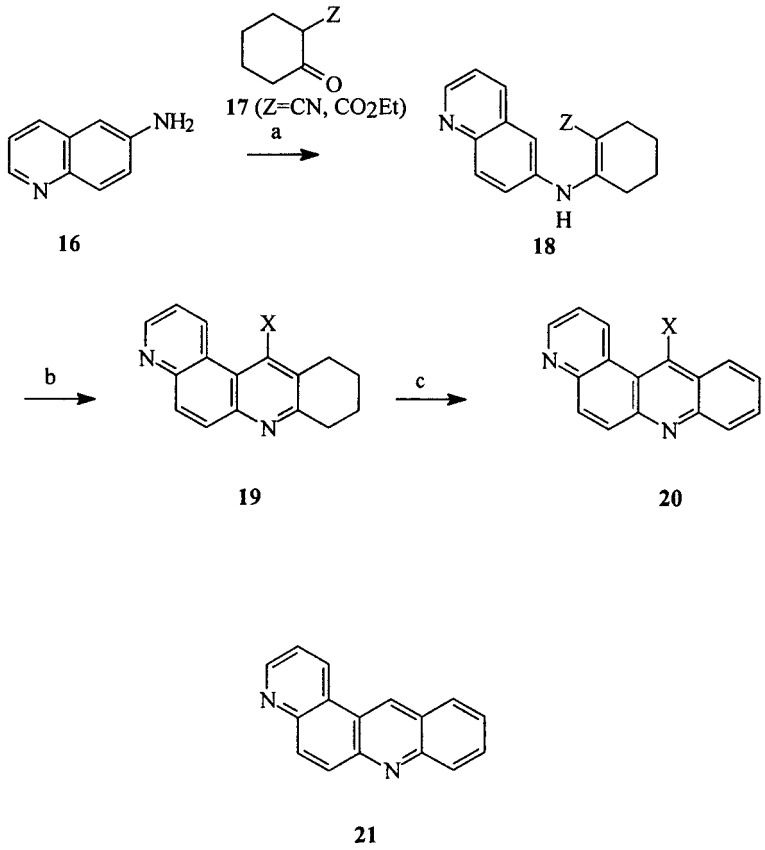


14 R=Me

15 R=H

The double Ullmann-amine coupling of *p*-phenylenediamine with 2-chlorobenzoic acid followed by two acid-catalyzed Friedel–Crafts acylations afforded quino[3,2-*a*]acridone **13** (52JCS1874). A similar regioselectivity was observed when 1,4-diiodobenzene was coupled with aminoacetophenone and the resultant diketone was treated with H_2SO_4 to give quino[3,2-*a*]acridine **14** (85LA501). The quino[3,2-*a*]acridine **15** was obtained after dehydrogenation of the minor product from *p*-phenylenediamine and 2-formylcyclohexanone (see Section II,B,1 on pyrido[2,3-*b*]acridines) (74IJC1324).

We have prepared pyrido[3,2-*a*]acridines, **20** and **21** (96TH1), by Lewis acid-catalyzed cyclization of enamines **18,** formed by the condensation of 6-aminoquinoline **16** with 2-cyano- **17a** (Z = CN) or 2-ethoxycarbonylcyclohexanone **17b** (Z = CO_2Et), to give the tetrahydropyrido[2,3-*a*]acridines **19.** Oxidation of these tetrahydro derivatives, with palladium on charcoal, gave the fully aromatic systems **20** (Scheme 5). Oxidation of the amino derivative **19a** also resulted in the formation of some of the deaminated product **21.**

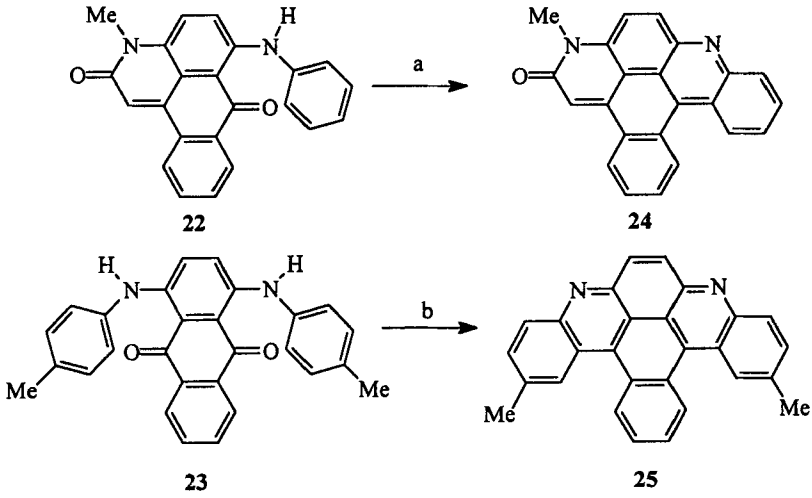


SCHEME 5. **a** X = NH_2, **b** X = OH. (a) $PhCH_3$, reflux; (b) $AlCl_3$, 190°C; (c) Pd-on-C, 270–300°C.

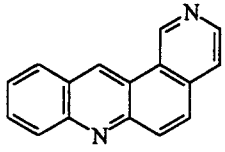
The synthesis of some hexa- and heptacyclic molecules **24** and **25** containing a pyrido[3,2-*a*]acridine nucleus has been reported, the principal step being the ring closure of anthraquinone-derived precursors **22** and **23** (Scheme 6) (84KGS962).

3. *Pyrido[3,4-a]acridines (Benzo[j][2,7]phenanthrolines)*

No natural or synthetic compounds based on this ring system **26** have been reported.



SCHEME 6. (a) PPA, 170°C, 96%; (b) PPA, 180°C, 79%.



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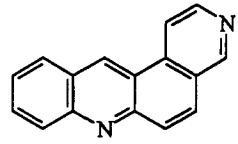


27

4. *Pyrido[4,3-a]acridines (Benzo[j][3,7]phenanthrolines)*

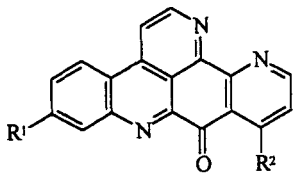
No natural or synthetic compounds based on this ring system **27** have been reported.

B. PYRIDO[*b*]ACRIDINES

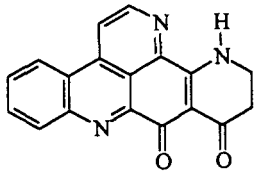
The auxiliary pyridine ring is fused at bond *b* of the acridine nucleus in this class of pyridoacridines and, depending on the position of nitrogen in the auxiliary pyridine, four different types of pyrido[*b*]acridines are possible.

1. *Pyrido[2,3-b]acridines*

This ring system can be seen in the pentacyclic alkaloids: ascididemin **28,** 2-bromoleptoclinidone **29,** 11-hydroxyascididemin **30,** 8,9-dihydro-11-hydroxyascididemin **31,** calliactine **32,** the heptacyclic eilatin **33,** and the octacyclic biemnadin **34.** (See Section II,D,1 on pyrido[2,3,4-*kl*]acridines.)



28 $R^1 = R^2 = H$
29 $R^1 = Br, R^2 = H$
30 $R^1 = H, R^2 = Br$



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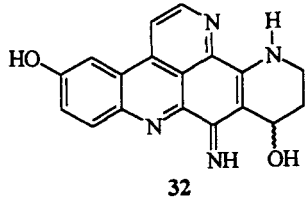

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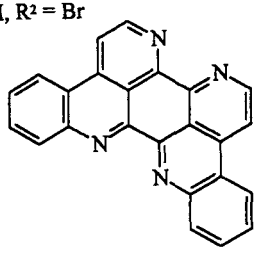

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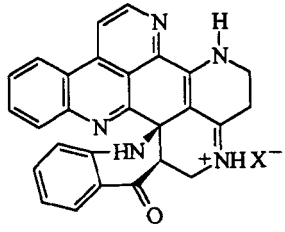
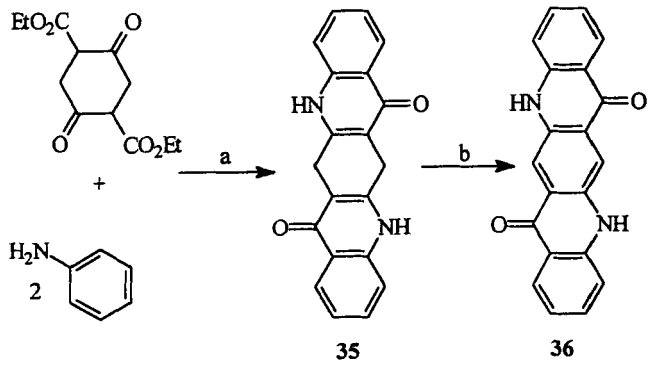


34

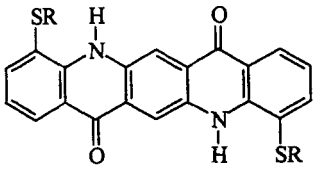
The organic pigments, the linear-*trans*-quinacridones, such as **36,** also possess this ring system. These quinacridones can be used in printing ink and as a colorant for plastics (67CRV1). They also exhibit photovoltaic and photoconductive properties (84CL1305; 87CL609). A large number of quinacridones have been synthesized. The synthetic methods have been reviewed by Labana and Labana (67CRV1). The most useful method involves the dehydrogenation of dihydroquinones, such as **35,** prepared from diethyl 2,5-dioxo-1,4-cyclohexanedicarboxylate and anilines (Scheme 7).

Some soluble quinacridones **37** have been prepared by applying this strategy (92JHC167). The introduction of long alkylthio groups into the 4 and 11 positions weakened the intermolecular hydrogen bonding and increased the solubility in different solvents. Diethyl 2,5-dioxo-1,4-cyclohexanedicarboxylate, on acid-catalyzed condensation with 2-aminobenzophenone followed by dehydrogenation with chloranil, afforded quinacridine **38** (88JHC1063).



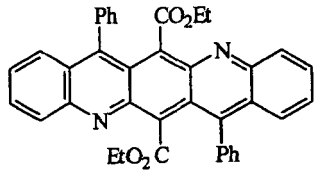
35 36

SCHEME 7. (a) Heat; (b) e.g., chloranil.



$R = C_6H_{13}, C_8H_{17}, C_{10}H_{21}, C_{12}H_{25}$

37



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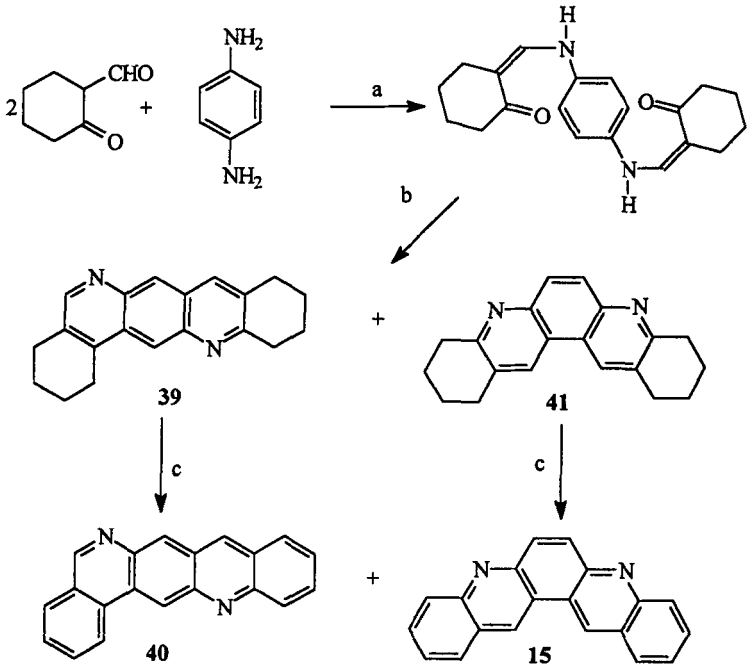
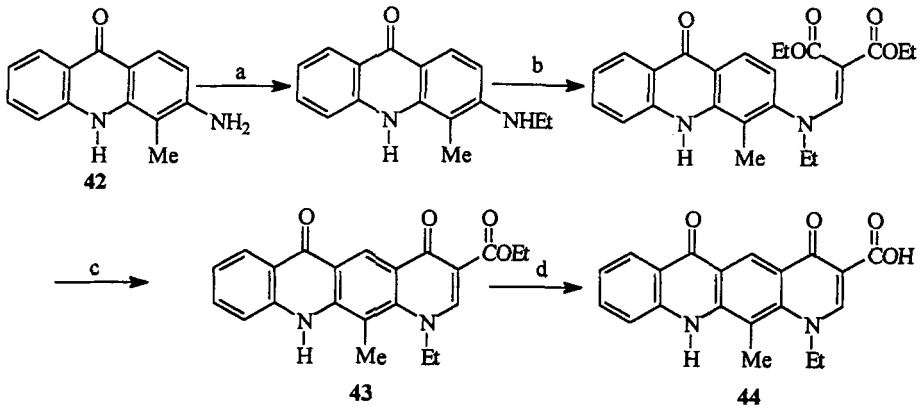
The synthesis of isoquino[3,4-*b*]acridine **40** from the interaction of *p*-phenylenediamine with 2-formylcyclohexanone, followed by ring closure (after *in situ* rearrangement) and then dehydrogenation of **39,** has been reported by Berde *et al.* (72IJC332). Further examination of the cyclodehydration reaction also gave octahydroquino[3,2-*a*]acridine **41** as the minor product, which was then dehydrogenated to provide quino[3,2-*a*]acridine **15** (Scheme 8) (74IJC1324).

2. *Pyrido[3,2-b]acridines*

Morton *et al.* (93H2757) have described a synthesis of pyrido[3,2-*b*]acridones **43** and **44** starting from 3-amino-4-methylacridin-9(10*H*)one **42** (Scheme 9). Both compounds were found to be inactive against cultured



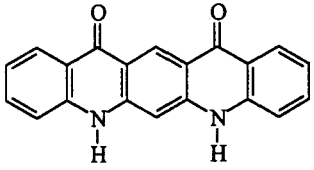
SCHEME 8. (a) EtOH, rt, 77%; (b) PPA, 180°C, 3 h, 51% (**39**), 14% (**41**); (c) Se, 300–330°C, 5–10 h, 25% (**40**), 38% (**15**).



SCHEME 9. (a) $NaBH_4$, AcOH, 10 h, 75%; (b) $EtOCH{=}C(CO_2Et)_2$, 155–160°C, 1.5 h,; (c) PPE, 120–125°C, 1.5 h, 72% (b,c); (d) NaOH, EtOH, 2 h, 67.5%.

L1210 cells at concentrations up to 10 μM and showed negligible antibacterial activity.

The acid-catalyzed conversion of *N,N'*-bis(2'-carboxyphenyl)-1,3-diaminobenzene to quino[3,2-*b*]acridone **45** has been described in a patent (64USP3124581). Kumar and Jain [79IJC(B)623] have reported the synthesis of the octahydroquinolino[*b*]quinoline **46** from the base-catalyzed condensation of *N*-benzoyldecahydroquinolin-7-one with 2-aminobenzaldehyde.



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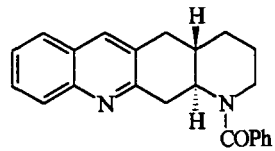

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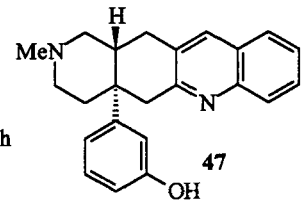


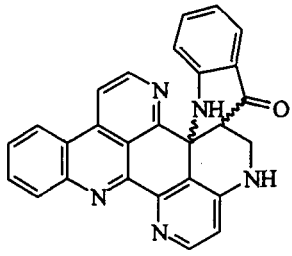
47

3. *Pyrido[3,4-b]acridines*

The synthesis of decahydropyrido[3,4-*b*]acridine **47,** by a Friedländer reaction, and its opioid-antagonistic activity (IC_{50} = 54 nM) has been claimed [92JAP(K)92/275288].

4. *Pyrido[4,3-b]acridines*

Pyridoacidine alkaloids, eudistone A **48** and B **49,** possess this ring as a part of their structures (see pyrido[2,3,4-*kl*]acridines).



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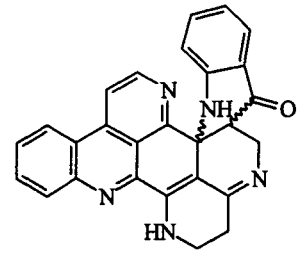

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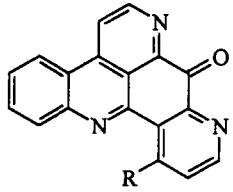
C. Pyrido[*c*]acridines (Benzo[*b*]phenanthrolines)

The auxiliary pyridine is fused at bond *c* of the acridine nucleus. Depending upon the position of the nitrogen in the auxiliary pyridine ring, four different types of pyrido[*c*]acridine are possible.

1. *Pyrido[2,3-c]acridines (Benzo[b][1,7]phenanthrolines)*

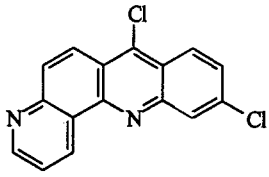
Among the pyridoacridine alkaloids, meridine **50** and cystodamine **51** exhibit this ring skeleton (see Section II,D,1 on pyrido[2,3,4-*kl*]acridines). This ring pattern can also be observed in quino[*a*]acridines **6** and **9** and triquinobenzene **5** (see Section II,A,1 on pyrido[2,3-*a*]acridines).



50 R = OH

51 R = NH_2

In search of potential anti-malarial agents, Dobson *et al.* (48JCS123) prepared 7,10-dichlorobenzo[*b*][1,7]phenanthroline **52** by the route described in Scheme 1, but with 5-aminoquinoline **48** as a precursor of 7-diethylaminopropylamino-10-chlorobenzo[*b*][1,7]phenanthroline **53.** No significant activity was observed when compound **53** was tested against *Plasmodium gallinaceum* (*in vivo*).



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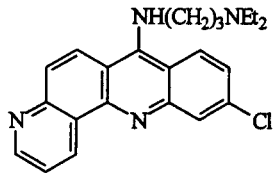
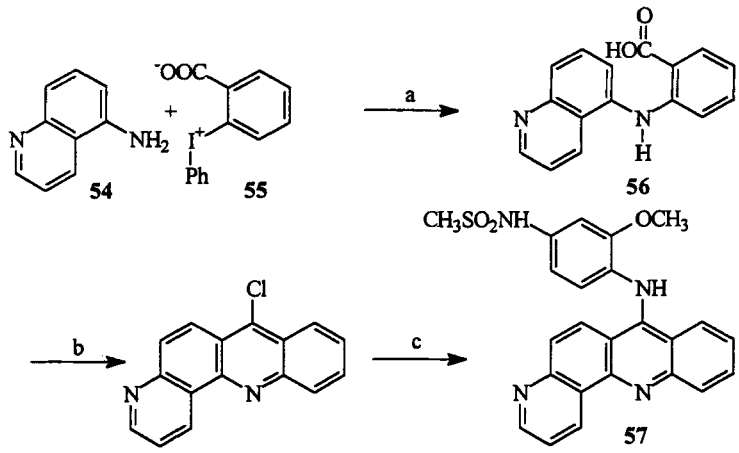


53

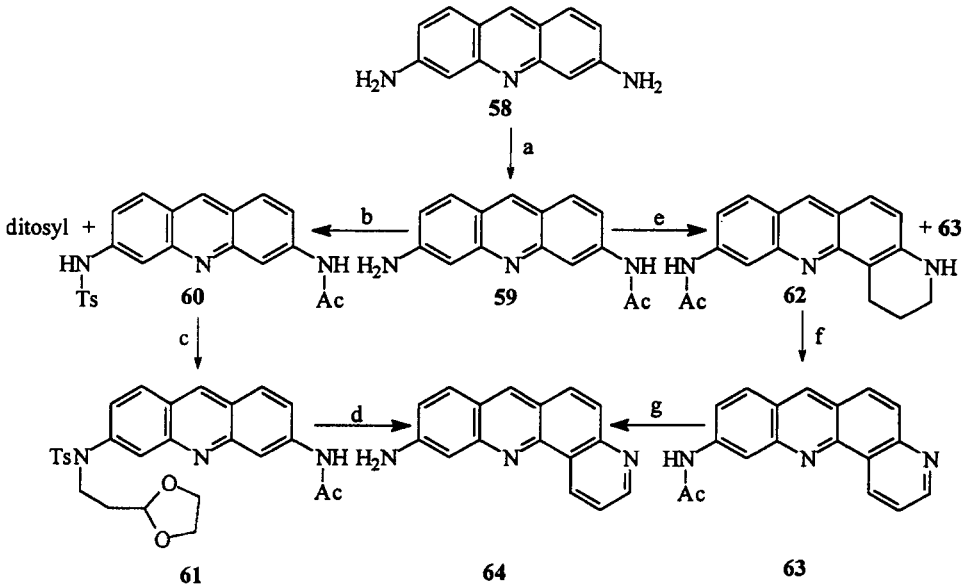
The coupling reaction between 5-aminoquinoline **54** and 2-chlorobenzoic acid gave a very poor yield (5%) of quinolylanthranilic acid **56.** With diphenyliodonium-2-carboxylate **55,** the yield increased to 80%. Quinolylanthranilic acid **56** was then converted to the sulfonamide **57** after cyclization with $POCl_3$ (Scheme 10) (87MI1). The sulfonamide **57** showed negligible activity against L1210 leukemia cells in culture, against P388 leukemia *in vivo,* and against the Lewis lung solid tumor.

Wardani and Lhomme (93TL6411) reported two routes for the synthesis of 10-aminobenzo[*b*][1,7]phenanthroline **64** from 3,6-diaminoacridine (proflavine) **58.** In first route the proflavine **58** was monoacylated to give **59.** Activation of the free amino group was achieved by tosylation. Alkylation of the monoacetyl monotosyl proflavine **60** with 3-bromopropionaldehyde ethylene acetal gave the intermediate **61.** Acidic treatment afforded 10-aminobenzo[*b*][1,7]phenanthroline **64** in an 18% overall yield starting from



SCHEME 10. (a) Cu^{2+} $(CH_3COO^-)_2$, *N*-methylpyrrolidone, 95°C, 12 h, 80%; (b) $POCl_3$, Δ; (c) 4-amino-3-methoxymethanesulfonanilide, H^+, MeOH.

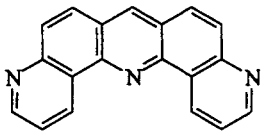
proflavine **58** (Scheme 11). The second route involves the Skraup cyclization. The monoacylated proflavine **59** was reacted with acrolein diethyl acetal in refluxing acetic acid. The resultant mixture of **62** and **63** was treated



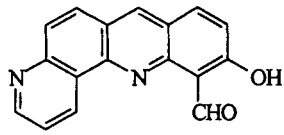
SCHEME 11. (a) Ac_2O, $EtCO_2H$, 20°C, 10 h, 83%; (b) TsCl, pyridine, Et_3N, 4°C, 10 h, 65% (**60**); (c) DMF, K_2CO_3, $BrCH_2CH_2CH(OCH_2)_2$, 80°C, 3 h, 72%; (d) H_2SO_4, 1 h, 40%; (e) AcOH, $CH_2{=}CHCH_2CH(OC_2H_5)_2$, reflux, 3 h; (f) DDQ, AcOH, 100°C, 15 min.; (g) 4 *M* HCl, 80°C, 1 h, 40% (e,f,g).

with DDQ in acetic acid to afford **63** as the sole product. Deprotection with 4 *M* HCl produced 10-aminobenzo[*b*][1,7]phenanthroline **64** (Scheme 11). The Skraup synthesis of dipyridoacridine **65** from proflavine **58** has also been reported [67JCS(C)1415].

The synthesis of a number of benzo[*b*][1,7]phenanthroline anticancer agents from 10-aminobenzo[*b*][1,7]phenanothroline **64** has been claimed (91MIP1). Thus, 11-formyl-10-hydroxybenzo[*b*][1,7]phenanthroline **66** exhibited cytotoxicity, with an IC_{50} of 6.5 μM, against L1210 leukemia cells.



65

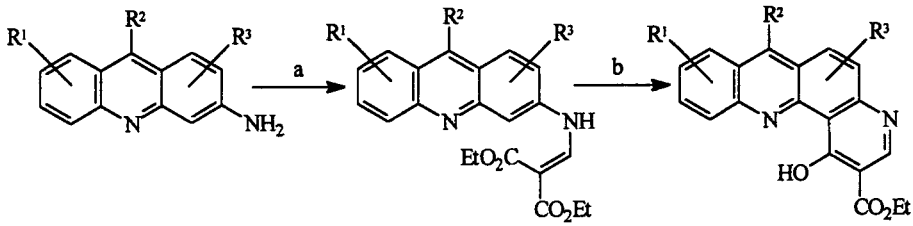


66

A large number of 1-hydroxy-2-ethoxycarbonylbenzo[*b*][1,7]phenanthrolines **68** have been synthesized from 3-aminoacridines **67** by using the route shown in Scheme 12, and potent antimicrobial activities and low toxicities have been claimed (78USP4060527).

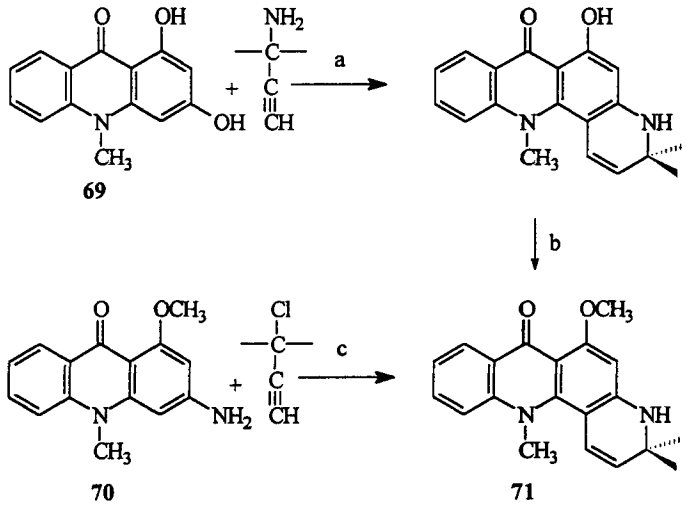
Reisch *et al.* (93JHC981) described two different methods for the synthesis of 4-azaacronycine **71.** One method involves the fusion of 1,3-dihydroxy-10-methyl-9(10*H*)-acridone **69** with 3-amino-3-methylbut-1-yne in the presence of $CuCl_2$ in a closed ampule, followed by methylation (Scheme 13). The second method involves the *N*-alkylation of 3-amino-1-methoxy-10-methyl-9(10*H*)-acridone **70** with 3-chloro-3-methylbut-1-yne, followed by *in situ* cyclization (Scheme 13).

We prepared a range of pyrido[2,3-*c*]acridines **74** by the base- or acid-catalyzed cyclization of the corresponding enamines **72,** followed by



67 **68**

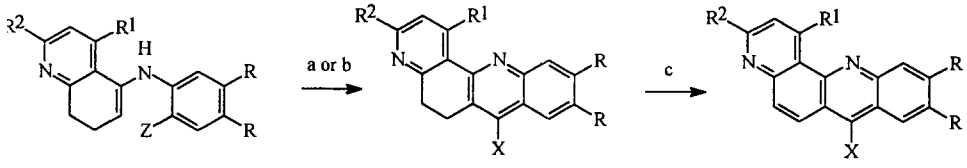
SCHEME 12. R^1, R^2, R^3 = H, alkyl, aryl, alkylamino, alkylthio, nitro, cyano, alkylsulfonyl, etc. (a) $EtOCH{=}C(CO_2Et)_2$, Δ; (b) Ph_2O, 260°C.



SCHEME 13. (a) $CuCl_2$, heat, closed ampule; (b) methylation, 10% (a,b); (c) DMF, K_2CO_3, KI, 120°C, 8 h, N_2, 20%.

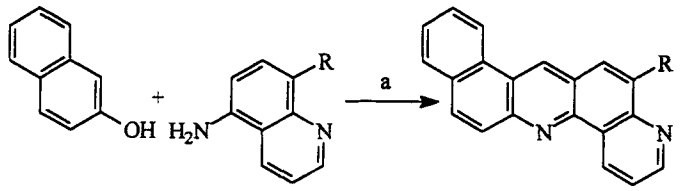
oxidation of the dihydro derivatives **73** (Scheme 14) (96TH1). The aminopyrido[2,3-*c*]acridine **74a** was tested for the inhibition of the spontaneous proliferation of a human gastric carcinoma cell line, MKN 45, and had an $IC_{50} < 1$ μmol dm^{-3}, but was noncytotoxic (95BRP9425409, 95MIP1).

Buu-Hoï [67JCS(C)213] used a quite different method for the construction of the benzo[*b*][1,7]phenanthroline ring system. Condensation of 2-naphthol with 5-aminoquinolines **75** and paraformaldehyde generated naphthaleno[*b*][1,7]-phenanthrolines **76** (Scheme 15).



72 (Z=CN, CO_2Et) **73** (X=NH_2, OH) **74** (X=NH_2, OH)

SCHEME 14. R = H or OMe, R^1 = H or OH, R^2 = H or OH. (a) $NaNH_2$, DME, reflux, 3 h; (b) H_3PO_4, 150–160°C; (c) MnO_2, DMF, reflux.

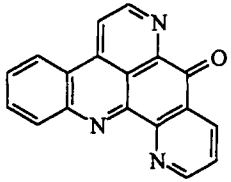


75 76

SCHEME 15. (a) Paraformaldehyde, 250°C, 17% (R = H), 43% (R = Me).

2. *Pyrido[3,2-c]acridines (Benzo[b][1,10]phenanthrolines)*

Eilatin **33** and eudistone A **48** and B **49** are pyridoacridine alkaloids that possess this ring skeleton. This ring system is also found in a synthetic isomer, isoascidemin **77,** of ascididemin **28** (see pyrido[*b*]acridines and pyrido[2,3,4-*kl*]acridines). Three other alkaloids, the plakinidines (A–C) **78–80** from *Plakortis* sponge, also share this ring system (90JA1, 90TL3271).



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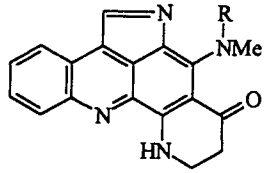
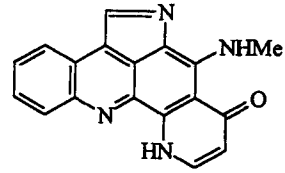


78 R = H

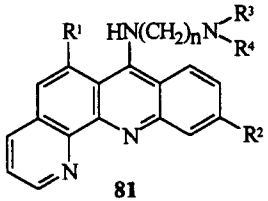
79 R = Me



80

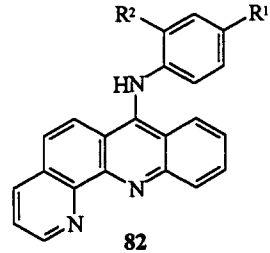
The synthesis of a number of 7-(mono and dialkylaminoalkylamino) derivatives **81** (46JCS151; 47JA1543; 62JMC546; 72JMC739), and 7-anilino derivatives **82** (87MI1; 93JPS262) of benzo[*b*][1,10]phenanthrolines by the route described in Scheme 1, but using 8-aminoquinolines instead of 7-aminoquinoline, and their biological evaluation has been reported. Benzo[*b*][1,10]phenanthrolin-7-ones **83** were also separated during these syntheses. Some of the alkylamino derivatives **81** were found to be highly effective against ascites tumors at low dosage (72JMC739). The anilino derivatives **82** were found to be active against L1210 murine leukemia (93JPS262), P388 leukemia cells (87MI1), and a Lewis lung solid tumor (87MI1). Using the same strategy, Wilkinson and Finar (48JCS288) have prepared some 7-aminobenzo[*b*][1,10]phenanthrolines **84** and related compounds. None of the amino derivatives showed significant antibacterial or

trypanocidal activity. The same route was used to prepare 7-dimethylaminopropylthiobenzo[*b*][1,10]phenanthroline **85** as a potential platelet aggregation inhibitor (72JMC61). No significant activity was observed.



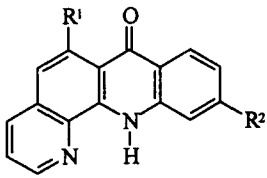
81

R^1 = H, OMe; R^2 = H, Cl
R^3 = H, alkyl, chloroalkyl, *etc.*
R^4 = alkyl, chloroalkyl, *etc.*



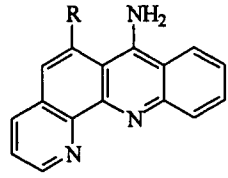
82

R^1 = H, Me_2N, $MeSO_2NH$, $PhSO_2NH$
R^2 = H, MeO, MeNH, Me_2N



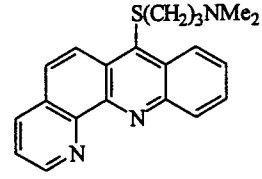
R^1 = H, MeO; R^2 =H, Cl

83



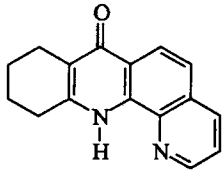
R = H, F, MeO

84



85

The synthesis and antileishmania activity of 8,9,10,11-tetrahydrobenzo[*b*][1,10]phenanthrolin-7(12*H*)-one **86** and 7-chloro-8,9,10,11-tetrahydrobenzo[*b*][1,10]phenanthroline **87** has been described by Satti *et al.* [93-IJC(B)978].



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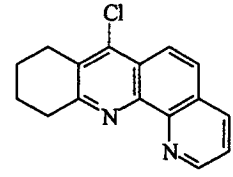
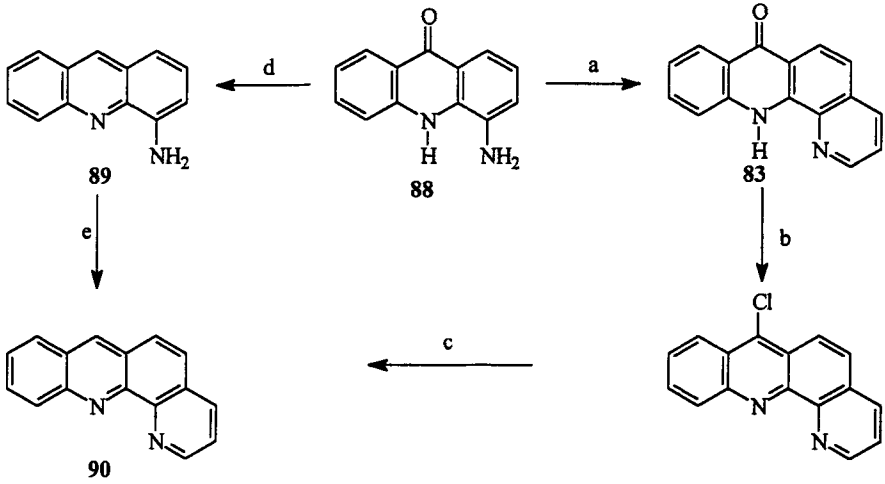


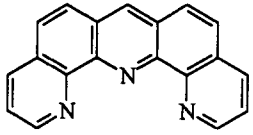
87

A quite different approach to the construction of the benzo[*b*][1,10]-phenanthroline ring system, for example, **90,** was used by Koft and Case

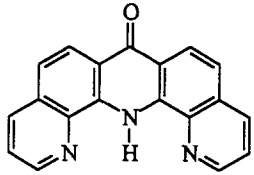


SCHEME 16. (a) $HOCH(CH_2OH)_2$, H_3AsO_4, H_2SO_4, H_2O, 130–140°C, 2.5 h, 53%; (b) $POCl_3/PCl_5$, reflux, 5 h, 81%; (c) 10% Pd on charcoal, H_2, EtOH, KOH, 3 h, 36%; (d) Na–Hg, EtOH, H_2O, $NaHCO_3$, 4–5 h, 47%; (e) $H_2C{=}CHCHO$, H_3AsO_4, H_3PO_4, 100–110°C, 1 h, 8.5%.

(62JOC865). They used 4-aminoacridone **88** and 4-aminoacridine **89** as the starting materials (Scheme 16). The Skraup synthesis was also applied to the preparation of quino[8,7-*b*][1,10]phenanthroline **91** and its 7-oxo derivative **92** (62JOC865).

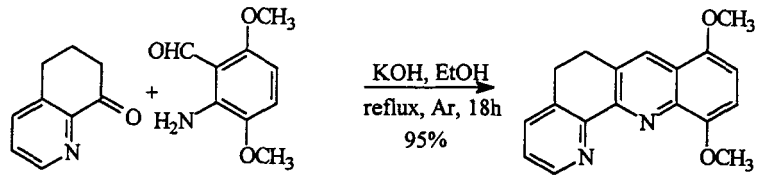


91



92

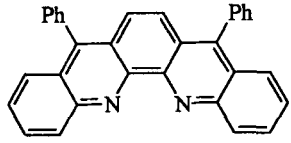
Condensation of 5,6-dihydroquinolin-8(7*H*)-ones, such as **93,** with 2-aminoaromatic aldehydes, such as **94,** afforded dihydrobenzo[*b*][1,10]phenanthrolines, such as **95** (Scheme 17), as precursors of a number of interesting compounds (88JA3673; 90AGE923; 93JOC1666). Condensation of 5,6-dihydroquinolin-8(7*H*)-one **93** with ternary iminium perchlorates, for example, **96,** in the presence of ammonium acetate has been reported to give compounds such as **97** that contain the benzo[*b*][1,10]phenanthroline ring system (Scheme 18) (93TL1775).



93 **94** **95**

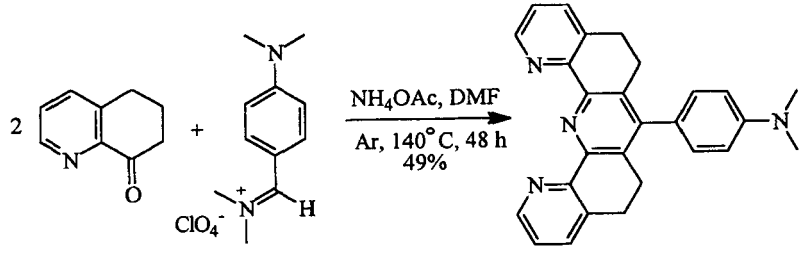
SCHEME 17

Cyclocondensation of 2-aminobenzoylformic acid **98** and cyclohexane-1,2-dione dioxime **99,** followed by decarboxylation with concomitant dehydrogenation of the diacid **100,** gave quino[3,2-*c*]acridine **101** (Scheme 19) (70JPR1105). The same skeleton **102** was obtained from the Ullmann-amine coupling reaction of 2-aminobenzophenone and 1,2-diiodobenzene, followed by ring closure (85LA1501).



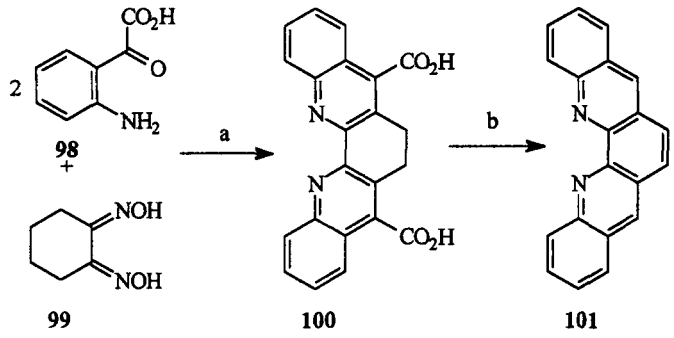
102

In a search for dyestuffs, *o*-phenylenediamine was reacted with 1-nitroanthraquinone and the resulting bisquinone **103** was cyclized with H_2SO_4 to give **104** (Scheme 20) (74MI1).



93 **96** **97**

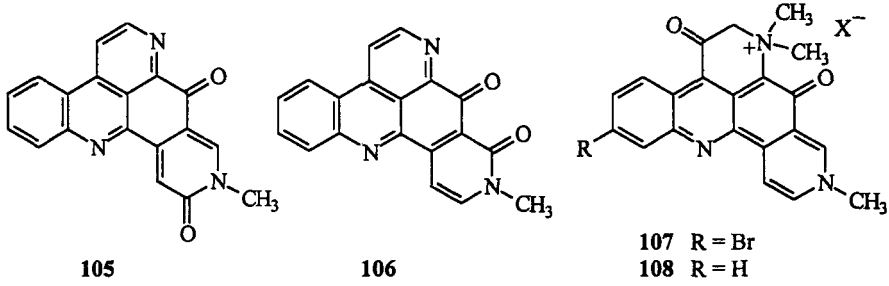
SCHEME 18

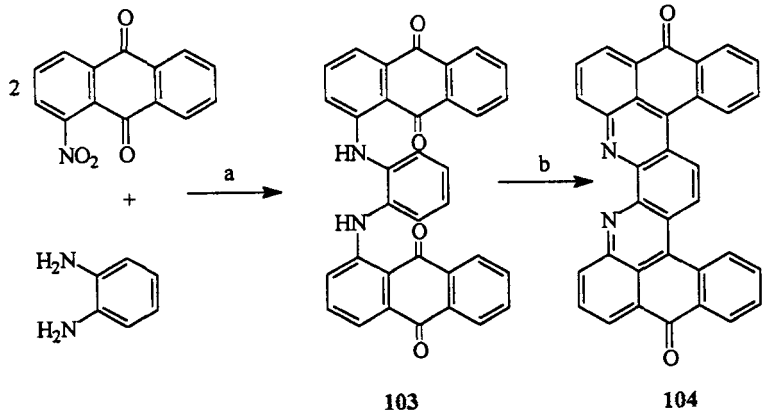


SCHEME 19. (a) H_2O, reflux, 22%; (b) paraffin oil, N_2, 320°C, 93%.

3. *Pyrido[3,4-c]acridines (Benzo[b][1,8]phenanthrolines)*

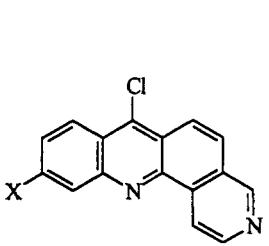
The pentacyclic pyridoacridine alkaloids (amphimedine **105,** neoamphimedine **106,** petrosamine **107,** and debromopetrosamine **108**) also contain this ring skeleton (see pyrido[2,3-4-*kl*]acridines).





SCHEME 20. (a) Na_2CO_3, Cu-bronze, $PhNO_2$; (b) 70% H_2SO_4, 160°C, 73% (a,b).

Elslager and Tendick (62JMC546) prepared 7-chloro[*b*][1,8]phenanthrolines **109,** via Ulllmann-amine coupling followed by cyclization, a route described in Scheme 1, but with 5-aminoisoquinoline, and converted them to potential amebicidal 7-(mono- and dialkylaminoalkylamino)benzo[*b*][1,-8]phenanthrolines **110.**



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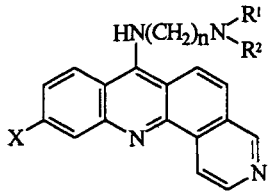

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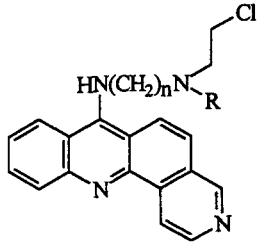
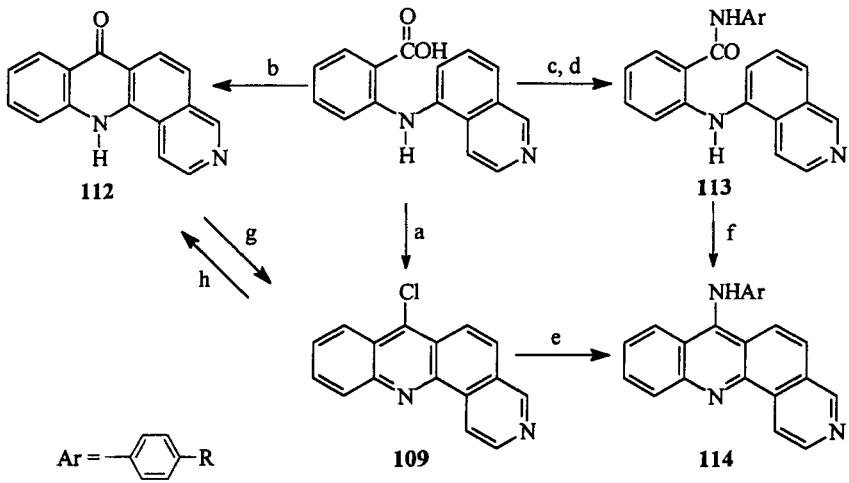


111

X = H, Cl; R^1 = H, alkyl; R^2 = alkyl

R = H, ethyl, chloroethyl

7-Chlorobenzo[*b*][1,8]phenanthroline **109** (X = H) was later used by Creech *et al.* (72JMC739) to prepare nitrogen mustard derivatives **111** of benzo[*b*][1,8]phenanthroline as antitumor agents, and by Sánchez *et al.* (90H2003) to prepare a series of 7-anilino derivatives of benzo[*b*][1,8]phenanthroline **114.** These anilino derivatives **114** were also prepared to cyclization of 2-(isoquinoline-5′-yl)benzanilides **113** with $POCl_3$ (Scheme 21)

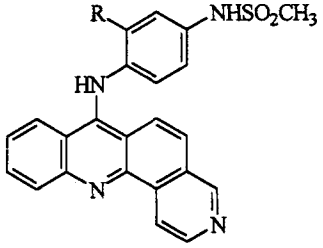


112 **113** **109** **114**

SCHEME 21. R = F, OMe, NMe_2, NHCOMe, SO_2Me, SO_2NH_2, $NHSO_2Ph$, $NHSO_2$-*p*-C_6H_4Me. (a) $POCl_3$, reflux, 39%; (b) H_2SO_4, heat, 60%; (c) PCl_5; (d) $ArNH_2$, EtOH, $MeSO_3H$; (e) ArNH, C_6H_6, moderate; (f) $POCl_3$, reflux, 42–62%, (c,d,f); (g) $POCl_3$, PCl_5; (h) H_3O^+.

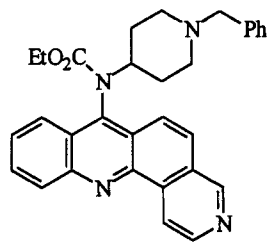
(90H2003). Biological evaluation of these anilino derivatives **114** along with 7-chlorobenzo[*b*][1,8]phenanthroline **109** (X = H) and benzo[*b*][1,8]-phenanthrolin-7(12*H*)-one **112** showed a tight binding tendency with DNA. Significant inhibition of L1210 murine leukemia cells by benzo[*b*]-[1,8]phenanthrolin-7(12*H*)-one **112** demonstrated that the anilino side chain was unnecessary for activity. No change in the activity was observed on substitution of electron-withdrawing or electron-donating substituents onto the aniline ring. 7-Chlorobenzo[*b*][1,8]phenanthroline **109** was found to be inactive (93JPS262).

Denny and Baguley (87MI1) used diphenyl iodonium-2-carboxylate **55** as an *N*-arylating agent in an Ullmann-amine coupling step, as described in Scheme 9, but with 5-aminoisoquinoline, and prepared some 7-anilino-benzo[*b*][1,8]phenanthrolines **115.** None of the anilino derivatives showed significant activity against the P388 leukemia and Lewis lung solid tumor, although they displayed tight binding with DNA. Another derivative **116** of benzo[*b*][1,8]phenanthroline was tested as an antinociceptive agent but was found to be inactive (91MI1).



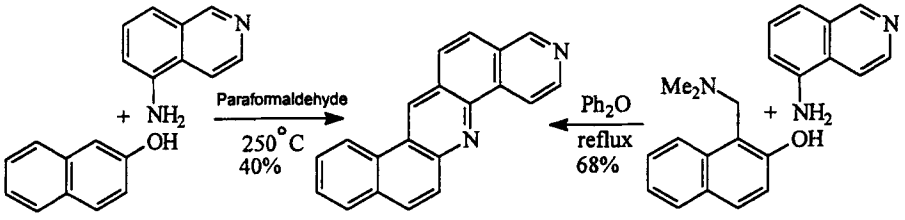
R = MeO, MeNH, Me_2N

115



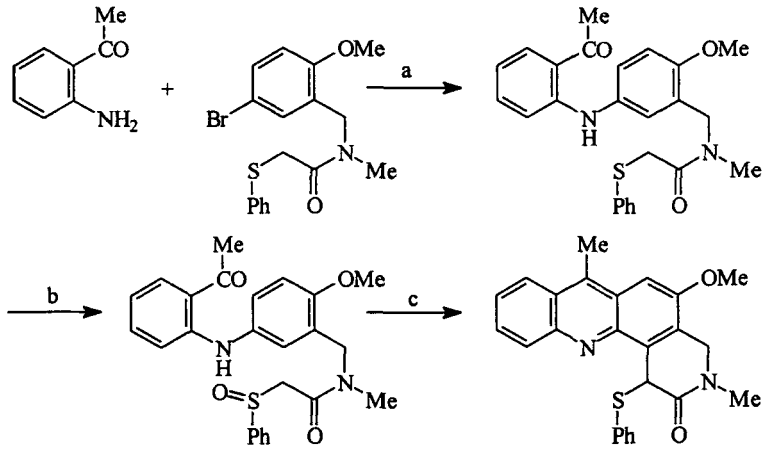
116

The Ullmann–Fetvadjian reaction has been applied to 5-aminoisoquinoline to prepare naphtho[2,1-*b*][1,8]phenanthrolines, such as **117** (Scheme 22) [67JCS(C)213; 80JCS(P1)1233].



117

SCHEME 22



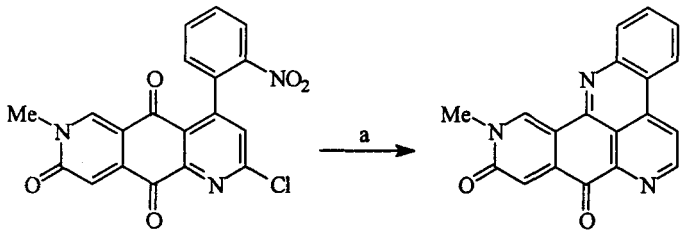
118

SCHEME 23. (a) Na_2CO_3, Cu, $PhNO_2$, reflux, 59%; (b) MCPBA, CH_2Cl_2, 0°C to rt, 87%; (c) H_2SO_4, AcOH, 130°C, 37%.

In the development of pyridone fused acridines, Kennedy *et al.* used a sulfoxide-based route to produce 3,7-dimethyl-5-methoxy-1-phenylthio-1,2,3,4-tetrahydro-2-oxobenzo[*b*][1,8]phenanthroline **118** (Scheme 23) [91-JCS(P1)2499].

4. *Pyrido[4,3-c]acridines (Benzo[b][1,9]phenanthrolines)*

Kubo and Nakahara have reported the formation of an isomer **119** of amphimedine **105,** which possesses this novel ring system (Scheme 24) (88H2095).

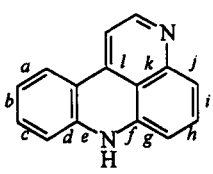


119

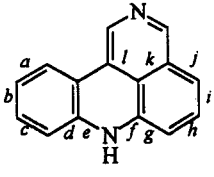
SCHEME 24. (a) 10% Pd/C, Et_3N, MeOH, rt 20 h, 18%.

D. Pyrido[*kl*]acridines

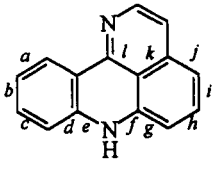
In this class, the extra pyridine ring is fused at bonds *k* and *l* of the acridine. Three types of pyrido[*kl*]acridines **120** are possible, depending on the position of the nitrogen in the fused pyridine ring.



120a



120b



120c

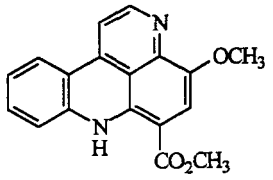
1. *Pyrido[2,3,4-kl]acridines*

a. *Isolation and Biological Activity.* The polycyclic aromatic alkaloids based on the pyrido[2,3,4-*kl*]acridine skeleton are members of a fast-growing class of marine sponge and ascidian (tunicate) metabolites. More than 50 alkaloids of this class have been isolated and characterized during the past 12 years.

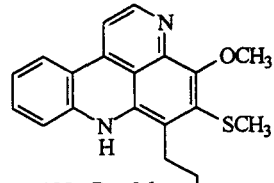
Norsegoline **121** is the simplest member of this class isolated from *Eudistoma* sp., a tunicate (88TL3861; 89JOC5331). Other tetracyclic alkaloids include varamines A **122** and B **123,** lissoclins A **124** and B **125,** diplamine **126,** cystodytins A–J **128–137,** and pantherinine **138.** Varamines A **122** and B **123,** isolated from the ascidian *Lissoclinum vareau,* are brilliant red pigments that were found to be cytotoxic toward L1210 murine leukemia, with IC_{50} values of 0.03 and 0.05 μg/ml, respectively (89JOC4256). Lissoclins A **124** and B **125,** isolated from *Lissoclinum* sp. collected from the Great Barrier Reef, Australia, did not show significant activity against the fungus *Candida albicans* (94JOC6600). Diplamine **126,** another tetracyclic alkaloid isolated from the tunicate *Diplosoma* sp., showed cytotoxicity towards L1210 murine leukemia cells (IC_{50} = 0.02 μg/ml) (89TL4201) and human colon cancer cell lines ($IC_{50} < 1.4\ \mu M$) (94JMC3819). DNA intercalation and topoisomerase II inhibition ($IC_{90} = 9.2\ \mu M$) by diplamine **126** was also observed (94JMC3819). The isolation of another homolog of this series, "isobutyramide" **127,** from an unidentified tunicate has been reported (93CRV1825).

The tunicate *Cystodytes dellechiajei* is a very rich source of pyrido[2,3,-4-*kl*]acridine alkaloids. Nine tetracyclic alkaloids, cystodytins A–I **128–136,** have been isolated from this species (88JOC1800; 91JNP1634). Except for cystodytin C **130,** all other cystodytins were isolated as inseparable isomeric pairs (3.5 : 1) of cystodytins, β,β-dimethylacrylate and tiglate amides

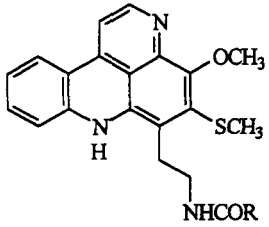
[cystodytins A **128** and B **129**, D **131** and E **132**, F **133** and G **134**, and H **135** and I **136**]. Cystodytin J **137**, isolated from a Fijian *Cystodytes* sp., was found to be a good DNA intercalator, a potent inhibitor of topoisomerase II (IC_{90} = 8.0 μM), and a potent cytotoxin against the human colon tumor cell line HCT 116 (IC_{50} = 1.6 μM) (94JMC3819). Cystodytins A–C **128–130** showed powerful Ca^{2+} releasing activity in sarcoplasmic reticulum and cytotoxicity against L1210 murine leukemia cells (IC_{50} ~ 0.2 μg/ml) (88JOC1800). Cytotoxic activity (IC_{50}s = 0.68–1.4 μg/ml) against both



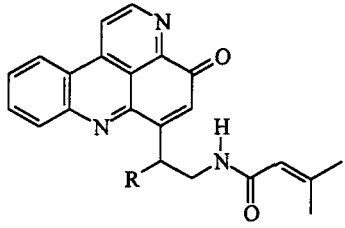
121



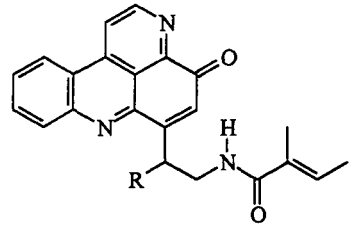
122 R = Me
123 R = Et



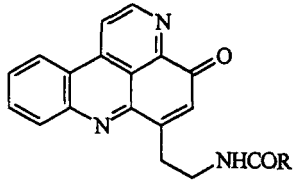
124 R = Me_2CHCH_2
125 R = *cis*-MeCH=CMe
126 R = Me
127 R = Me_2CH



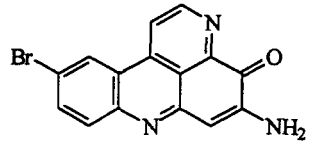
128 R = H
131 R = OH
133 R = OMe
135 R = OOleoyl



129 R = H
132 R = OH
134 R = OMe
136 R = OOleoyl



130 R = $Me_2C(OH)CH_2$
137 R = Me



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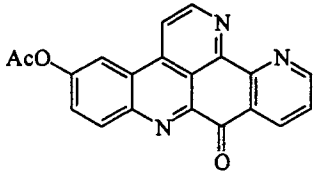
L1210 cells and epidermoid carcinoma KB cells was also observed for other cystodytins (91JNP1634). A bromo-substituted tetracyclic alkaloid pantherinine **138** has been isolated from the ascidian *Aplidium pantherinum,* and a moderate cytotoxic activity (ED_{50} = 4.5 μg/ml) against P388 murine leukemia cells has been reported by Kim *et al.* (93JNP1813).

Pentacyclic alkaloids contain an additional fused heterocyclic ring, such as tetrahydropyridine, pyridine (pyridone), thiazine, or thiazole. Calliactine was shown to be a pyridoacridine alkaloid (87T4023) nearly half a century after its isolation from the Mediterranean anemone *Calliactis parasitica* in 1940 (40BSF608). Although the exact structure of the alkaloid is still unclear, the structural analysis shows that it contains an additional tetrahydropyridine ring (87T4023). The structure of neocalliactine acetate **139,** derived from calliactine by heating with water (aromatization) followed by reaction with acetic anhydride, has been established by a total synthesis (92LA1205; 93H943). On the basis of spectral data and the establishment of the neocalliactine acetate **139** structure, structure **32** is the most favorable among the four proposed by Cimino *et al.* for calliactine (87T4023).



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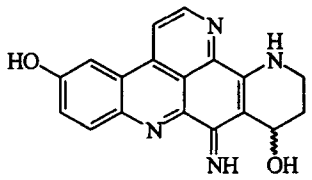


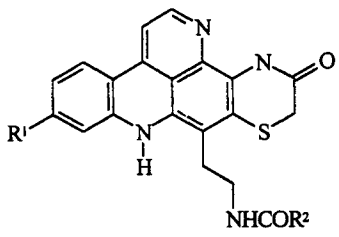
32

Amphimedine **105,** the first pyridoacridine to be fully characterized, was isolated from the Guamanian sponge, *Amphimedon* sp. (83JA4835). Its regioisomer, neoamphimedine **106,** was isolated from the Micronesian sponge *Xestospongia* cf. *carbonaria,* along with amphimedine **105** and debromopetrosamine **108** (93CRV1825). Neoamphimedine **106** was found to be a potent inhibitor of mammalian topoisomerase II (IC_{50} = 1.3 μM), but not of topoisomerase I. Intercalation of neoamphimedine **106** into DNA was observed with a K_m of 2.8 × 10^5 M^{-1} and a binding site size of 1.8 base pairs per molecule. Amphimedine **105,** debromopetrosamine **108,** and petrosamine **107** (from the sponge (*Petrosia* sp.) have little effect on topoisomerase I or II activity, despite comparable cytotoxicity (40BSF608).

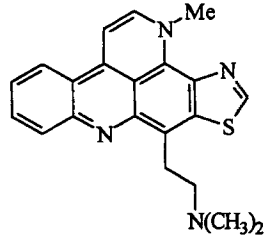
Ascididemin **28,** from *Didenum* sp. (88TL1177), and 2-bromoleptoclinidone **29,** from *Leptoclinides* sp. (87JA6134; 89TL1069), were the first polycyclic aromatic metabolites to be isolated from ascidians. Both compounds show cytotoxcity toward leukemia cell lines with IC_{50}s of 0.4 μg/ml, whereas ascididemin also inhibits topoisomerase II (IC_{50} = 75 μM) and causes release of calcium ions in the sarcoplasmic reticulum (91JOC804). Two

regioisomers, meridine **50** and 11-hydroxyascididemin **30** were isolated from the ascidians *Amphicarpa meridina* and *Leptoclinides* sp., respectively (91JOC804). Both of these isomers, along with 8,9-dihydro-11-hydroxyascididemin **31,** have also been isolated from the Okinawan marine sponge *Biemna* sp. (93T8337). Meridine **50** exhibits cytotoxicity against P388 murine leukemia cells (IC_{50} = 0.3–0.4 μg/ml) (91JOC804), and 8,9-dihydro-11-hydroxyascididemin **31** exhibits cytotoxicity against human epidermoid carcinoma KB (IC_{50} = 0.2 μg/ml) and murine lymphoma L1210 (IC_{50} = 0.7 μg/ml) cells *in vitro* (93T8337). A new pentacyclic alkaloid, cystodamine **51,** has been isolated from the ascidian *Cystodytes dellechiajei* (94TL7023). The new alkaloid shows cytotoxicity against CEM human leukemic lymphoblasts (IC_{50} = 1.0 μg/ml).

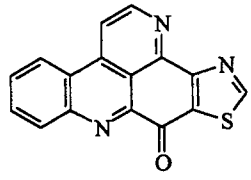
Shermilamines A **140,** B **141,** and C **142** are thiazinone-containing pentacyclic alkaloids isolated from the purple tunicate *Tridemum* sp. (**140** and **141**) (88JOC4619; 89JOC4231) and a Fijian *Cystodytes* sp. (**141** and **142**) (94JMC3819). Shermilamine B **141** has been reported to exhibit cytotoxicity against KB cells (IC_{50} = 5.0 μg/ml) (91JOC804) and HCT cells (IC_{50} = 13.8 μM) (94JMC3819), and shermilamine C **142** exhibits cytotoxicity against HCT cells (IC_{50} = 16.3 μM). Shermaline B **141** and C **142** also inhibit topoisomerase II (IC_{90} = 118 μM and 138 μM, respectively) (94JMC3819).



140 R^1=Br, R^2=Me
141 R^1=H, R^2=Me
142 R^1 = H, R^2 = Me_2C=CH



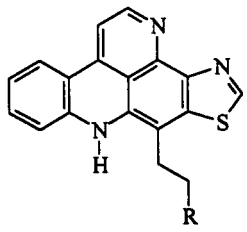
143



146

A series of pentacyclic aromatic alkaloids that incorporate a thiazole ring were isolated from sponges, ascidians (tunicates), and the lamellariidae molusk *Chelynotus semperi.* Dercitin **143** (88JA4356; 92JOC1523), a metabolite of deep-water sponge *Dercitus* sp., exhibits a remarkable biological activity. It inhibits a variety of cultured cell clones at nanomolar concentrations and exhibits antitumor activity (in mice) and antiviral activity (against herpes simplex and A-59 murine corona virus) at micromolar concentrations. Burres *et al.* (89MI2) observed the inhibition of both DNA and RNA syntheses by dercitin **143** by up to 83% at 400 nM and inhibition of protein synthesis to a lesser extent. Inhibition of DNA polymerase and DNase nick translation at 1.0 nM by dercitin **143** was also reported. Dercitin showed a

potent intercalation into nucleic acids and little inhibition of topoisomerases (89MI2). New structural types of anti-HIV drugs based on dercitin have been proposed by Taraporewala *et al.* (92JMC2744).

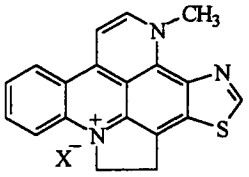


144 R = Me_2N
145 R = MeNH
147 R = Me_2CHCH_2CONH
148 R = EtCONH
149 R = MeCONH
150 R = Me_2C=CHCONH

Nordercitin **144,** dercitamine **145,** and dercitamide (kuanoniamine C) **148** were also isolated from *Dercitus* sp. and *Stelleta* sp., along with dercitin **143** (89TL4359; 92JOC1523). Kuanoniamines A–D **146–149** and shermilamine B **141** were found in the mollusc *Chelynotus semperi* and its prey, an unidentified tunicate (90JOC4426). A new kuanoniamine, the dehydrokuanoniamine B **150,** has been isolated along with kuanoniamine D **149** and other alkaloids from a Fijian *Cystodytes* sp. (94JMC3819). Kuanoniamines A **146,** B **147,** and D **149** exhibit cytotoxicities against KB cells, with IC_{50} values of 2.0, >10, and 1.0 μg/ml, respectively (90JOC4426). Cytotoxicities against HCT cells (IC_{50} 7.8 and 8.3 μM) for dehydrokuanoniamine B **150** and kuanoniamine D **149** were also reported (94JMC3819). Kuanoniamine D **149** can form complexes with Fe(II), Co(II), Cu(II), and Zn(II) ions (92JOC1523).

Two hexacyclic alkaloids, cyclodercitin **151** and stelletamine **152** from *Stelleta* sp. (89TL4359; 92JOC1523), and three optically active hexacyclic alkaloids, segoline A **153,** segoline B **154,** and isosegoline A **155** from the Red Sea tunicate, *Eudistoma* sp., have been isolated along with tetra- and pentacyclic alkaloids (88TL3861; 89JOC5331). Another interesting compound isolated from *Eudistoma* sp. was the symmetrical, heptacyclic eilatin **33** (88TL6655; 94JMC3819). Cytotoxicity (IC_{50} = 5.3 μM) of eilatin **33** against HCT cell lines has been reported (94JMC3819). This compound was also found to regulate cell growth and to affect cAMP-mediated cellular processes (93MI1). Because of the presence of the 1,10-phenanthroline skeleton, eilatin **33** is capable of chelating metal ions such as Ni(II) (88TL6655).

Two octacyclic alkaloids, eudistones A **48** and B **49,** along with ascididemin **28,** have been isolated from another tunicate of the genus *Eudistoma* (from the Seychelles) (91JOC5369). These compounds are optically active, but their absolute configurations are still unknown. Another octacyclic alkaloid, biemnadin **34,** isolated from the Okinawan marine sponge *Biemna*



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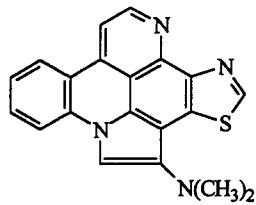

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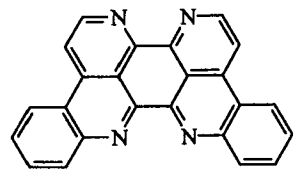

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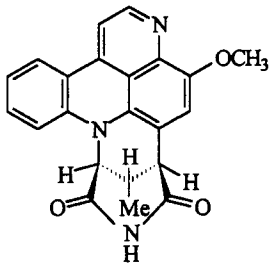

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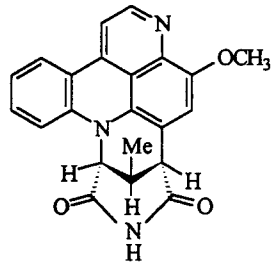

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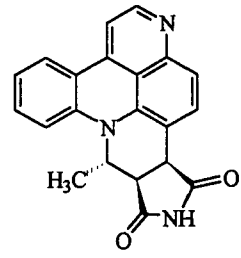


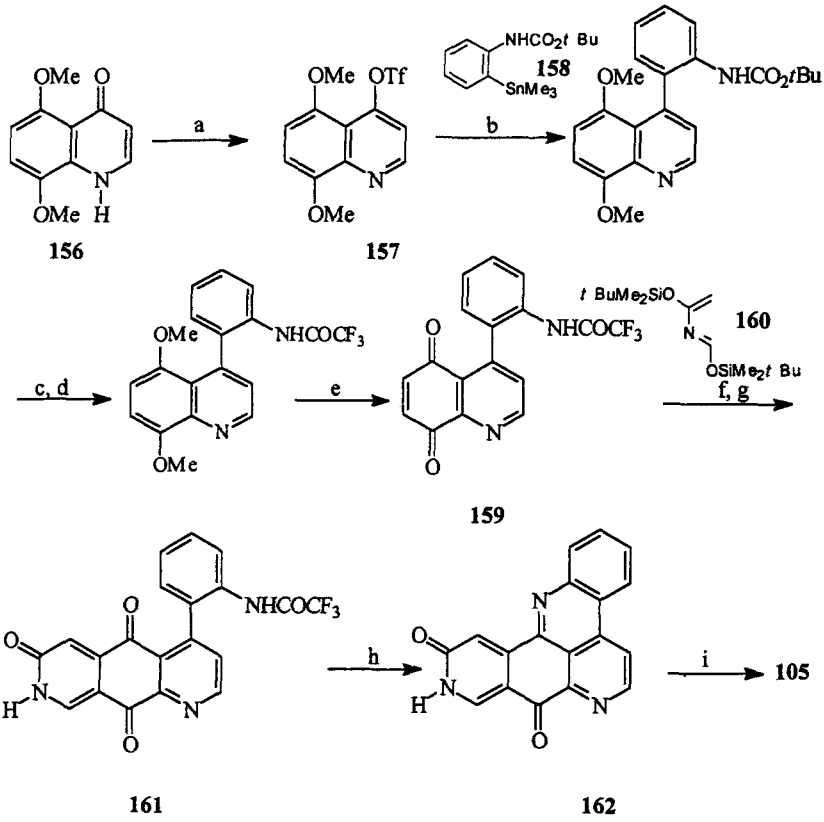
155

sp., has been shown to exhibit cytotoxicity against human epidermoid carcinoma KB and murine lymphoma L 1210 cells *in vitro* (93T8337).

b. *Syntheses.* The biological activity and the novel ring systems of these pyridoacridine alkaloids make them appealing targets for synthesis. A number of approaches have been developed for the synthesis of these compounds.

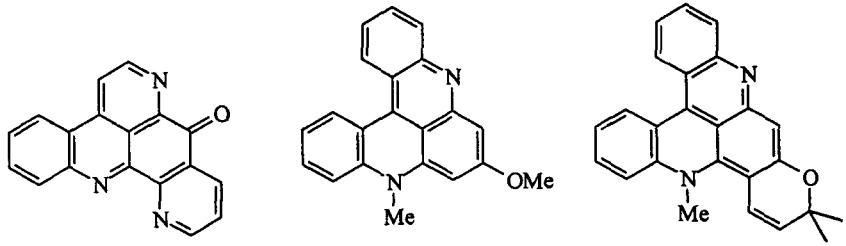
Imine formation. An example of this route is Echavarren and Stille's use of a simple intramolecular imine formation between a quinone moiety and an amino group to complete the nucleus (Scheme 25) of amphimedine **105** (88JA4051). The quinone **159** was prepared by a palladium-catalyzed cross-coupling of 5,8-dimethoxyquinolin-4-yl triflate **157** (from 5,8-dimethoxyquinolin-4-one **156**) with 2-*t*-butoxycarbonyl-aminophenyltrimethyltin **158,** followed by deprotection of the amino group, reprotection by the triflouroacetyl group, and then oxidation with ceric ammonium nitrate (CAN). The aza-Diels–Alder reaction of the resultant quinone **159** with Ghosez's diene **160** afforded an intermediate **161.** Deprotection of the amino group with aq. HCl and *in situ* formation of the imine gave a precursor **162** of the amphimedine **105,** which was obtained by methylation with dimethyl sulfate.

Similar strategies have been employed by Kubo and Nakahara (88H2095) for the synthesis of amphimedine **105;** by Szczepankiewicz and Heathcock (94JOC3512) for the synthesis of diplamine **126;** by Nakahara *et al.* (93H1139) for the synthesis of eilatin **33;** by Gómez-Bengoa and Echavarren

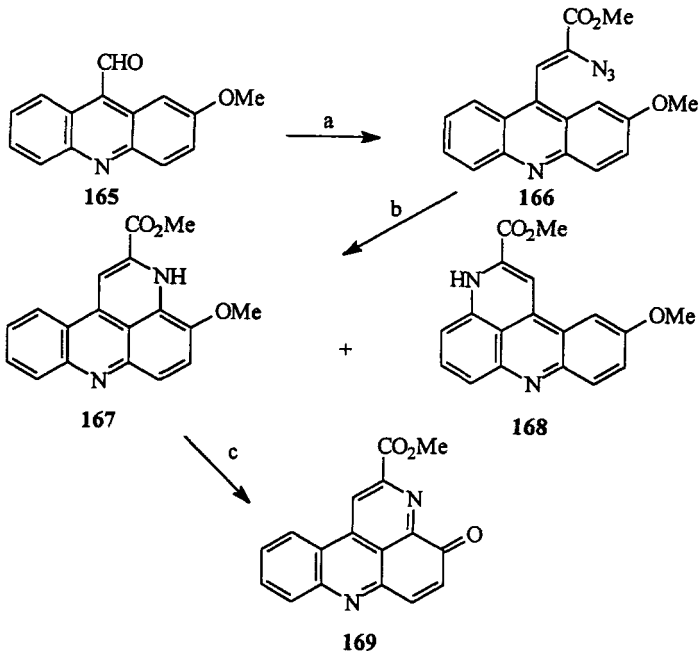


SCHEME 25. (a) $(Tf)_2O$, 2,6-lutidine, CH_2Cl_2, 92–95%; (b) $Pd(PPh_3)_4$, LiCl, dioxane, 7 h, 100°C; (c) TFA; (d) TFAA, $(iPr)_2NEt$, 82–87% (b,c,d); (e) CAN, CH_3CN/H_2O, 23°C, 15 min; (f) THF, 23°C, 16 h; (g) pyridinium–HF, 48% (e,f,g); (h) 6 *M* HCl, THF aq., 70–80°C, 86%; (i) Me_2SO_4, K_2CO_3, DME, 96%.

(91JOC3497) for the synthesis of isoascididemin **77,** a regioisomer of the naturally occuring ascididemin **28;** and by Jolivet *et al.* for the synthesis of a series of quino- and pyranoquinoacridines, such as **163** and **164** [95JCS(P1)2333].



77 163 164

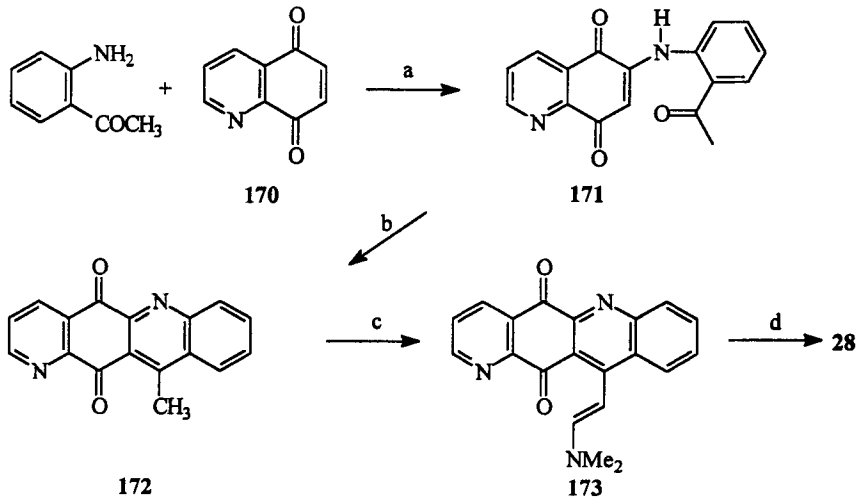


SCHEME 26. (a) $MeO_2CCH_2N_3$, NaOMe, MeOH, −10 to 0°C, 48%; (b) xylene, 140°C, 78% (**167**), 19% (**168**); (c) MnO_2/H_2SO_4, 75%.

Nitrene insertion. A nitrene insertion reaction is central to many syntheses of pyridoacridine alkaloids and their analogues. For example, Labarca *et al.* [87JCS(P1)927] have reported a three-step synthesis of a pyridoacridine **169** starting from 2-methoxyacridine-9-carboxaldehyde **165** (Scheme 26). Cyclization of the vinyl azide **166** by thermolysis is believed to involve a nitrene insertion reaction, to give either **167** or **168.**

Ciufolini and his co-workers have completed the total syntheses of pyridoacridine alkaloids such as cystodytins A **128** (91JA8016), B **129** (91JA8016), and J **137** (92JA10081), diplamine **126** (92JA10081), dercitin **143** (92JA10081; 95JA12460), nordercitin **144** (92JA10081; 95JA12460), kuanoniamine D **149** (92JA10081; 95JA12460), and shermilamine B **141** (92JA10081) by using nitrene insertion methodology. Nitrene insertion is also involved in the Gellerman synthesis of the pyrido[2,3,4-*kl*]acridines (92TL5577), and a similar approach was used by McKillop and his coworkers for the synthesis of norsegoline **121** and other analogs [92JCS(CC)1453; 93JCS(P1)879].

Cyclodehydration. This route has been used by Bracher for the synthesis of ascididemin **28** (Scheme 27) (89H2093). Freshly prepared 2-aminoaceto-



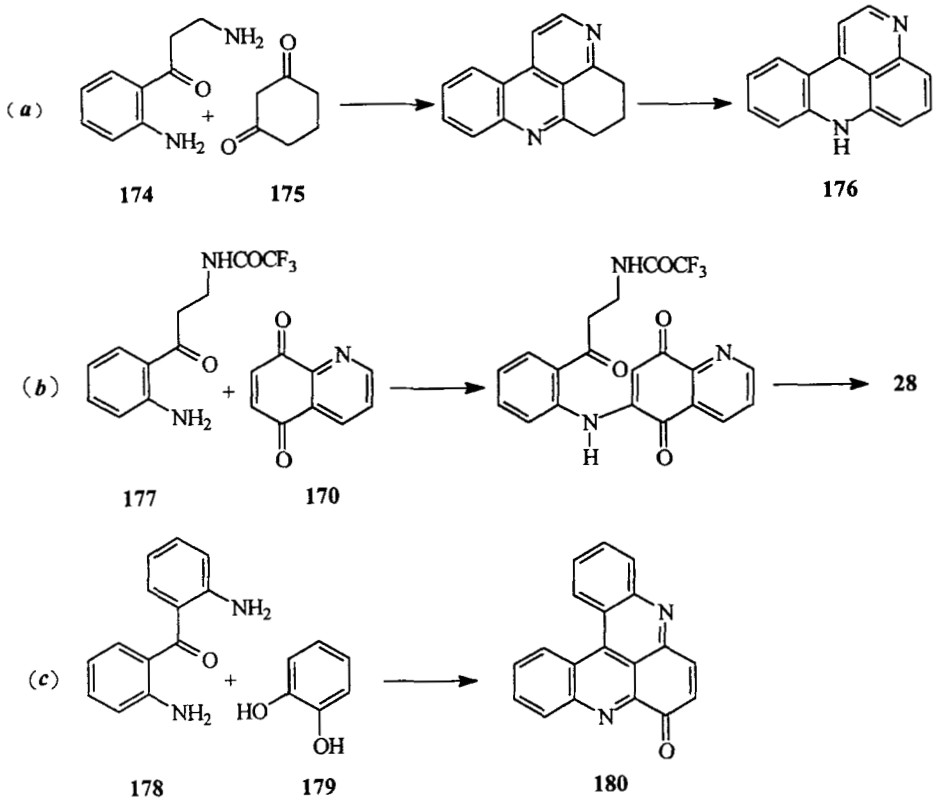
SCHEME 27. (a) O_2, $Ce(SO_4)_2$, 78%; (b) $AcOH/H_2SO_4$, 94%; (c) $Me_2NCH(OEt)_2$, DMF; (d) NH_4Cl, AcOH, 59% (c,d).

phenone was used for oxidative amination of *p*-quinolinoquinone **170** in the presence of air and cerium ions, to give intermediate **171,** which cyclized to the linear pyridoacridine **172** on heating in a mixture of conc. sulfuric and acetic acids. Condensation of the side-chain methyl group of **172** with dimethylformamide diethyl acetal afforded an enamine **173,** which cyclized to ascididemin **28.**

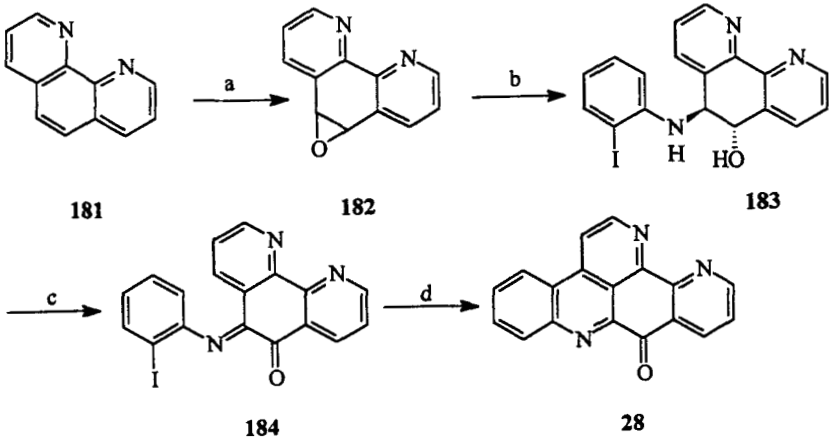
The same strategy has been applied to the preparation of a number of pyridoacridine alkaloids, which include 2-bromoleptoclinidone **29** (90LA205), 11-hydroxyascididemin **30** (93H943) and kuanoniamine A **146** (93H943), and also for the synthesis of neocalliactine acetate **139** (92LA1205; 93H943) (a derivative of calliactine **32**).

Biomimetic synthesis. Kashman and his co-workers have reported novel biomimetic syntheses of pyrido[2,3,4-*kl*]acridines by the reaction of kinuramine **174** or its derivatives, such as **177,** and other analogs, such as **178,** with a variety of diones (e.g., **175**), quinones (e.g., **170**), and hydroquinones (e.g., **179**) (Scheme 28) (93TL1823; 93TL1827; 94S239, 94T12959). Using this strategy they have prepared a number of pyridoacridines, including the marine alkaloids, eilatin **33** (93TL1827), ascididemin **28** (94S239), their derivatives, and other analogs such as **176** and **180** (93TL1823; 94T12959).

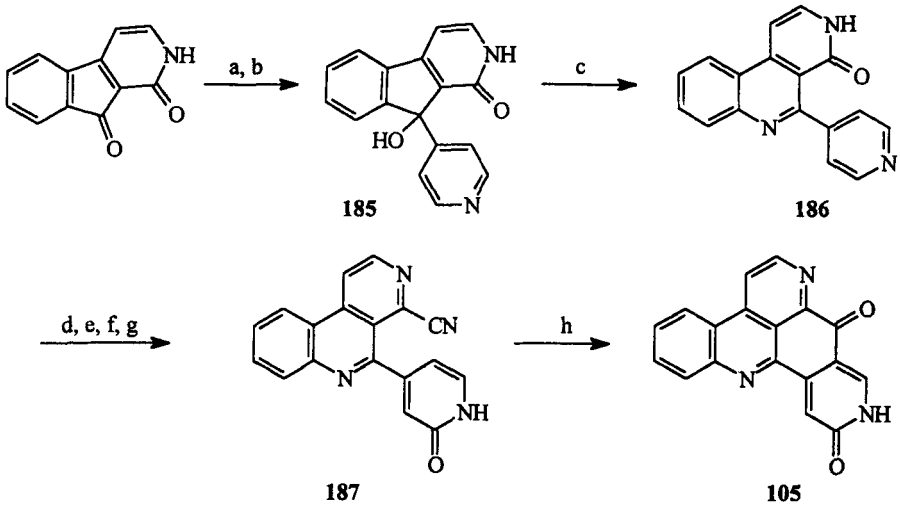
Miscellaneous syntheses. Moody *et al.* (90TL4375; 92T3589) have described a synthesis of ascididemin **28** that involves the epoxidation of 1,10-phenanthroline **181,** ring opening of the epoxide **182** with 2-iodoaniline to afford the amino alcohol **183,** and oxidation followed by photocyclization of the *o*-iminoquinone **184** (Scheme 29).



SCHEME 28



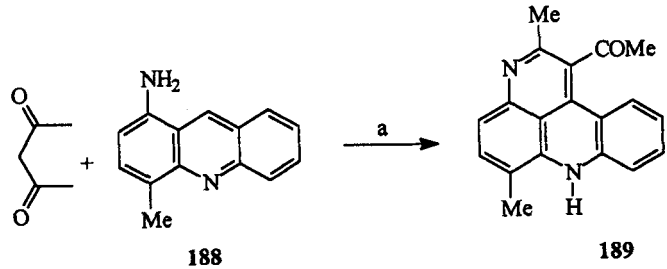
SCHEME 29. (a) NaClO, aq.; (b) 2-iodoaniline, Et_3Al, CH_2Cl_2, 79%; (c) $Ba(MnO_4)_2$, CH_2Cl_2, 83%; (d) $h\nu$, quartz, H_2SO_4, 32%.



SCHEME 30. (a) Me_3SiCl, Et_3N, THF, 60°C; (b) 4-pyridylithium, −40 to 20°C, 2 h, 87% (a,b); (c) NaN_3, PPA, 45°C, 20 h, 69%; (d) PCl_5, DMF (cat.) $POCl_3$, 180°C, 20 h; (e) $MeOS_2OF$, 20°C, 40 min; (f) KOH, $K_3[Fe(CN)_6]$, 20°C, 10 h; (g) CuCN, DMSO, 150°C, 4 h, 38% (d,e,f,g); (h) PPA, 90°C, 5 h, 35%.

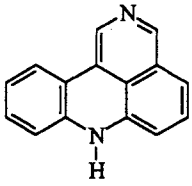
A novel synthesis of amphimedine **105** has been reported by Prager *et al.* (89H847; 91AJC277). It involves an azido ring expansion of a pyridylazafluorenol **185,** by the Schmidt reaction, to 5-(4-pyridyl)benzo[*a*]-[2,7]naphthyridin-4-one **186,** and then refunctionalization to the α-cyano precursor **187,** followed by cyclization in polyphosphoric acid (Scheme 30). Guillier *et al.* (95JOC292) have described a new synthesis of the intermediate **186.**

Taking advantage of the activity of the 9-position of acridines toward active methylenes, Gellerman *et al.* (92TL5577) have developed a



SCHEME 31. (a) AmOH, cat. H_2SO_4, 130°C, 1.5 h.

method for the preparation of pyrido[2,3,4-*kl*]acridines starting from 1-aminoacridines. Thus, acid-catalyzed condensation of acetylacetone with 1-amino-4-methylacridine **188** gave a pyridoacridine **189** (Scheme 31).



190

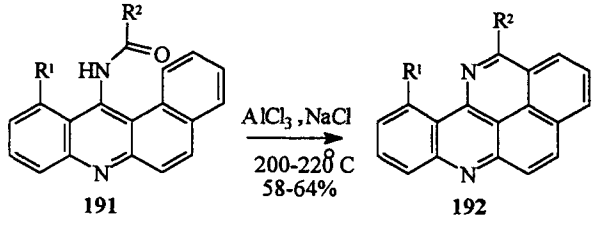
2. *Pyrido[3,4,5-kl]acridines*

No natural or synthetic compounds based on this ring system **190** have been reported.

3. *Pyrido[4,3,2-kl]acridines*

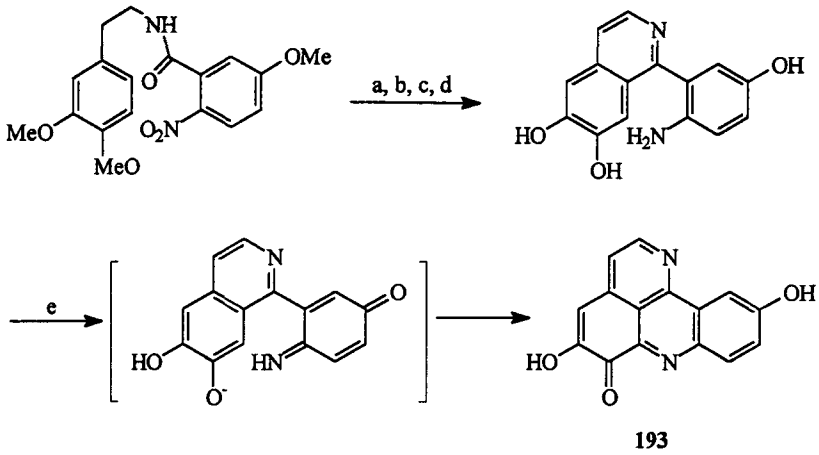
Only a few examples of this ring system have been reported. Grout *et al.* [68JCS(C)2689] have cyclized *N*-acyl derivatives **191** of 9-aminobenzo[*a*]acridines to pyrido[4,3,2-*kl*]acridines **192** by heating with $AlCl_3$/NaCl at 200–220°C (Scheme 32).

The only natural product based on this ring system is necatorone **193.** This alkaloid was isolated from a toadstool, *Lactarius necator* (84TL3575). This fungal metabolite showed a considerable mutagenic activity in the Ames test. A synthesis of necatorone **193** involving oxidative cyclization has been reported (Scheme 33) (85TL5975).



191 **192**

SCHEME 32. R^1 = H, Me; R^2 = H, Me.



193

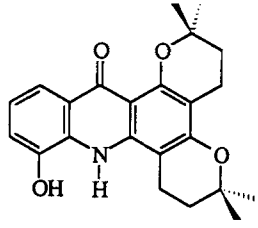
SCHEME 33. (a) $POCl_3$, CH_3CN, 85–93%; (b) MnO_2, C_6H_6, reflux, 24 h, 90–98%; (c) 48% HBr, 64%; (d) H_2/Pd–C, 82–85%; (e) aq. NaOH (5%), O_2, 67%.

III. Pyranoacridines

Only a few pyranoacridine ring systems have been reported in the literature.

A. Pyrano[2,3-*a*]acridines

The pentacyclic alkaloid bicyclo-*N*-methylatalaphylline **194,** isolated from *Atlantia monophylla* Correa, possesses this ring system as a part of its structure (72JOC3035). Formation of this ring system (e.g., **196**) from isoprene-containing acridone alkaloids or their derivatives (3-OH protected, e.g., **195**) has been reported (Scheme 34) [70T2905; 82P1771; 83JCS(P1)1681].



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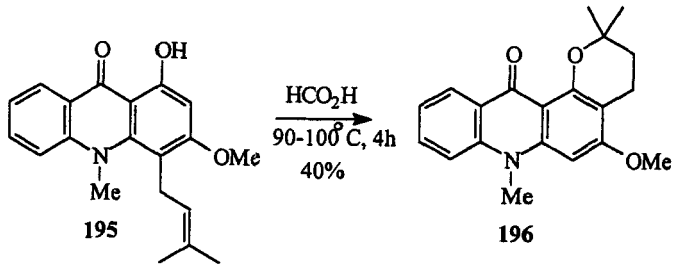
Bhavsar and his co-workers reported the formation of pyrano[2,3-*a*] acridin-2-ones, such as **199,** from 8-aroyl-7-hydroxy-benzopyran-2-ones,

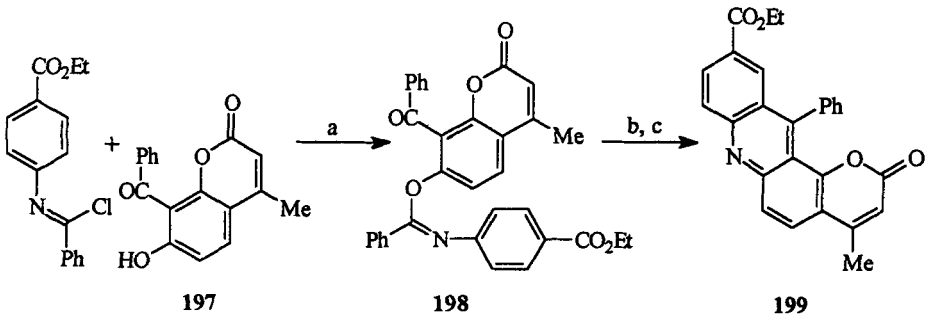


SCHEME 34

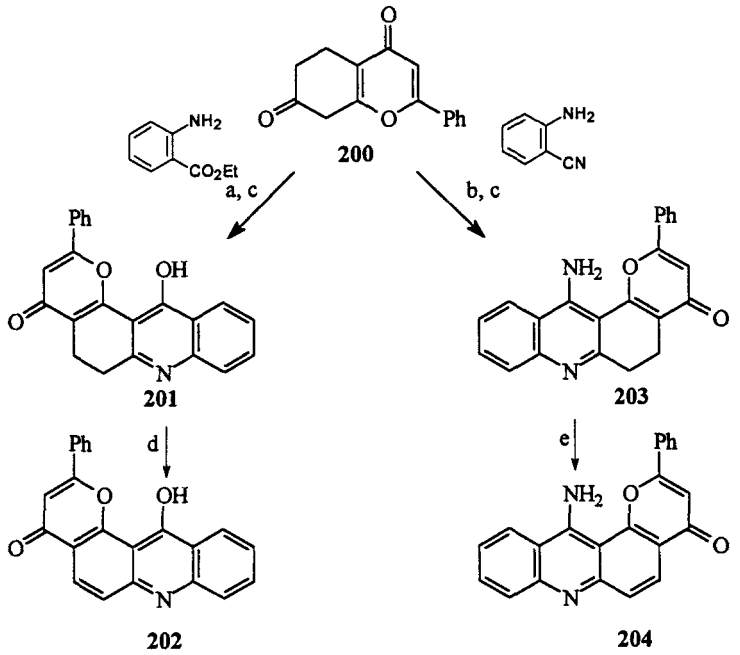
such as **197,** by using the Chapman–Mumm rearrangement of an imino ester **198** (Scheme 35) (87MI2, 87MI3).

We have described a novel method for the construction of this ring system that involves the condensation of 7-oxo-5,6,7,8-tetrahydroflavone **200** with ethyl anthranilate or anthranilonitrile, followed by base-catalyzed cyclization and then dehydrogenation of the dihydro derivatives, **201** and **203** (Scheme 36) [94JCS(P1)173]. 12-Amino-2-phenylpyrano[2,3-*a*]acridin-4-one APPA **204** was found to be a very potent inhibitor (IC_{50} = 1.9 μmol dm^{-3}) of the EGF-dependent proliferation of DHER cells, and of the spontaneous proliferation of a human gastric carcinoma cell line, MKN 45, with an IC_{50} of 0.1 μmol dm^{-3}. In addition, APPA **204** was tested against 60 cancer cell lines as part of the NCI Developmental Therapeutics Program and was shown to have an activity profile similar to that of known topoisomerase II inhibitors.

We have also developed an alternative synthesis [97JCS(P1) 601] of this ring system that utilizes the von Strandtmann flavone annellation procedure.

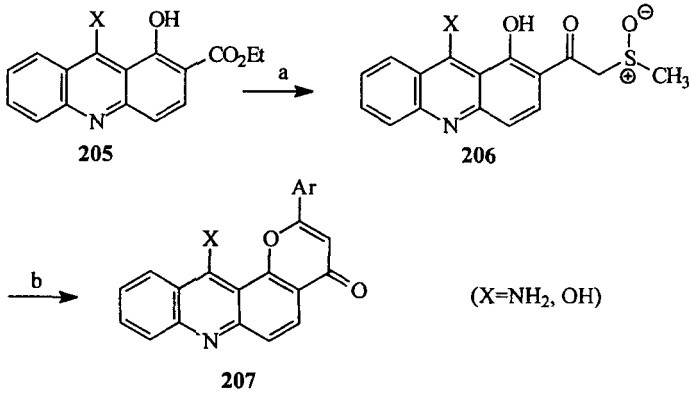


SCHEME 35. (a) Base, (b) heat, (c) H_3O^+.



SCHEME 36. (a) PTSA, toluene, reflux, 47%; (b) PTSA, toluene, reflux, 65%; (c) $NaNH_2$, DME, reflux, 64% (**201**), 29% (**203**); (d) $Hg(OAc)_2$, DMSO, 51%; (e) MnO_2, toluene, reflux, 72%.

Thus, the esters **205** were treated with the dimsyl anion to give the β-ketosulfoxides **206,** which were cyclized to the pyranoacridinones **207** upon treatment with an aromatic aldehyde in the presence of piperidine (Scheme 37).

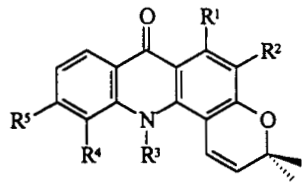


SCHEME 37. (a) $^{-}CH_2SOCH_3$, DMSO; (b) ArCHO, piperidine, DMSO.

B. Pyrano[2,3-*c*]acridines

1. *Isolation and Biological Activity*

Most of the pyranoacridone alkaloids are based on this ring system. Acronycine (acronine) **208** was the first pyranoacridine alkaloid to be isolated, in 1948 by Hughes and co-workers from the bark of *Baurella simplicifolia* (*Acronychia baueri,* an Australian Rutaceae plant) [48NAT(L)223] and in 1949 by Lahey and Thomas from *Vepris amphody* (49MI1). The correct structure was established in 1966 by degradative studies supported by NMR studies (66AJC275, 66T3245) and finally by X-ray crystallographic studies [70AX(B)853]. Acronycine **208** has broad-spectrum antineoplastic activity (85MI1; 89MI1; 92MI1), although its poor solubility in aqueous media is a major hindrance to its development as a clinical agent. Efforts were continued to isolate more alkaloids based on this skeleton, from other plants of Rutaceae family and also through molecular variation, to improve the cytostatic activity of acronycine **208.** Other alkaloids based on this system include noracronycine **209** [66T3245; 78MI1; 83JCS(P1)1681; 84JNP285], de-*N*-methylacronycine **210** [78MI1; 83JCS(P1)1681], de-*N*-methylnoracronycine **211** [78MI1; 83JCS(P1)1681], citracridone-I **212** [78MI1; 82H273; 83CPB901, 83JCS(P1)1681; 90JCS(P1)1593], citracridone-II **213** [82H273; 83CPB895; 90JCS(P1)1593], citracridone-III **214** (91H1781), 11-hydroxynoracronycine **215** [82H273; 83CPB895, 83JCS(P1)1681; 90JCS(P1)1593], 11-methoxynoracronycine (baiyamine A) **216** (86H1595), 11-hydroxy-20-methoxynoracronycine **217** (84JNP325), acrifoline **218** (95JNP1629), atalaphyllidine **219** (75E1387; 82IJC16), atalaphyllinine **220** [82IJC16, 82P1771; 83JCS(P1)1681], *N*-methylatalaphyllinine (11-hydroxy-*N*-methylseverifoline) **221** [82IJC16, 82P1771; 83JCS(P1)1681; 96P235], severifoline **222** (82P1771), *N*-methylseverifoline **223** [82P1771; 83JCS(P1)1681], acronycine epoxide **224** (88MI3), *trans*-1,2-dihydroxy-1,2-dihydrocitracridone-I **225** (95H187), (+)-1-hydroxy-1,2-dihydro-de-*N*-methylacronycine **226** (87H2057), (−)-*cis*-1,2-dihydroxy-1,2-dihydro-de-*N*-methylacronycine **227** (86JNP1091), 1-oxo-1,2-dihydro-de-*N*-methylacronycine **228** (87H2057), bicyclo-*N*-methylatalaphylline **194** (72JOC3035), acrignine **229** (93CPB406), neoacrimarines C **230** and D **232** (93CPB1757), ataline **231** [73JCS(CC)615], glycobisamines A–C **233, 234a,** and **234b** [93JCS(P1)471], and buntanbismine **235** (96P221). These alkaloids have been isolated from various species of *Citrus, Glycosmis, Severinia, Sarcomelicope,* and other plants (all Rutaceae family), and some of them have demonstrated significant biological activity. For example, 11-hydroxynoracronycine **215** showed significant effects on Epstein–Barr virus-EA activation (95MI1), whereas glycobisamine A **233** showed *in vitro* antimalarial activity comparable to that of chloroquine diphosphate (91AAC377).



208 $R^1 = OMe, R^3 = Me, R^2 = R^4 = R^5 = H$

209 $R^1 = OH, R^3 = Me, R^2 = R^4 = R^5 = H$

210 $R^1 = OMe, R^2 = R^3 = R^4 = R^5 = H$

211 $R^1 = OH, R^2 = R^3 = R^4 = R^5 = H$

212 $R^1 = R^5 = OH, R^2 = H, R^3 = Me, R^4 = OMe$

213 $R^1 = OH, R^2 = H, R^3 = Me, R^4 = R^5 = OMe$

214 $R^1 = R^4 = R^5 = OH, R^2 = H, R^3 = Me$

215 $R^1 = R^4 = OH, R^2 = R^5 = H, R^3 = Me$

216 $R^1 = OH, R^2 = R^5 = H, R^3 = Me, R^4 = OMe$

217 $R^1 = R^4 = OH, R^2 = H, R^3 = Me, R^5 = OMe$

218 $R^1 = R^5 = OH, R^2 = R^3 = H, R^4 = OMe$

219 $R^1 = R^4 = OH, R^2 = R^3 = R^5 = H$

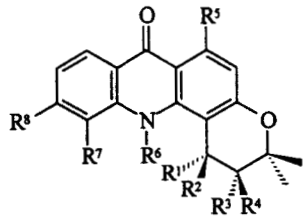
220 $R^1 = R^4 = OH, R^2 = X, R^3 = R^5 = H$

221 $R^1 = R^4 = OH, R^2 = X, R^3 = Me, R^5 = H$

222 $R^1 = OH, R^2 = X, R^3 = R^4 = R^5 = H$

223 $R^1 = OH, R^2 = X, R^3 = Me, R^4 = R^5 = H$

$X = Me_2C{=}CHCH_2$



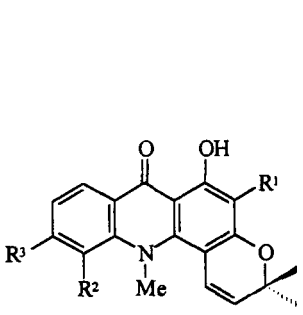
224 $R^1 = R^3 = R^7 = R^8 = H, R^5 = OMe, R^6 = Me, R^2R^4 = O$

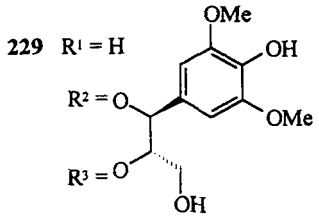
225 $R^1 = R^4 = R^5 = R^8 = OH, R^2 = R^3 = H, R^6 = Me, R^7 = OMe$

226 $R^1 = R^3 = R^4 = R^6 = R^7 = R^8 = H, R^2 = OH, R^5 = OMe$

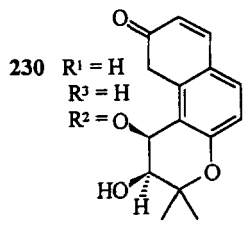
227 $R^1 = R^3 = R^6 = R^7 = R^8 = H, R^2 = R^4 = OH, R^5 = OMe$

228 $R^1R^2 = O, R^3 = R^4 = R^6 = R^7 = R^8 = H, R^5 = OMe$

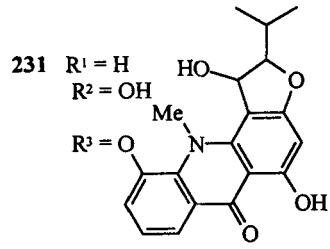




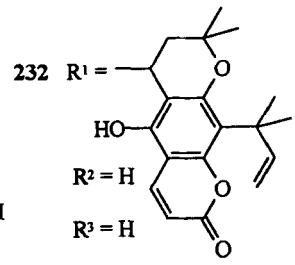
229 $R^1 = H$, $R^2 = O$, $R^3 = O$



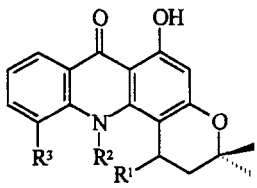
230 $R^1 = H$, $R^3 = H$, $R^2 = O$

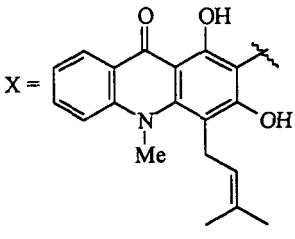


231 $R^1 = H$, $R^2 = OH$, $R^3 = O$

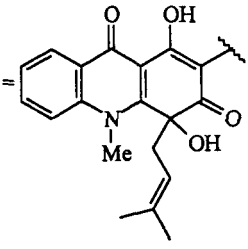


232 $R^1 =$, $R^2 = H$, $R^3 = H$





X =



Y =

233 $R^1 = X$, $R^2 = R^3 = H$

234a $R^1 = Y$, $R^2 = R^3 = H$

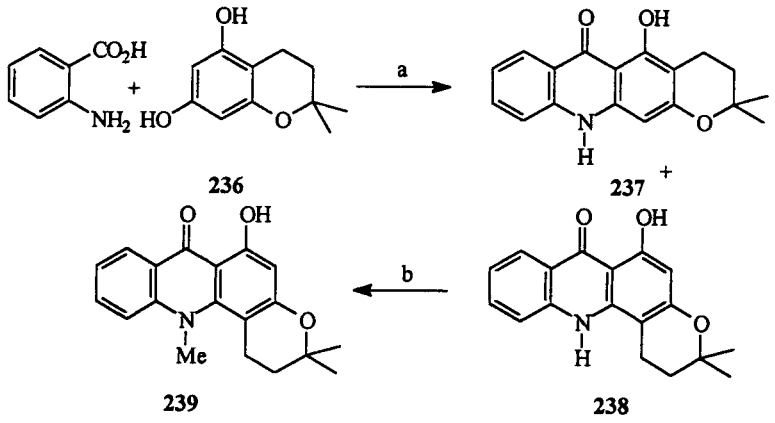
234b diastereoisomer of **234a**

235 $R^1 = X$, $R^2 = Me$, $R^3 = OH$

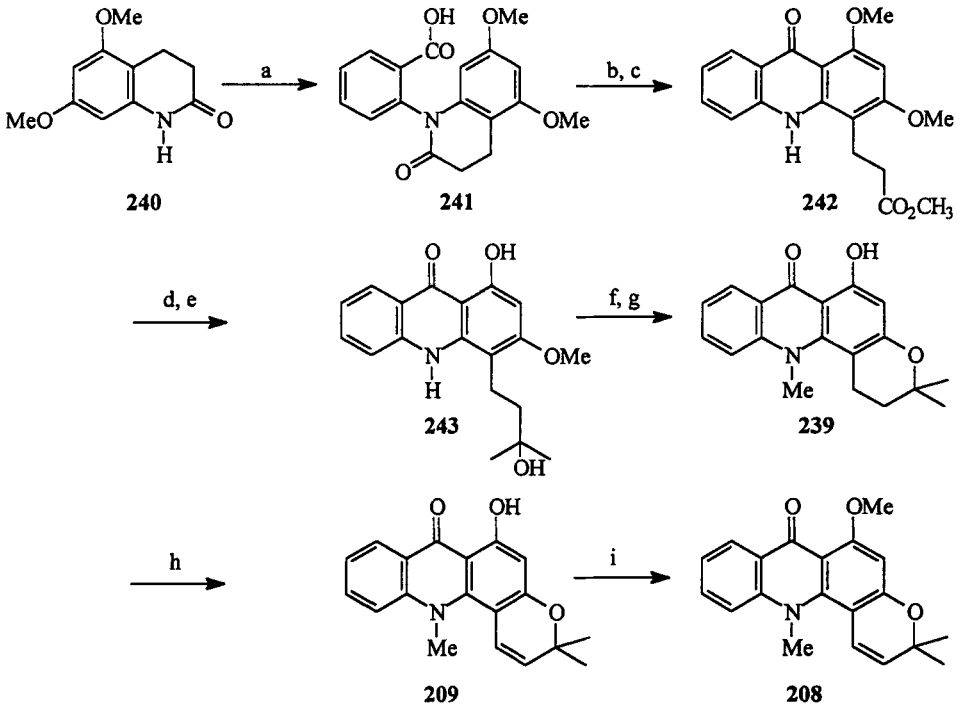
2. *Syntheses*

Various approaches have been used to synthesize acronycine **208** and its derivatives. Lahey and Stick's synthesis (Scheme 38) involves the condensation of 2,3-dimethylchroman-5,7-diol **236** with anthranilic acid, followed by *N*-methylation of the minor product **238** to produce 1,2-dihydronoracronycine **239** (73AJC2311).

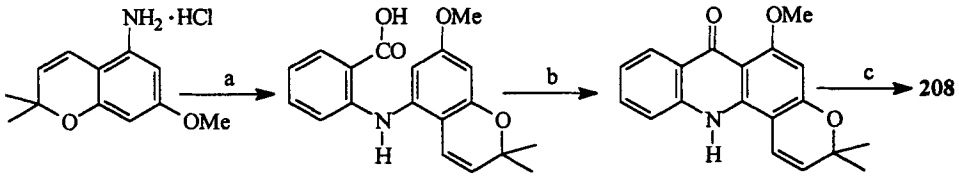
Beck *et al.* (68JA4706) have reported three interrelated syntheses of acronycine. One synthesis (Scheme 39) used 5,7-dimethoxy-1,2,3,4-tetrahydroquinolin-2(1*H*)-one **240,** which was coupled with 2-iodobenzoic acid to give the acid **241.** Ring closure with PPA, followed by refluxing with



SCHEME 38. (a) $ZnCl_2$, BuOH, reflux, 2 h; (b) MeI, K_2CO_3, acetone.



SCHEME 39. (a) 2-Iodobenzoic acid, CuI, nitrobenzene, K_2CO_3, 165–175°C, 6.5 h, 40%; (b) PPA, 90°C, 1.5 h; (c) MeOH, HCl, reflux, 2.5 h, 82% (b,c); (d) BCl_3, CH_2Cl_2; (e) MeLi, ether/HCl, 64% (d,e); (f) pyridinium chloride, 190–200°C, (g) MeI, K_2CO_3, acetone, 20% (f,g); (h) DDQ, toluene, 40–45%; (i) Me_2SO_4, K_2CO_3, acetone, 16 h, 60%.

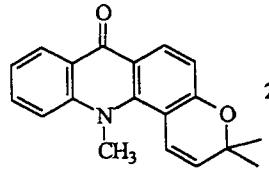


244 245 210

SCHEME 40. (a) 2-Bromobenzoic Acid, $Cu(AcO)_2$, KAcO, Et_3N, *t*BuOH, 58%; (b) TFAA, CH_2Cl_2, rt, 3 days, 62%; (c) CH_3I, $PhCH_2NEt_3Cl$, NaOH (aq.), 2-butanone, 96%.

methanolic HCl, afforded methyl 1,3-dimethoxy-9-oxacridin-4-propionate **242.** Ether cleavage at C-1, followed by reaction with an excess of MeLi, yielded the tertiary alcohol **243.** Fusion with pyridinium chloride at high temperature caused *O*-demethylation at C-3 with concomitant ring closure. Treatment of the crude product with MeI under basic conditions produced dihydronoracronycine **239.** Dehydrogenation with DDQ afforded noracronycine **209,** which was converted to acronycine **208** by *O*-methylation with dimethyl sulfate.

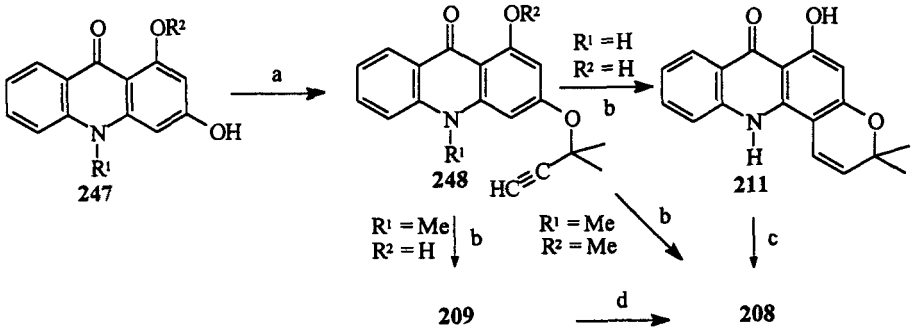
Loughhead (90JOC2445) coupled 5-amino-2,2-dimethyl-7-methoxychromene **244** with 2-bromobenzoic acid, and the resultant product **245** was cyclized with TFAA. The de-*N*-methylacronycine **210** was then converted to acronycine **208** by methylation under phase-transfer conditions (Scheme 40). The same approach has been used by Elomri *et al.* to prepare 6-demethoxyacronycine **246** which was found to be more potent than acronycine **208** in some biological assays (92H799).



246

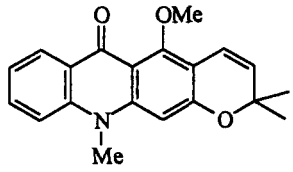
Hlubucek *et al.* annelated dimethylpyran rings onto 3-hydroxyacridones **247** by a Claisen-type rearrangement of their α,α-dimethyl propargyl ethers **248** (Scheme 41) [69CI(L)1809; 70AJC1881]. Similar strategies, with some modifications, were used by others to prepare acronycine **208** and its derivatives and analogs (72JMC266; 76JNP399; 82BSB33; 84LA31, 84T5181; 89AP31; 91AP67; 92JHC1293, 92M473; 93JHC1469).

Bandaranayaka *et al.* [74JCS(P1)998] devised an efficient synthesis of acronycine **208** that involves the condensation of 1,3-dihydroxyacridin-



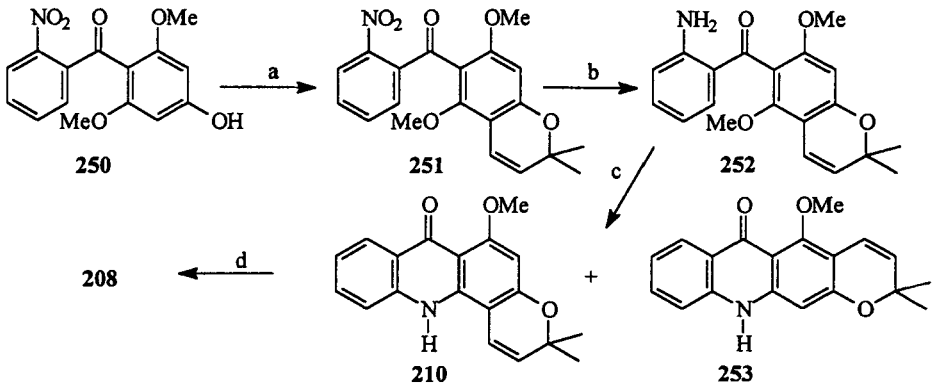
SCHEME 41. (a) $HC{\equiv}C{-}C(CH_3)_2Cl$, K_2CO_3, KI, DMF, 50–70°C, N_2, 14–18 h; (b) DMF, 130°C, 5h; (c) Me_2SO_4, DMF, NaH, N_2, 45°C, 1 h, 85%; (d) Me_2SO_4, DMF, K_2CO_3, N_2, 60°C, 18 h, 86%.

9(10*H*)-one **247** ($R^1 = R^2 = H$) with 1,1-dimethoxy-3-hydroxy-3-methylbutane in pyridine at 150°C, followed by methylation of the angular pyranoacridine **211,** which was isolated by repeated crystallization. Methylation of the unpurified condensation product also gave isoacronycine **249** and noracronycine **209,** in addition to acronycine **208.** Use of citral and farnesal in place of 1,1-dimethoxy-3-hydroxy-3-methylbutane provided mono- or diprenyl-substituted acridones and their cyclized product. The same approach was used by Ramesh and Kapil [86IJC(B)684] to prepare 11-hydroxynoracronycine **215** and atalaphyllidine **219.**



Lewis and his co-workers have reported three interrelated syntheses of acronycine **208** (81T209). In one synthesis, 2,6-dimethoxy-4-hydroxy-2′-nitrobenzophenone **250,** obtained as a minor product from Friedel–Crafts acylation of 3,5-dimethoxyphenol with 2-nitrobenzoylchloride, was treated with 3-chloro-3-methylbut-1-yne under basic conditions. The resultant nitro compound **251** was reduced to the amine **252** with zinc. Upon reaction with sodium hydride in DMSO, this amine provided a mixture of de-*N*-methylisoacronycine **253** and de-*N*-methylacronycine **210.** De-*N*-methylacronycine **210** was converted to acronycine **208** by methylation with methyl iodide (Scheme 42).

Coppola (84JHC913) condensed *N*-methylisatoic anhydride **254** with the lithium enolate of 2,6,7,8-tetrahydro-2,2-dimethylbenzopyran-5-one **255** to

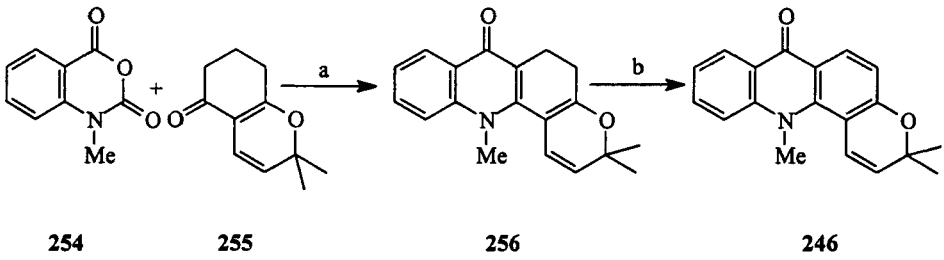


SCHEME 42. (a) $HC{\equiv}C{-}C(CH_3)_2Cl$, DMF, K_2CO_3, KI, 65°C, N_2, 14 h, 90%; (b) Zn/EtOH, rt 5 days, 98%; (c) NaH, DMSO, rt, 6 days, 29% (**210**), 43% (**253**); (d) MeI, K_2CO_3, acetone, reflux, 11 h, 80%.

obtain 5,6-dihydro-6-demethoxyacronycine **256.** Dehydrogenation with DDQ provided 6-demethoxyacronycine **246** (Scheme 43).

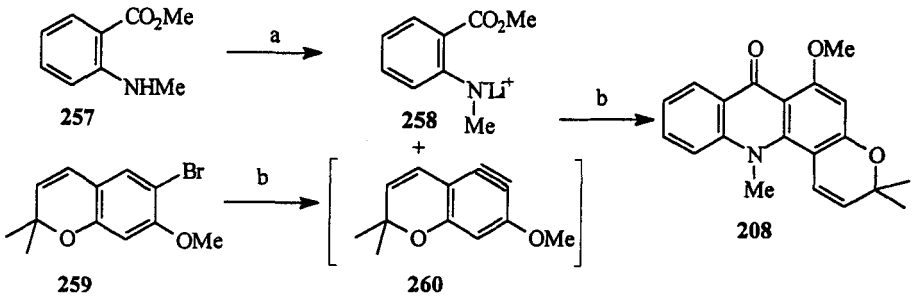
Watanabe *et al.* (84CPB1264) have reported a one-step synthesis of acronycine **208.** Lithium methyl(2-methoxycarbonyl)phenyl amide **258** generated from methyl *N*-methylanthranilate **257** *in situ* in the presence of excess lithium cyclohexylamide (LCA), was reacted with 6-bromo-2, 2-dimethyl-7-methoxychromene **259** to produce acronycine **208.** A benzyne intermediate **260** is believed to be involved in this reaction (Scheme 44).

A regiospecific synthesis of acronycine **208** from 3-acetyl-4-chloro-2-cyanomethylquinoline **261** has been described by Anand and Sinha (Scheme 45) [90H1733; 91JCS(P1)2339]. This synthesis involves alkylation of the cyanomethylene **261** with 1-bromo-3-methylbut-2-ene, methanolysis of the resulting nitrile **262** to give the ester **263,** and finally, ring closure and hydroxy-dechlorination to afford norglycocitrine II **264.** Oxidative cyclization of this acridone **264** with DDQ gave de-*N*-methylnoracronycine **211,**



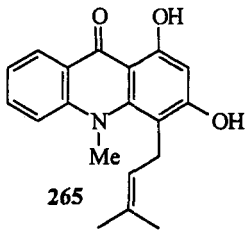
254 **255** **256** **246**

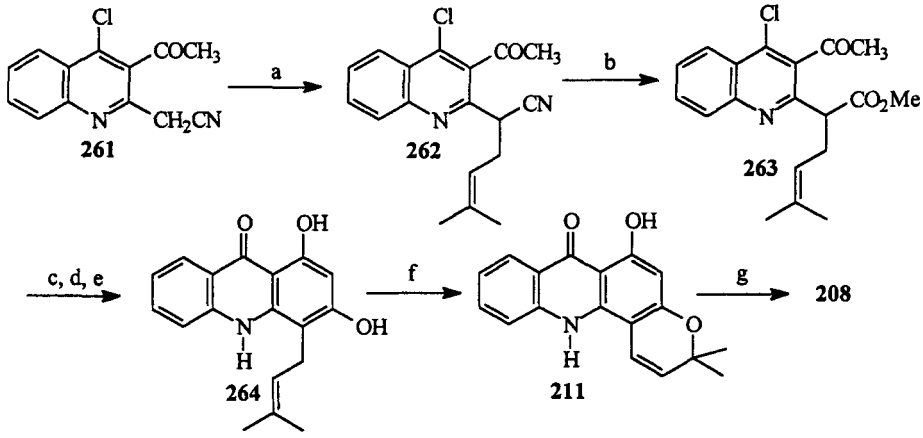
SCHEME 43. (a) LDA, THF, N_2, −65°C, 56%; (b) DDQ, 88%.



SCHEME 44. (a) LCA, THF, N_2, −78°C; (b) LCA, THF, N_2, −10°C, 41% (a,b).

which was converted to acronycine **208** by methylation with methyl iodode. In another reaction, glycocitrine II **265** was converted to noracronycine **209** by oxidative cyclization with benzeneselenyl chloride followed by hydrogen peroxide [83JCS(P1)1681].



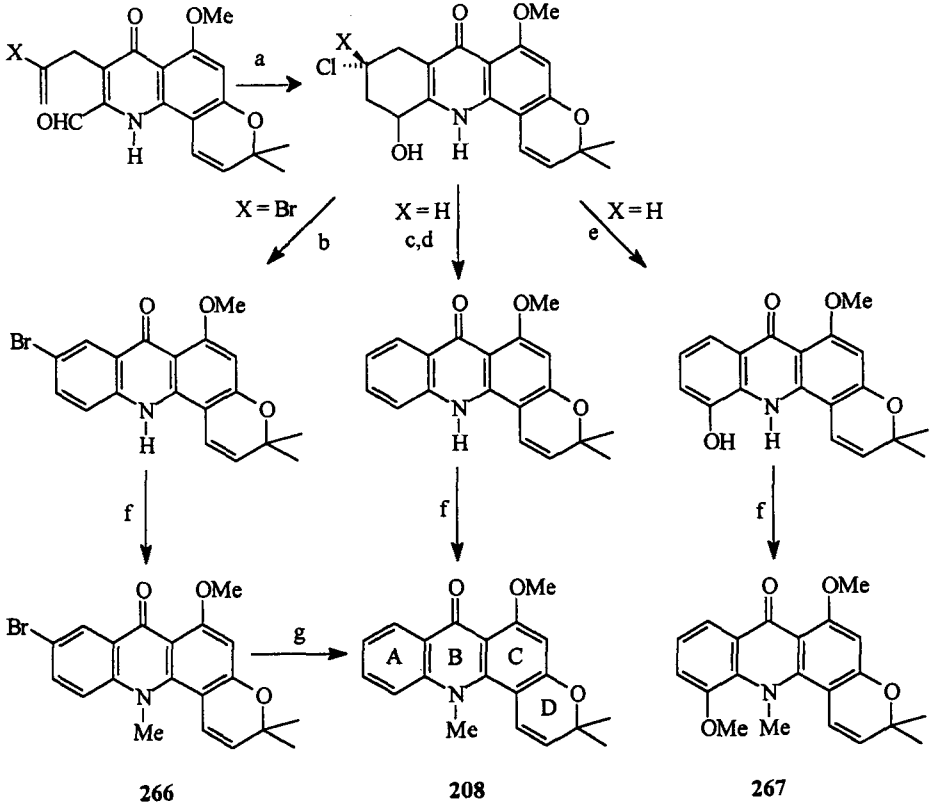


SCHEME 45. (a) $(CH_3)_2C{=}CHCH_2Br$, K_2CO_3, DMF, reflux, 30 h, 48%; (b) MeOH, HCl, 70%; (c) NaH, THF, 3 h; (d) PhOH, 100°C, 3 h; (e) HCl, MeOH, 10 h, 47% (c,d,e); (f) DDQ, toluene, 52%; (g) NaH, DMF, MeI, 85%.

The syntheses of acronycine **208** and its derivatives, such as **266, 267** reported by Blechert *et al.*, have novelty in that they involve the formation of ring "A" (Scheme 46) (78CB439; 80LA503).

Microbial conversions of acronycine **208** to its hydroxy derivatives have been reported by two research groups (74JMC599, 74JMC653). Among many microbial agents, *Aspergillus alleaceus, Cunninghamella echinulata,* and *Streptomyces spectablicus* are found to be effective.

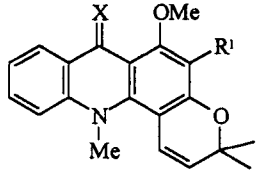
The reaction of organolithium compounds with noracronycine provided 7-substituted derivatives [95JCS(P1)511]. The reaction of acronycine with P_4S_{10} produced the thio analog **268** (79JPS36; 82S493), and oxidation of acronycine **208** resulted in one or more products that include acronycine epoxide **224,** 1-hydroxy-2-oxo-1,2-dihydroacronycine **269,** *cis*-1,2-dihydroxy-1,2-dihydroacronycine **270,** and 5-hydroxyacronycine **271,** de-



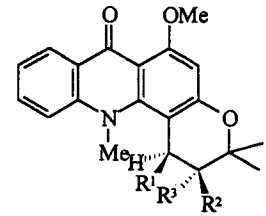
266 **208** **267**

SCHEME 46. (a) $TiCl_4$, CH_2Cl_2, rt 2 h, 60% (X = Br); (b) heat, 16%; (c) Ac_2O; (d) *t*BuOK; (e) DMSO, pyridine, TFA, DCC, rt 20 h; (f) MeI, K_2CO_3, acetone, 68% (X = Br); (g) BuLi, ether, 0°C, 4 h, 38%.

pending on the nature of the oxidizing agent (86JNP1091; 90M709; 94LA317, 94M731). The synthesis of 1-hydroxy-1,2-dihydroacronycine **272** and 2-hydroxy-1,2-dihydroacronycine **273** from acronycine **208** has also been reported (88MI2).

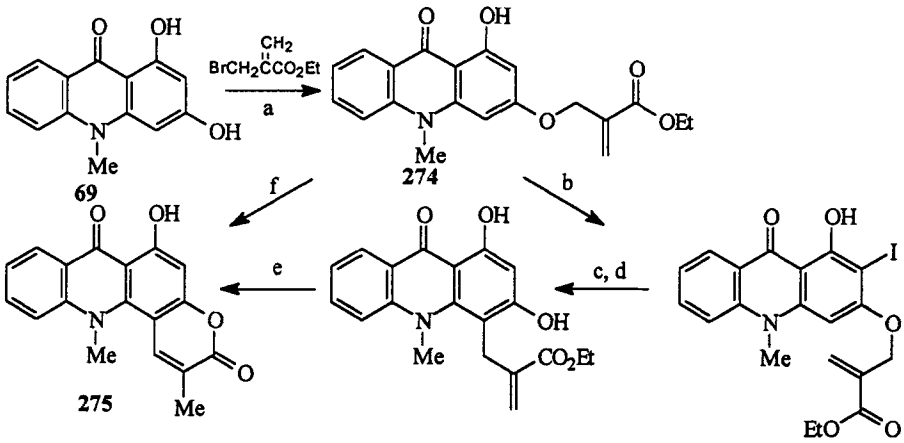


268 X = S; R^1 = H
271 X = O; R^1 = OH

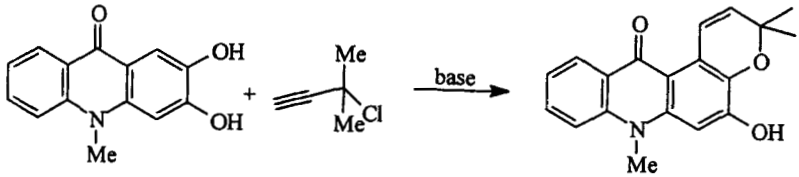


269 R^1 = OH; R^2R^3 = O
270 R^1 = R^2 = OH; R^3 = H
272 R^1 = OH; R^2 = R^3 = H
273 R^1 = R^2 = H; R^3 = OH

Reisch and Gunaherath [89JCS(P1)1047] have reported the synthesis of 2,12-dimethyl-6-hydroxypyrano[2,3-*c*]acridine-3,7(12*H*)-dione **275** by two different routes starting from the alkylation of 1,3-dihydroxy-10-methylacridin-9(10*H*)-one **69** to give the α,β-unsaturated ester **274** (Scheme 47).



SCHEME 47. (a) K_2CO_3, acetone, reflux, 2 h, 73%; (b) I_2, HIO_4 (aq.), EtOH, rt, 2 h, 90%; (c) Ac_2O, pyridine, 100°C, 3 h, 32%; (d) K_2CO_3, MeOH, reflux, 15 min, 77%; (e) PEG, 200°C, 30 min, 71%, (f) PEG, 220°C, 15 min, 45%.



276 **277**

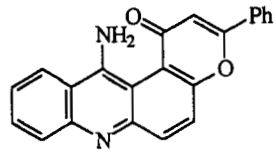
SCHEME 48

C. PYRANO[3,2-*a*]ACRIDINES

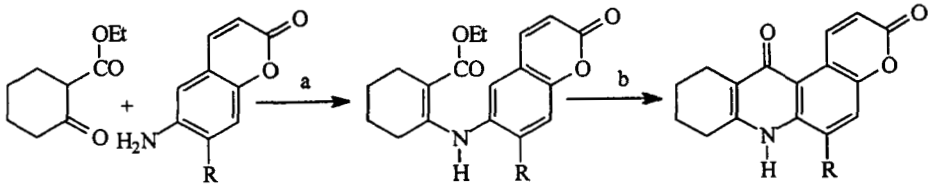
The coupling of 2,3-dihydroxy-10-methylacridin-9(10*H*)-one **276** with 3-chloro-3-methylbut-1-yne afforded a pyrano[3,2-*a*]acridine **277** (Scheme 48) (83MI1).

6-Aminobenzopyran-2-ones **279** undergo the Conrad–Limpach reaction with 2-ethoxycarbonylcyclohexanone **278** to give anils **280,** which, on heating in diphenyl ether at reflux, give cyclized products **281** (Scheme 49) (83JHC775).

We have prepared a series of pyrano[3,2-*a*]acridines (e.g., **282**) by the route described in Scheme 34, but using 6-oxo-5,6,7,8-tetrahydroflavone instead of 7-oxo-5,6,7,8-tetrahydroflavone (84TH1).



282

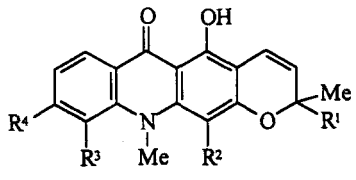


278 **279** **280** **281**

SCHEME 49. (a) Xylene, reflux, 29–30%; (b) Ph_2O, heat, 52%.

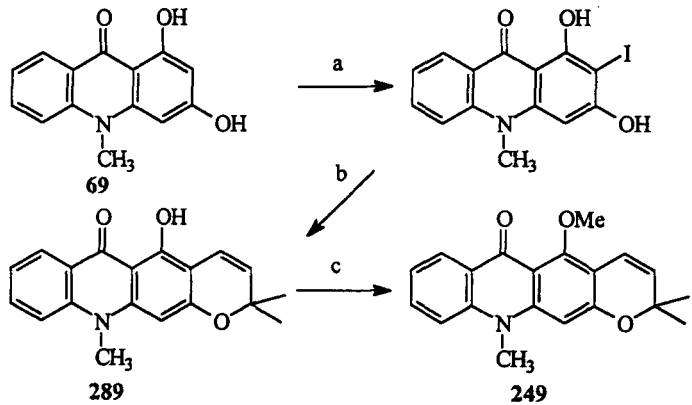
D. Pyrano[3,2-*b*]acridines

Linear pyranoacridines are very rare in nature. Only a few acridone alkaloids based on the pyrano[3,2-*b*]acridine ring system have been isolated and characterized. These include pyranofoline **283** and glycofoline **284** from *Glycosmis citrifolia* (Willd.) Lindl. [83JCS(P1)1681], honyumine **285** from *Citrus grandis* (86H41) and *Citrus funadoko* [90JCS(P1)1593], junosidine **286** from *Citrus junos* Tanaka (87H2077), and yukocitrine **287** from *Citrus yuko* Hort plant (92H2123) and, with 4-(2′-hydroxy-3′-methylbut-3′-enyl)-yukocitrine **288,** from *Bosistoa transversa* (96P235). Isoacronycine **249** or its de-*N*-methyl or de-*O*-methyl precursors have been separated as side products in most of the acronycine **208** syntheses (see pyrano[2,3-*c*] acridines).



283 R^1 = Me; R^2 = OMe; R^3 = OH; R^4 = H
284 R^1 = $Me_2C{=}CHCH_2$; R^2 = R^4 = H; R^3 = OH
285 R^1 = Me; R^2 = H; R^3 = OMe; R^4 = OH
286 R^1 = Me; R^2 = R^4 = H; R^3 = OMe
287 R^1 = Me; R^2 = R^4 = H; R^3 = OH
288 R^1=Me; R^2=CH_2=$C(CH_3)CH(OH)CH_2$; R^3=OH; R^4=H

Reisch *et al.* (91LA685) have reported a regioselective synthesis of isoacronycine **249** from 1,3-dihydroxy-10-methylacridin-9(10*H*)-one **69** that involves iodination at C-2, followed by palladium-catalyzed Heck condensation with 3-hydroxy-3-methylbut-1-ene to give isonoracronycine **289.** Methylation of isonoracronycine **289** with MeI gave isoacronycine **249** (Scheme 50).



Scheme 50. (a) I_2, H_5IO_6, EtOH, rt, 92%; (b) $Pd(OAc)_2$, $(nBu)_4N^+Br$, $CH_2{=}CH{-}C(OH)Me_2$; $NaHCO_3$, DMSO/DMF, N_2, 80°C, 36 h, 48%; (c) MeI, NaH, THF, 12 h, 80%.

We have prepared a linear pyranoacridine **291** by the condensation of *N*-benzyl anthranilonitrile with 7-oxo-5,6,7,8-tetrahydroflavone **200,** followed by base-catalyzed cyclization of the resultant enamine **290** (Scheme 51) (94TH1).

IV. Pyrroloacridines

Pyrroloacridines have been scarcely reported in the literature; only a few ring systems have been described.

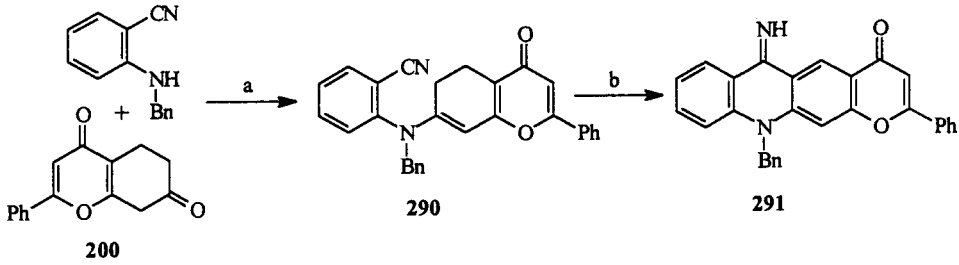
A. Pyrrolo[2,3-*b*]acridines

Bilgic and Young have reported the formation of the benzo[*j*]pyrrolo[2,3-*b*]acridine **294** in a reaction between 1-(*N,N*-dimethylaminomethyl)naphth-2-ol **292** and 5-aminoindole. A quinone methide **293** is believed to be involved as an intermediate (Scheme 52). The reaction of the naphthol **292** with 5-aminoindazole gave the angular pyrazoloacridine **295** [80JCS(P1) 1233].

B. Pyrrolo[2,3-*c*]acridines

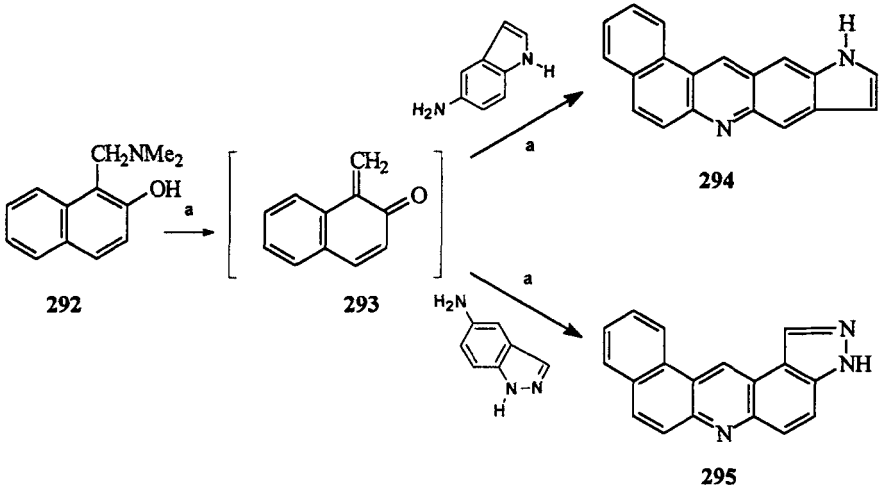
Takagi *et al.* have synthesized a number of 4,5-dihydropyrrolo[2,3-*c*] acridines **297** from 4-oxo-4,5,6,7-tetrahydroindoles **296** (Scheme 53) (73BSF2807). Syntheses of condensed heterocyclic compounds based on 4-oxotetrahydroindoles have also been reported in the Russian literature (75MI1).

Another strategy involves the fusion of a pyrrole ring onto the acridine nucleus. The Japp–Klingemann reaction of the diazonium salt **298** of 3-



200 **290** **291**

Scheme 51. (a) PTSA, toluene, reflux; (b) LDA, THF, N_2, −78°C.

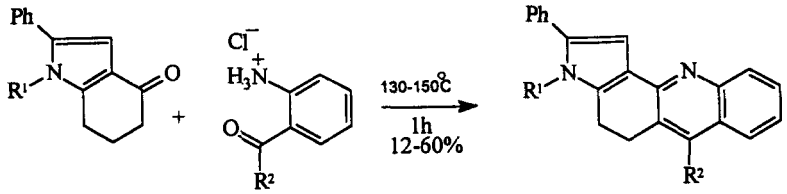


SCHEME 52. (a) Ph_2O, N_2, reflux, 16 h, 67% **294**, 61% **295**.

aminoacridine with ethyl 2-methylacetoacetate provided a hydrazone **299**, which was cyclized to pyrrolo[2,3-*c*]acridine **300** in the presence of $ZnCl_2$ (Scheme 54) (78KGS1277; 79KGS1092).

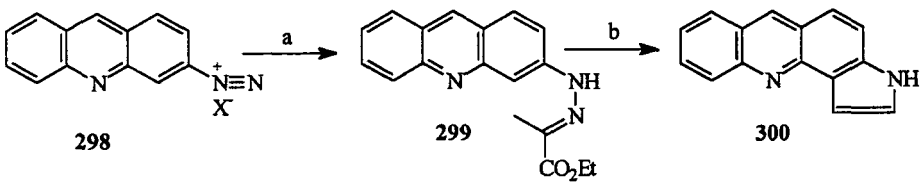
Wardani and Lhomme (93TL6411) used a different pathway for the construction of the pyrrole ring. Base-catalyzed alkylation of *N*-acetyl-*N'*-tosylproflavine **60** with bromoacetaldehyde diethyl acetal, followed by deprotection of the acetal function with concomitant ring closure and deacylation in acidic media yielded 9-amino-3-tosylpyrrolo[2,3-*c*]acridine **301.** Detosylation was achieved by basic hydrolysis to give 9-aminopyrrolo[2,3-*c*]acridine **302** (Scheme 55).

We have prepared pyrrolo[2,3-*c*]acridines **304** by our standard method, involving the base-catalyzed cyclization of the enamines **303,** followed by oxidation (Scheme 56) (96TH1).

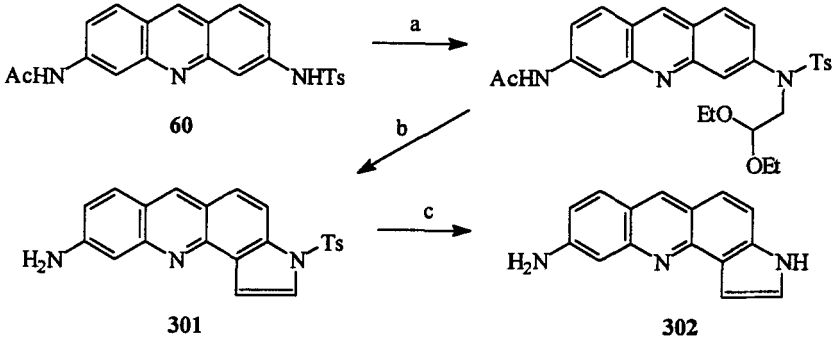


296 **297**

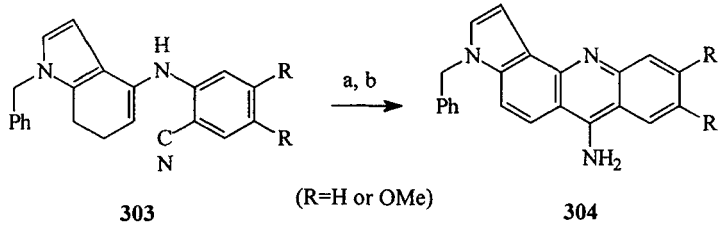
SCHEME 53. R^1 = H, Me, Et, Ph, *p* An, β-Naph; R^2 = Me, Ph.



SCHEME 54. (a) Ethyl 2-methylacetoacetate/base, 51%; (b) $ZnCl_2$.



SCHEME 55. (a) DMF, K_2CO_3, $BrCH_2CH(OEt)_2$, 80°C, 4 days; (b) CH_3SO_3H/CH_2Cl_2 (1:9) reflux, 24 h, 40% (a,b); (c) KOH; DMF–H_2O, 78°C, 5 h, 75%.



SCHEME 56. (a) $NaNH_2$, DME; (b) MnO_2, DMF, reflux.

C. Pyrrolo[2,3,4-*kl*]acridines

Three polycyclic alkaloids that contain this ring system as part of their structures, plakinidines A **78,** B **79,** and C **80,** were isolated from the marine sponge *Plakortis* sp. (see Section II,C,1 on pyrido[3,2-*c*]acridines).

Gellerman *et al.* (94T12959) have described the biomimetic synthesis of a pyrrolo[2,3,4-*kl*]acridine **305** (Scheme 57).

V. Thienoacridines

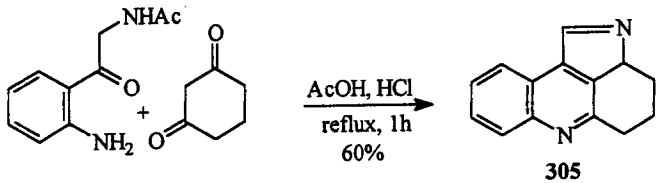
Only a few thienoacridine ring systems are known, and all are synthetic.

A. Thieno[2,3-*c*]acridines

The Pfitzinger reaction of 6,7-dihydrobenzothiophen-4(5*H*)-ones **306** with isatins **307** produced 4,5-dihydrothieno[2,3-*c*]acridine-6-carboxylic acids **308** (Scheme 58) (50RTC1053; 55BSF1252, 55JCS21; 58JCS2418). Decarboxylation of the acid **308** (R = Me, X = H) upon heating above the melting point has been reported to give the dihydro derivative **309** (50RTC1053; 55BSF1252), and Buu-Hoï has reported the decarboxylation with concomitant dehydrogenation of the acid **308** (R = Et, X = Br) to give 6-bromo-2-ethylthieno[2,3-*c*]acridine **310** (Scheme 58) (58JCS2418).

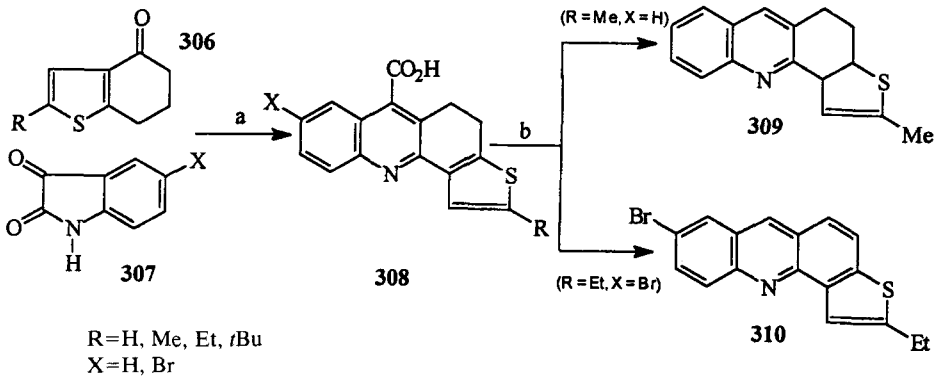
Remers *et al.* (71JMC1127) have used a quite different approach, which involves the Vilsmeier–Haack formylation of 6,7-dihydrobenzothiophen-4(5*H*)-one **306** (R = H) followed by cyclocondensation with aniline to give 4,5-dihydrothieno[2,3-*c*]acridine **311** (Scheme 59).

Strekowski *et al.* (90JOC4777) condensed the 6,7-dihydrobenzothiophen-4(5*H*)-one **306** (R = H) with 2-trifluoromethylaniline and then cyclized the resultant imine **312** with lithium 4-methylpiperazide to afford this ring system **313** (Scheme 60).

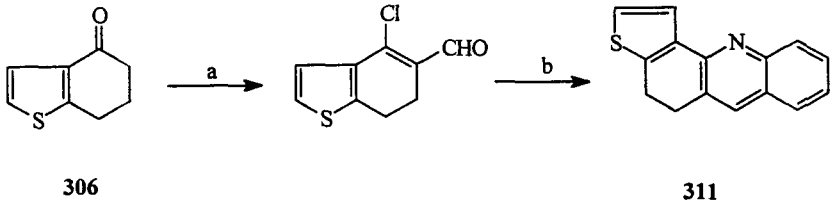


305

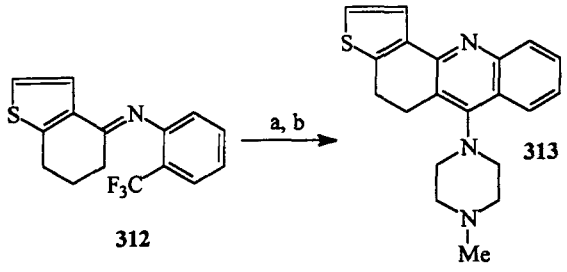
Scheme 57



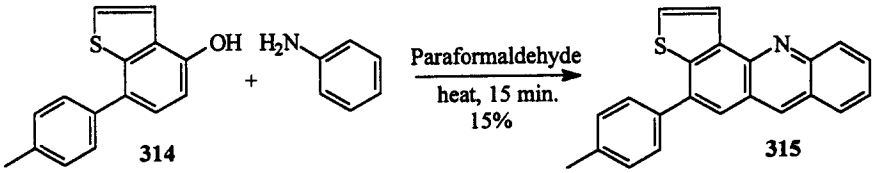
SCHEME 58. (a) KOH, EtOH, reflux, 10–24 h; (b) Heat > 300°C.



SCHEME 59. (a) $POCl_3$–DMF, 100°C, 1 h, 17%; (b) aniline, AcOH, reflux, 3 h, 67%.



SCHEME 60. (a) Lithium 4-methylpiperazide, Et_2O, −10°C, 30 min; (b) H_3O^+.



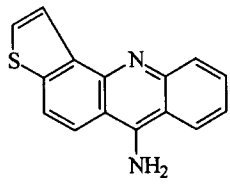
314 315

SCHEME 61

The Fetvadjian–Ullmann reaction between 4-hydroxy-7-(*p*-tolyl)benzothiophene **314,** aniline, and paraformaldehyde provides another pathway for the construction of thieno[2,3-*c*]acridines, such as **315** (Scheme 61) (81JHC1519).

Suresh *et al.* (93SUL7) have described a novel route for the preparation of thieno[2,3-*c*]acridines **316** that involves photocyclization (Scheme 62).

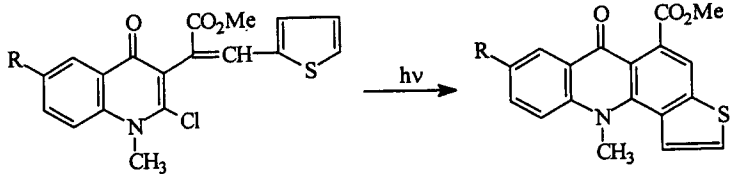
We have used the strategy developed for the synthesis of pyrido[2,3-*c*]acridines to prepare thieno[2,3-*c*]acridines, such as **317** (96TH1).



317

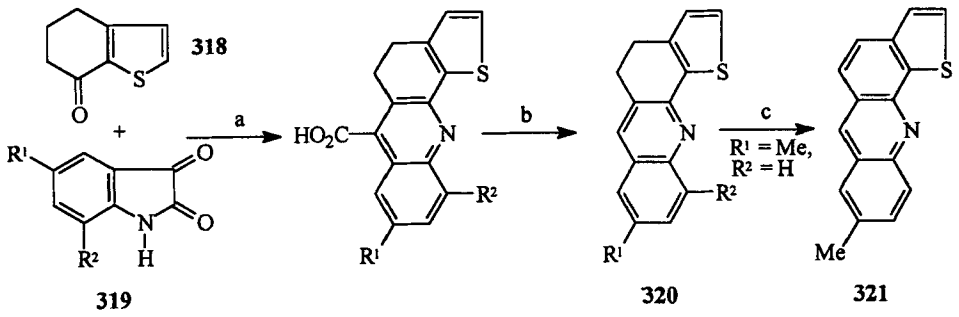
B. THIENO[3,2-*c*]ACRIDINES

Buu-Hoï and Royer (46CR806) obtained a series of thieno[3,2-*c*]acridines **320** by using the Pfitzinger reaction between 4,5-dihydrobenzothiophene-7(6*H*)-one **318** and isatins **319,** followed by decarboxylation at high temperature (Scheme 63). One of the decarboxylated products **320** (R^1 = Me, R^2 = H) was dehydrogenated with PbO at 310°C to give the fully aromatic system **321.**



316

SCHEME 62



SCHEME 63. R^1 = H, Me, Br; R^2 = H, Me. (a) KOH, EtOH; (b) heat; (c) PbO, 310°C.

C. THIENO[3,4-*c*]ACRIDINES

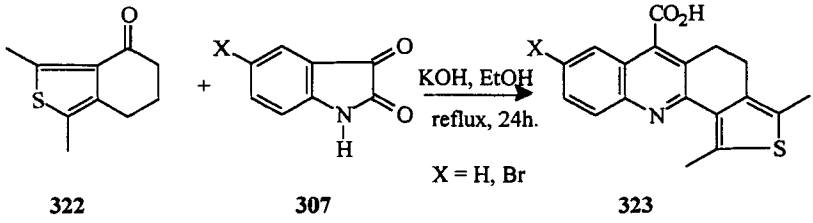
Isatins **307** on reaction with 1,3-dimethyl-6,7-dihydroisothiophene-4(5*H*)-one **322** gave 2,3-dimethyl-4,5-dihydrothieno[3,4-*c*]acridine-6-carboxylic acids **323** (Scheme 64) (50RTC1053).

VI. Furoacridines

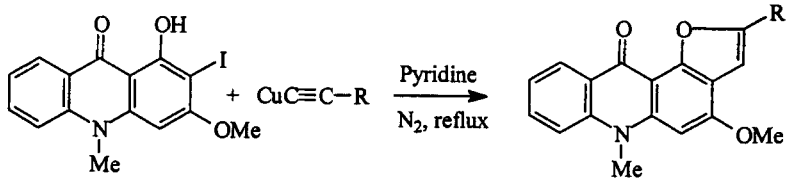
Only three furoacridine ring systems have been reported.

A. FURO[2,3-*a*]ACRIDINES

The reactions of copper(I) phenylacetylide **325a** and copper(I) isopropenylacetylide **325b** with 1-hydroxy-2-iodo-3-methoxy-10-methylacridin-9(10*H*)-one **324** gave furo[2,3-*a*]acridones **236a** and **236b** (Scheme 65) (84LA31).



SCHEME 64



324 **325a** R = Ph **326a** R=Ph (15%)

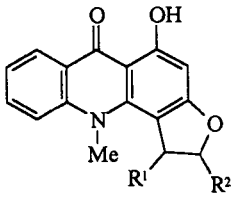
325b R = CH_2=C–CH_3 **326b** R = CH_2=C–CH_3 **(58%)**

SCHEME 65

B. FURO[2,3-*c*]ACRIDINES

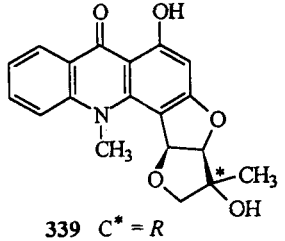
1. *Isolation*

This ring system is the basic skeleton of a number of acridone alkaloids isolated from intact plants or cell tissue cultures of various species from the Rutaceae family. Most of the dihydrofuroacridone alkaloids have been isolated from *Ruta graveolens:* rutacridone **327** (67MI1; 81MI1; 87PHA67; 88MI1; 90PHA500; 91MI3), rutacridone epoxide **328** (81MI1, 81ZN200; 82ZN132; 85MI2; 87PHA67; 88MI1; 90PHA500; 91MI2), 20-hydroxyrutacridone epoxide **329** (82ZN132; 85MI2), 1-hydroxyrutacrodine epoxide **330** (85MI2), gravacridonol **331** (81MI1; 85MI2), gravacridone chloride **332** (73P2359; 87PHA67; 88MI1), isogravacridone chloride **333** (77P151; 91MI1), gravacridondiol **334** (72P2121; 76MI1, 76P240), gravacridondiol acetate **335** (91MI2), gravacridondiol monomethyl ether **336** (72P2121), gravacridontriol **337** (76MI1, 76P240), gravacridonolchlorine **338** (72P2121, 72P2359), and rutagravin **339** (85MI2). Rutacridone **327** and its epoxide **328** have also been detected in *Boenninghausenia albiflora* (78P169).



327 R^1 = H; R^2 = H_2C=CCH_3 (Me)

328 R^1 = H; R^2 = 



339 C^* = *R*

340 C^* = *S*

329 $R^1 = H$; $R^2 =$ 

330 $R^1 = OH$; $R^2 =$ 

331 $R^1 = H$; $R^2 = H_2C{=}CCH_2OH$

332 $R^1 = H$; $R^2 = H_3CC(Cl)CH_2OH$

333 $R^1 = H$; $R^2 = H_3CC(OH)CH_2Cl$

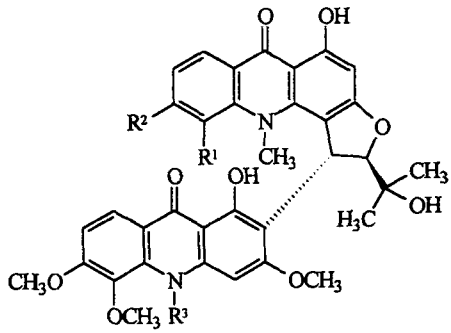
334 $R^1 = H$; $R^2 = H_3CC(OH)CH_2OH$

335 $R^1 = H$; $R^2 = H_3CC(OH)CH_2OAc$

336 $R^1 = H$; $R^2 = H_3CC(OH)CH_2OMe$

337 $R^1 = H$; $R^2 = HOC(CH_2OH)_2$

338 $R^1 = H$; $R^2 = ClC(CH_2OH)_2$



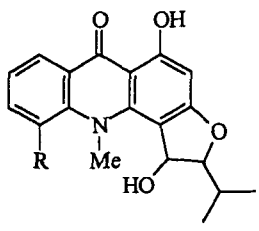
341 $R^1 = OH$; $R^2 = R^3 = H$

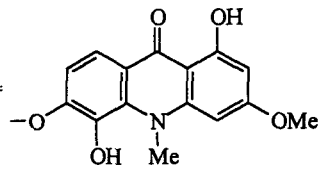
342 $R^1 = OMe$; $R^2 = OH$; $R^3 = H$

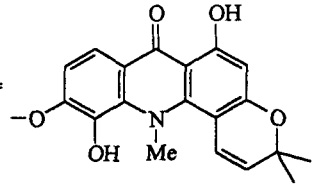
343 $R^1 = OMe$; $R^2 = OH$; $R^3 = Me$

Some of these dihydrofuroacridones, **327, 328, 331, 333, 334,** and **337,** have been separated by Baumert *et al.* from the cell culture of *Thamnosma montana* (94MI1). They have also obtained the glucosides of gravacridonol, gravacridondiol, and gravacridontriol. The last two glucosides were also isolated from roots and tissue culture of *Ruta graveolens* (76MI1, 76P240).

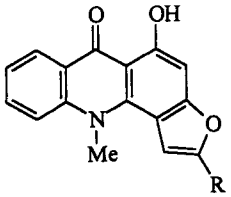
Three bisacridone alkaloids, citbisamines A **341,** B **342,** and C **343,** containing a C—C bond linkage between the dihydrofuroacridone and the acridone ring systems, have been isolated by Takemura *et al.* from the roots of Marsh grapefruit (*Citrus paradisi*) and Hirado-buntan (*Citrus grandis*) (95CPB1340). Previously, Fraser and Lewis reported the isolation of two dimeric alkaloids (containing *O*-linkages), atalanine **344** and ataline **231,** from *Atlantia ceylanica* [73JCS(CC)615].



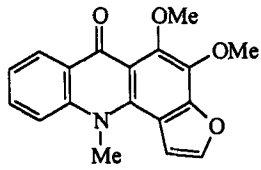
344 R = 

231 R = 

A fully dehydrogenated furoacridine (furacridone = furofoline-I) **345** was detected for the first time in *Ruta graveolens* by Reisch *et al.* (77P151) as a mixture with 1-hydroxy-3-methoxy-10-methylacridin-9(10*H*)-one. Wu *et al.* [83JCS(P1)1681] were able to isolate furofoline-I **345** and furofoline II **346** from *Glycosmis citrifolia* (willd.) Lindl.



345 R = H
346 R = $C(OH)Me_2$
347 R = COMe



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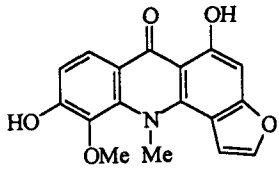


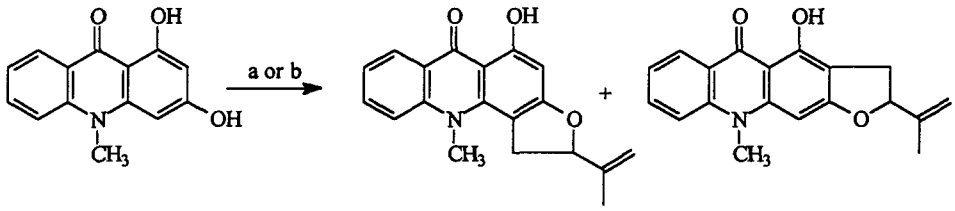
349

Hallacridone **347** was isolated from *Ruta graveolens* by Baumert *et al.*, along with the dihydrofuroacridones **327, 328,** and **332** (87PHA67; 88MI1). Its structure was revised by Reisch and Gunaherath [89JCS(P1)1047] on the basis of spectroscopic evidence and total synthesis. It was also isolated from tissue cultures of *Ruta graveolens* (90PHA500) and *Thamnosma montana* (94MI1). Isolation of two new alkaloids, thehaplosine **348** (93MI2) and furoparadine **349** (95H187), has been achieved from the aerial parts of *Halophyllum thesioides* and roots of Marsh grapefruit (Rutaceae), respectively.

2. *Syntheses*

Rutacridone **327** was synthesized for the first time by Mester *et al.* (81H77) by base-catalyzed alkylation, with concomitant cyclization, of 1,3-dihydroxy-10-methylacridin-9(10*H*)-one **69** with 1,4-dibromo-2-methylbut-2-ene. The linear isomer, isorutacridone **350,** was also obtained as a by-product (Scheme 66). A better yield of rutacridone **327** was obtained when Al_2O_3 was used as the catalyst (90M829). Once again, isorutacridone **350** was obtained as a by-product (Scheme 66).

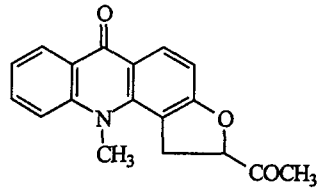
Maier *et al.* have observed that microsomes (from *Ruta graveolens* cell cultures) catalyze the condensation of 1,3-dihydroxy-10-methylacridin-9(10*H*)-one **69** with isopentenyl pyrophosphate or dimethylallyl pyrophosphate, in the presence of NADPH and O_2, to produce rutacridone **327,** and also that the reaction involved glycocitrine-II **265** as an intermediate (90MI2; 93P691). A possible precursor **351** of rutacridone **327** has also been isolated from a reaction of glycocitrine-II **265** with *m*-chloroperbenzoic acid (MCPBA) (Scheme 67) (93CPB383).



69 **327** **350**

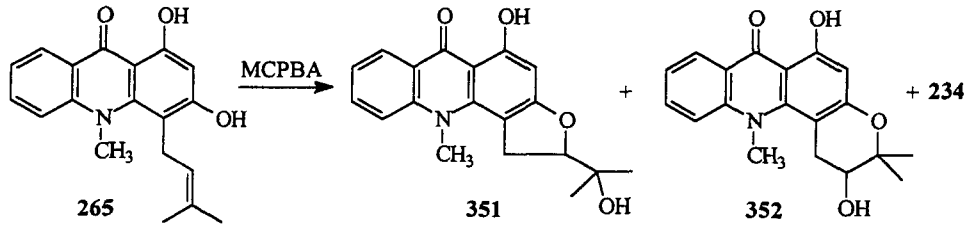
SCHEME 66. (a) Na, MeOH, $BrCH_2CH{=}C(CH_3)CH_2Br$, 15.5% (**327**), 5.2% (**350**); (b) Al_2O_3, $ClCH_2CH{=}C(CH_3)CH_2Br$.

Selective hydroxylation of rutacridone **327** with SeO_2 in the presence of *t*BuOOH provided gravacridonol **331** (91LA299), and oxidation with $KMnO_4$ afforded rutagravin **339,** isorutagravin **340,** gravacridondiol **334,** and dihydrohallacridone **353** [69CI(L)1809]. Dehydrogenation of dihydrohallacridone with DDQ produced hallacridone **347** [94JCR(S)157].



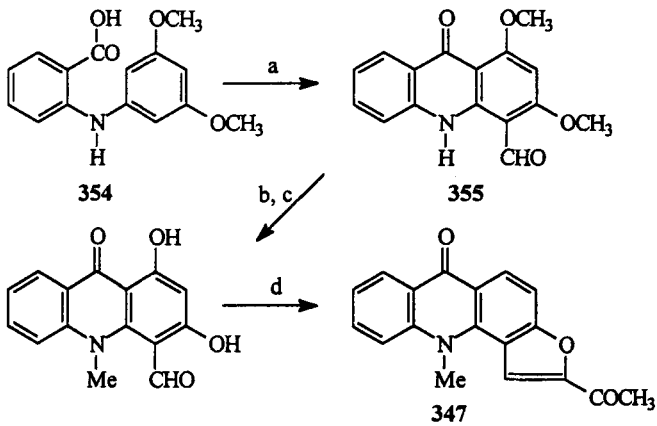
353

To confirm its structure, Reisch *et al.* have synthesized hallacridone **347** (Scheme 68) [89JCS(P1)1047]. Ullmann-amine coupling of 2-chlorobenzoic acid and 3,5-dimethoxyaniline gave an amine **354** that, on treatment with DMF-$POCl_3$, provided 4-formyl-1,3-dimethoxyacridin-9(10*H*)-one **355.** *N*-Methylation, *O*-demethylation, and subsequent condensation with 1-chloropropan-2-one in basic media gave hallacridone **347.**



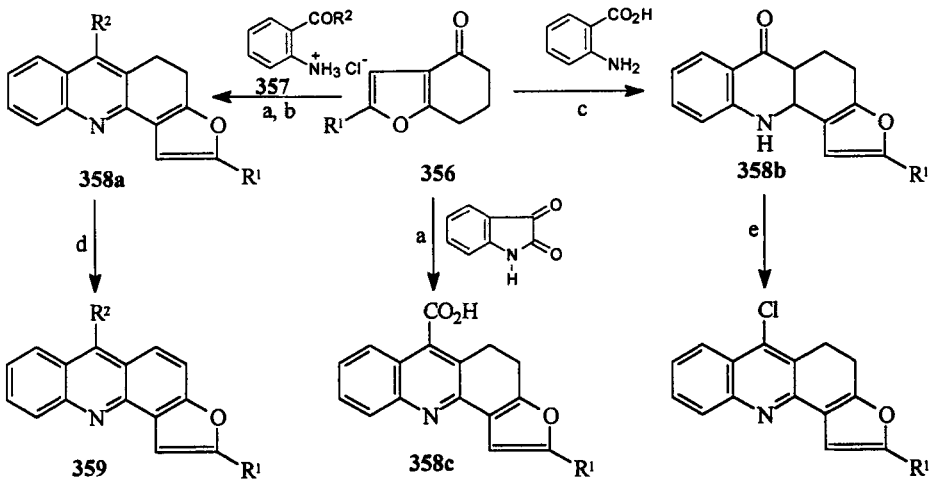
265 **351** **352**

SCHEME 67

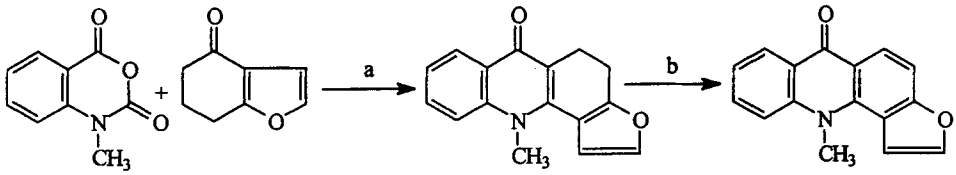


SCHEME 68. (a) $POCl_3$, DMF, rt, 1.5 h, 15%; (b) MeI, Ag_2O, DMF, 16 h, 76%; (c) BCl_3, CH_2Cl_2, rt 72 h, 64%; (d) $ClCH_2COCH_3$, K_2CO_3, acetone, reflux, 2 h, 50%.

Takagi and Ueda have prepared a number of 4,5-dihydrofuro[2,3-*c*]acridines **358a–c** from 4,5,6,7-tetrahydrobenzofuran-4-ones **356** by condensing with isatin, anthranilic acid, and 2-aminophenylcarbonyl hydrochlorides **357** using a range of conditions (Scheme 69) (71CPB1218; 72CPB380,



SCHEME 69. R^1 = Me, Ph, *p*MeO-Ph, *p*Br-Ph; R^2 = Me, Ph. (a) KOH, EtOH, reflux, 50–64 h, 18–31% (**358c**); (b) heat 110–140°C, 1 h, 40–71%, (a,b); (c) 120–200°C, 1 h, 16–38%; (d) Pd/C, 260–290°C, 15 min, 40–54%; (e) $POCl_3$, 135°C, 2 h, 71%.



254 **356** **360** **361**

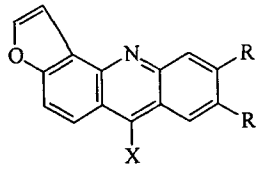
SCHEME 70. (a) LDA, −65 to −40°C, 2 h, 67%; (b) DDQ, toluene, 70°C, 15 min., 100%.

72CPB2051). Dehydrogenation of 4,5-dihydrofuro[2,3-*c*]acridines **358** has also been reported to give the aromatic systems **359.**

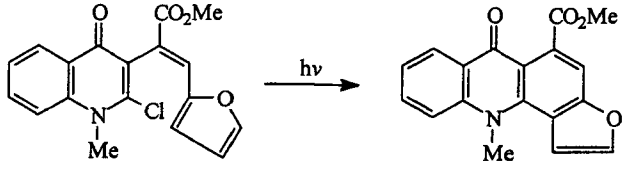
Coppola (84JHC1569) condensed *N*-methylisatoic anhydride **254** with the lithium enolate of 4,5,6,7-tetrahydrobenzofuran-4-one **356** (R = H) and obtained *N*-methylfuro[2,3-*c*]acridin-6-one **361** after dehydrogenation of the resultant 4,5-dihydrofuroacridone **360** (Scheme 70).

The method of Jayabalan and Shanmugan is novel in that it involves the construction of a ring between a quinoline and furan moieties to complete this skeleton (Scheme 71) (91ZN558).

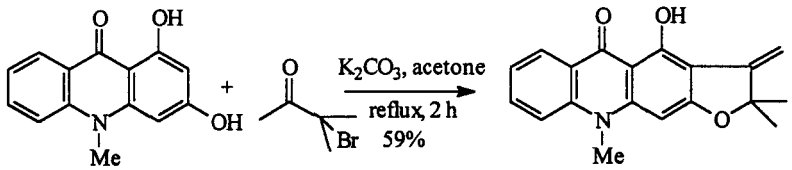
Once again, we have used the strategy developed for the synthesis of pyrido[2,3-*c*]acridines to prepare furo[2,3-*c*]acridines **362** (96TH1).



362 (R=H or OMe)



SCHEME 71



69 **363**

SCHEME 72

C. FURO[3,2-*b*]ACRIDINES

Reisch and co-workers have isolated isorutacridone **350** as a by-product during their base-catalyzed (81H77) and Al_2O_3-catalyzed (90M829) synthesis of rutacridone **327** (Scheme 66). They observed that the use of an ion-exchange resin as the catalyst favored the formation of isorutacridone **350** as the major product (81H77). The same group also reported the formation of another linear furoacridine, 4-hydroxy-3-methylene-2,2,10-trimethyl-2,3-dihydrofuro[3,2-*b*]acridin-5(10*H*)-one **363** (Scheme 72) (89JHC1849).

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