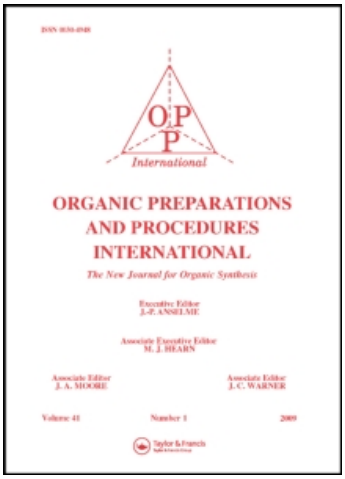

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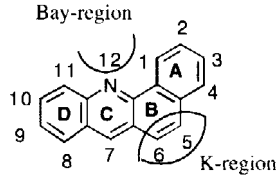
INTRODUCTION

Benz[*c*]acridines have been recently identified as environmental pollutants and they have also been isolated from various sources such as lake sediments[1-3] and coastal sediments.[4] The mutagenicity[5] and carcinogenicity,[6-9] chromatographic[1,10] and spectroscopic properties,[11] and metabolism by enzymes such as monooxygenases[12] on benz[*c*]acridines have been extensively studied.[1c] When benz[*c*]acridines are fed to animals[13] or incubated with hepatocytes[13,14] or lung and liver microsomal preparations,[14-16] various oxygenated benz[*c*]acridines are produced. For example, 7-methylbenz[*c*]acridine, when incubated with rat liver microsomal preparations, produces *trans*-8,9-dihydro-8,9-dihydroxy-7-methylbenz[*c*]acridine, 7-hydroxymethylbenz[*c*]acridine, and *trans*-5,6-dihydro-5,6-dihydroxy-7-methylbenz[*c*]acridine.[15] In most cases, metabolites are the primary or secondary oxidation products of benz[*c*]acridines which are produced under enzymatic action such as cytochrome P-448 or cytochrome P-450.[14b] Due to dosage limitations and other factors, the amount of the recovered metabolites from *in vivo* and *in vitro* experiments are limited.

The various oxidized metabolites of the benz[*c*]acridines acquire their carcinogenic properties by the metabolic activation, since it is very likely that the benz[*c*]acridines follow mechanisms analogous to the metabolic activation of carcinogen polycyclic aromatic hydrocarbons (PAHs).[17] Benz[*c*]acridines have carcinogenic regions of K- and bay-region or non-K-region. Two regions on benz[*c*]acridine ring system have been recognized as the sites of oxidation and other biological detoxification reactions. Current research has implicated bay region oxygenated metabolites, particularly bay region diol epoxides, as the active carcinogenic forms. Methods employed for the synthesis of oxygenated metabolites of the benz[*c*]acridines are largely based on methods developed for the

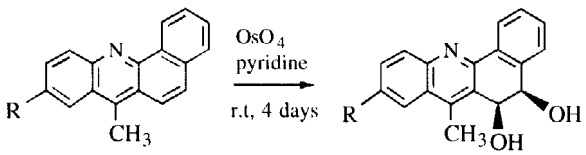
synthesis of the carcinogenic metabolites of PAHs.[18] This review summarizes the syntheses of potential carcinogenic oxygenated benz[*c*]acridines. The literature is covered up to the end of 1992, with some 1993 papers being included as well.



I. SYNTHESES OF OXYGENATED DERIVATIVES OF BENZ[*c*]ACRIDINES

1. Syntheses of K-region Oxygenated Benz[*c*]acridines

Reactions of eleven benz[*c*]acridine derivatives with osmium tetroxide (OsO_4) in the presence of pyridine gave the corresponding *cis*-5,6-dihydro-5,6-dihydroxy-benz[*c*]acridine derivative-OsO_4-pyridine (1:1:2) complexes.[19] OsO_4/pyridine was used to convert 7-methylbenz[*c*]acridine (**1**) to *cis*-5,6-dihydro-5,6-dihydroxy-7-methylbenz[*c*]acridine (**2**) in 72% yield.[20] 7,9-Dimethylbenz[*c*]acridine (**3**) also gave *cis*-5,6-dihydro-5,6-dihydroxy-7,9-dimethylbenz[*c*]acridine (**4**) under the same reaction conditions.[21,22]

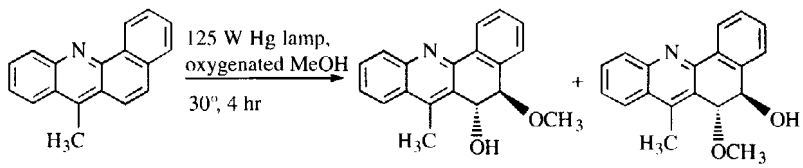


1: R = H
3: R = CH_3

2: R = H
4: R = CH_3

(1)

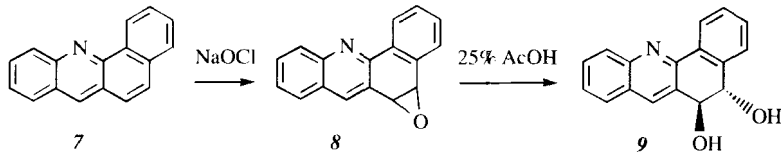
Photolysis of **1** in oxygenated MeOH has produced *trans*-6-hydroxy-5-methoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (**5**) and *trans*-5-hydroxy-6-methoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (**6**).[23]



1 *5* *6*

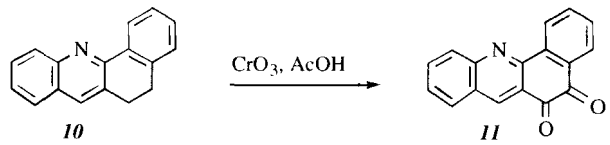
(2)

Benz[*c*]acridine-5,6-oxide (**8**) was synthesized[24] in 42% yield from benz[*c*]acridine (**7**) by using sodium hypochlorite and the method of Krishman and co-workers.[25] Hydrolysis of **8** under acidic conditions afforded *trans*-5,6-dihydroxy-5,6-dihydrobenz[*c*]acridine (**9**) in 23% yield.[24]



7 8 9 (3)

Chromic acid oxidation of 5,6-dihydrobenz[*c*]acridine (**10**) produced benz[*c*]acridine-5,6-dione (**11**),[26] while CrO_3 oxidation of dibenz[*b,h*]acridine (**12**) gave dibenz[*b,h*]acridine-8,13-dione (**13**) in 90% yield.[27]



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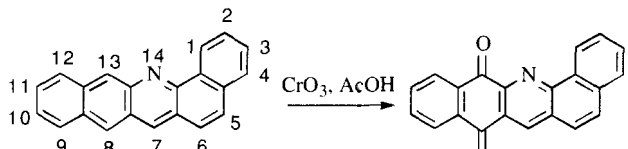
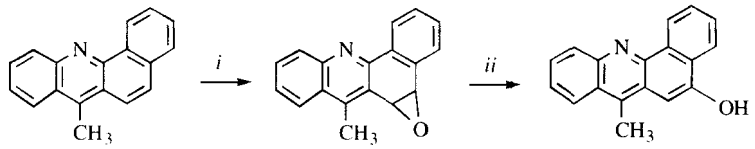


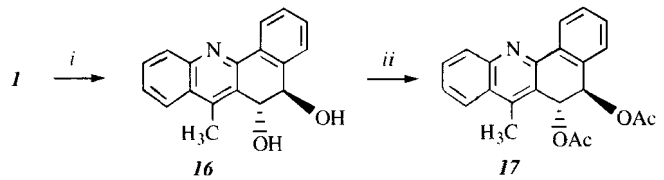
12 13 (5)

5,6-Epoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (**14**) was obtained in 49% yield when **1** was oxidized in $CHCl_3$ by 0.6M aqueous NaOCl containing 0.8M sodium phosphate buffer (pH 8.5), in the presence of tetrabutylammonium hydrogen sulfate (0.45 equiv.). Treatment of **14** with 0.2% H_2SO_4 in AcOH gave 5-hydroxy-7-methylbenz[*c*]acridine (**15**). On the other hand, when the reaction was carried out without the buffer, **14** was contaminated with 7-nor-analog; **8** was probably formed *via* oxidation of 7-methyl group and decarboxylation. **1** was oxidized by CF_3CO_3H to *trans*-5,6-dihydroxy-7-methyl-5,6-dihydrobenz[*c*]acridine (**16**); **1** was converted to **2** by OsO_4 oxidation. Both **16** and **2** were acetylated by perdeuterated Ac_2O to give *trans*- (**17**) and *cis*-5,6-diacetoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (**18**), respectively.[28]



1 14 15 (6)

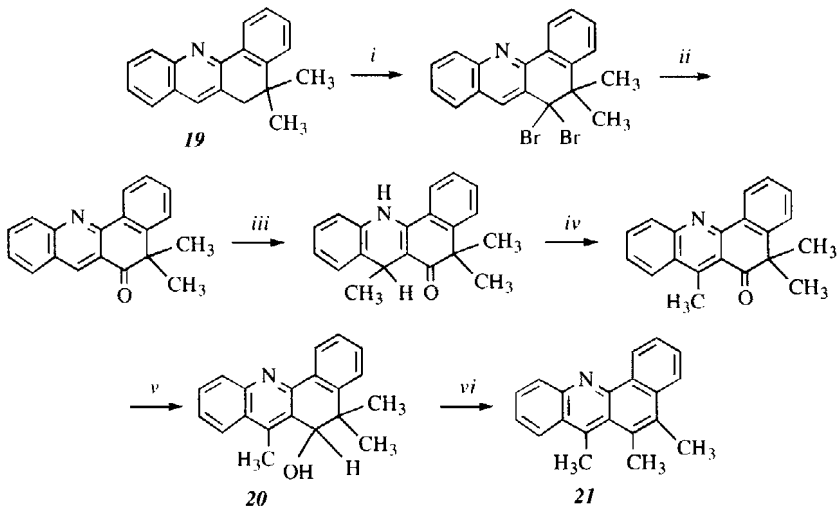
i) NaOCl, $CHCl_3$, $[CH_3(CH_2)_3]_4NHSO_4$, pH 8.5 phosphate buffer *ii*) 0.2% H_2SO_4, AcOH



16 17 (7)

i) CF_3CO_3H *ii*) Ac_2O, pyridine

5,6,7-Trimethylbenz[*c*]acridine (**21**) was obtained by six steps from 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (**19**) *via* 6-hydroxy-5,5,7-trimethyl-5,6-dihydrobenz[*c*]acridine (**20**).[29]



(8)

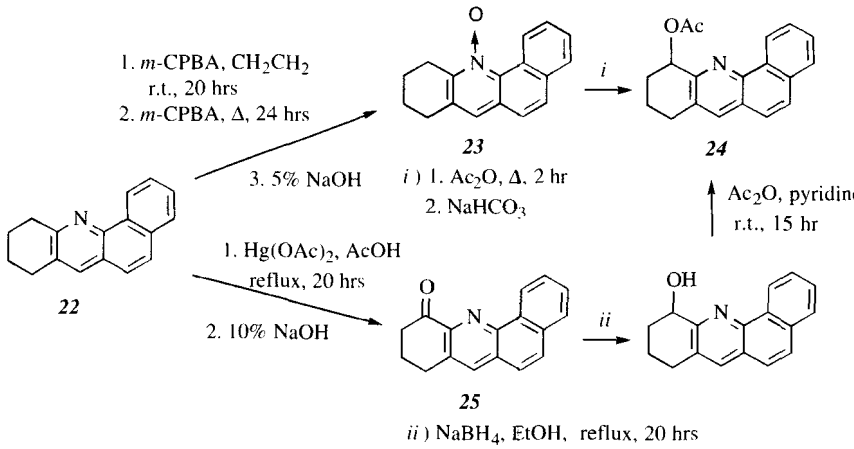
i) NBS, CCl_4 , Δ, 1.5 hr *ii*) 1. aq.3% MeOH 2. 50% KOH *iii*) $(Me_2Cu)Li$
iv) 1. DDQ, $CHCl_3$ 2. 10% NaOH *v*) 1. $NaBH_4$, diglyme 2. 50°, 18 hr
vi) 1. 95% H_2SO_4, stir 2 hr, 2. 50% NaOH

2. Syntheses of Non-K-region Benz[*c*]acridines

a) Syntheses of D-ring Oxygenated Benz[*c*]acridines

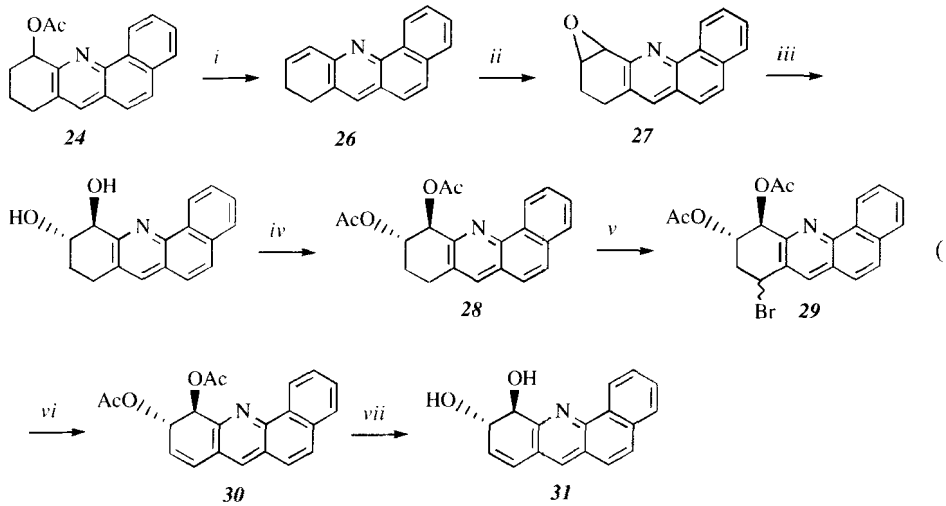
Synthetic approaches to the D-ring dihydrodiol derivatives of benz[*c*]acridine are most conveniently based on the tetrahydrobenz[*c*]acridines. Introduction of a double bond into the tetrahydrobenz[*c*]acridine is a key step. Conversion of these olefins to the corresponding tetrahydrodiols is readily accomplished through epoxidation with *m*-CPBA followed by hydrolysis which is used for the synthesis of metabolites of PAHs.[18] Dehydrogenation of the tetrahydrodiols to the corresponding dihydrodiols is accomplished smoothly via the bromination-dehydrobromination sequence. The starting compound, 8,9,10,11-tetrahydrobenz[*c*]acridine (**22**), may be prepared in large quantities by a literature procedure.[30] Recently, compound **22** has been synthesized in 65% yield from the readily available 2-chlorocyclohex-1-ene-1-carbaldehyde in a one-pot procedure by condensation with 1-naphthylamine, followed by thermal cyclization.[31]

In order to introduce the oxygen functionality into the 11-position of **22**, two synthetic routes have been developed.[24] First, reaction of **22** with *m*-CPBA yielded *N*-oxide (**23**) which was treated with excess acetic anhydride to afford 11-acetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (**24**) in good overall yield. Second, a novel approach involved treatment of **22** with mercuric acetate to yield 11-oxo-8,9,10,11-tetrahydrobenz[*c*]acridine (**25**). Reduction of **25** with $NaBH_4$ followed by acetylation allowed the isolation of **24** in 55-60% overall yield from **22**.



(9)

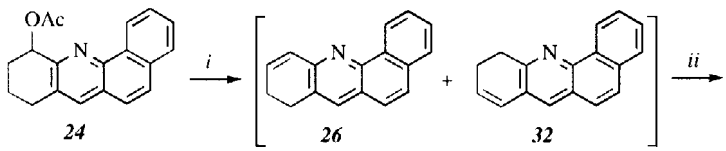
Conversion of **24** to 8,9-dihydrobenz[*c*]acridine (**26**) was accomplished with polyphosphoric acid (PPA) at 100° for 2 hrs in 91% yield. Attempts to synthesize *trans*-10,11-diacetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (**28**) from the alkene **26** by the Prévost reaction[32] were unsuccessful, as **26** was resistant to addition of acetyl hypoiodite. However, epoxidation of **26** with *m*-CPBA followed by ring opening with formic acid, and acetylation with Ac_2O/pyridine afforded **28** in 55% overall yield. Bromination of **28** with NBS in CCl_4, followed by dehydrobromination of the resulting 8-bromo-10α,11β-diacetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (**29**), yielded *trans*-10,11-diacetoxy-10,11-dihydrobenz[*c*]acridine (**30**), which was hydrolyzed to *trans*-10,11-dihydroxy-10,11-dihydrobenz[*c*]acridine (**31**) in 86% yield.[24]

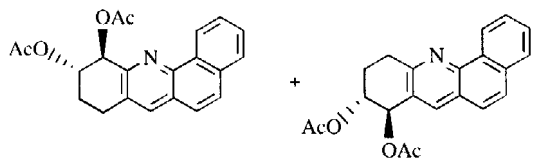


(10)

i) PPA, 100°, 2hr *ii*) 1. *m*-CPBA, CH_2CH_2, 17 hr 2. 5% NaOH *iii*) 88% HCOOH, 60-65°, 3 hr
iv) Ac_2O, pyridine, r.t., 24 hr) NBS, AIBN, CCl_4, 70-75°, 30 min (an 1:1 stereoisomeric mixture)
vi) $NaHCO_3$, xylene, Δ, 30 min*vii*) NH_3, MeOH, THF

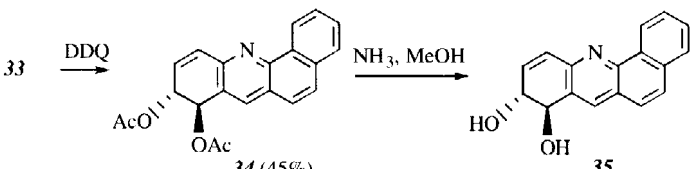
To synthesize 8,9-dihydroxy-8,9-dihydrobenz[*c*]acridine (**35**), 10,11-dihydrobenz[*c*]acridine (**32**) is needed as a starting compound.[24] Alkene **32** could not be prepared in a regiospecific manner but was produced by heating **24** at 165° in PPA. It is to be noted that **32** was not formed at 100° as described in the preparation of **26**. Under these conditions, an 1:3 mixture of **32**:**26** is produced from **24** in 67% yield. The alkene mixture was treated with *m*-CPBA, formic acid, followed by acetic anhydride to give a mixture of *trans*-8,9-diacetoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (**33**) and **28** in the manner described for **28**.[24] At this stage, separation of **33** and **28** was achieved by column chromatography on silica gel. The overall yield of **33** from **24** was 8%. Oxidation of **33** with DDQ in refluxing dioxane gave *trans*-8,9-diacetoxy-8,9-dihydrobenz[*c*]acridine (**34**) in 45% yield. Finally, ammonolysis of **34** with ammonia in methanol gave the corresponding *trans*-8,9-dihydroxy-8,9-dihydrobenz[*c*]acridine (**35**) in 55% yield.[24] A more convenient route to **35** has been recently reported.[33] Thus, Fremy's salt oxidation of 8-hydroxybenz[*c*]acridine (**36**), which was synthesized by the method developed originally, gave 8,9-dioxo-dihydrobenz[*c*]acridine (**37**) in 76% yield. Then, sodium borohydride reduction of **37** produced **35** in 80% yield.[33]

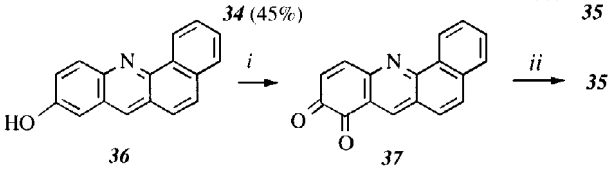




(11)

i) PPA, 165°, 3hr *ii*) 1. *m*-CPBA 2. HCO_2H 3. Ac_2O





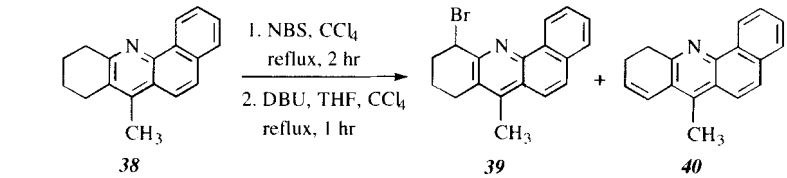
(12)

i) Fremy's salt *ii*) $NaBH_4$, EtOH

Holder *et al.* have reported the synthesis of the D-ring dihydrodiols of **1**.[34] The routes employed follow those previously described for the D-ring dihydrodiols of benz[*c*]acridine by Lehr and Kumar.[24] Despite the high reactivity of 7-methyl group and its ability to participate in reactions such as the Mannich condensation[35] and its reaction with aldehydes[35,36] and nitroso compounds,[37-40]

there is no report of its interference in any of the reactions in the synthesis of the D-ring dihydrodiols of **1**.

To synthesize the D-ring dihydrodiols of **1**, 7-methyl-8,9,10,11-tetrahydrobenz[*c*]acridine (**38**) prepared by hydrogenation of **1** in trifluoroacetic acid over Adams catalyst in 27% yield,[41] was chosen as a starting compound. Bromination of **38** followed by mild treatment with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) allowed the isolation of 11-bromo-7-methyl-8,9,10,11-tetrahydrobenz[*c*]acridine (**39**) and 10,11-dihydro-7-methylbenz[*c*]acridine (**40**).[34] Treatment of **39** with DBU afforded 8,9-dihydro-7-methylbenz[*c*]acridine (**41**) which was epoxidized with *m*-CPBA to give 10,11-epoxy-7-methyl-8,9,10,11-tetrahydrobenz[*c*]acridine (**42**). Ring opening of **42** with CF_3CO_2H, followed by acetylation with Ac_2O/pyridine afforded *trans*-10,11-diacetoxy-7-methyl-8,9,10,11-tetrahydrobenz[*c*]acridine (**43**) which was brominated with NBS to give 8-bromo-10β,11α-diacetoxy-7-methyl-8,9,10,11-tetrahydrobenz[*c*]acridine (**44**). Dehydrobromination of **44** with DBU afforded 11-acetoxy-7-methylbenz[*c*]acridine (**45**) and *trans*-10,11-diacetoxy-10,11-dihydro-7-methylbenz[*c*]acridine (**46**), respectively. Ammonolysis of **46** with methanolic NH_3 gave *trans*-10,11-dihydroxy-10,11-dihydrobenz[*c*]acridine (**47**).[34]



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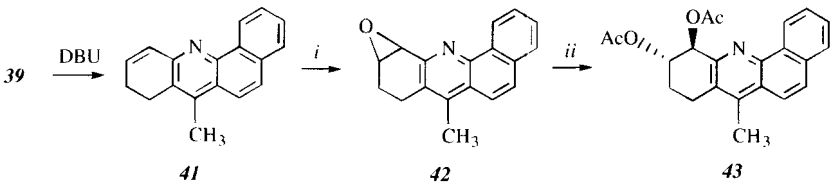

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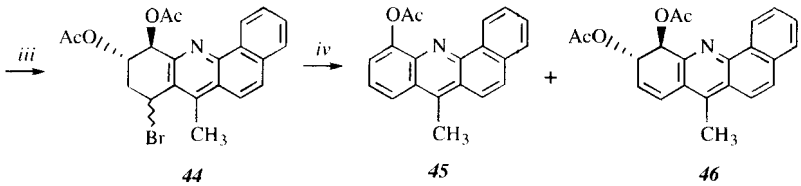
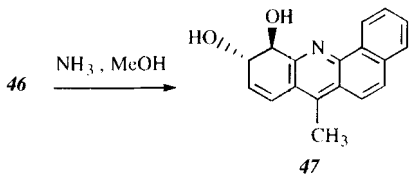
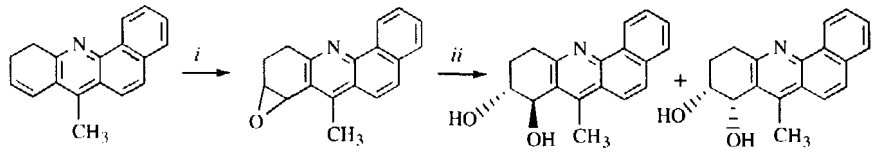




(15)

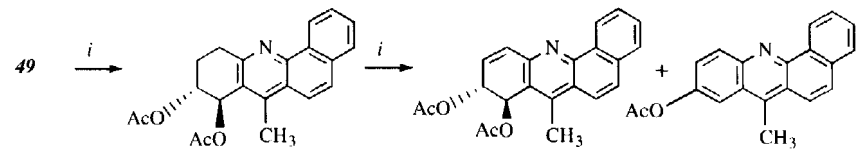
i) 1. *m*-CPBA, CH_2CH_2, 10% $NaHCO_3$, 0°, 10 min, 20°, 50 min 2. 5% NaOH
ii) 1. CF_3COOH, AcOH, r.t., overnight $2Ac_2O$, pyridine
iii) NBS, AIBN, CCl_4, reflux, 35 min*iv*) DBU, THF, r.t., 17 hr

trans-8,9-Dihydroxy-8,9-dihydro-7-methylbenz[*c*]acridine (**51**) was synthesized from **40**. Thus, epoxidation of **40** with *m*-CPBA afforded 8,9-epoxy-7-methyl-8,9,10,11-tetrahydrobenz[*c*]acridine (**48**) which was treated with acetic acid and aqueous ammonia to give a separable 2:1 mixture of *trans*- and *cis*-8,9-dihydroxy-7-methyl-8,9,10,11-tetrahydrobenz[*c*]acridine, **49** and **50**. A *cis* isomer was not previously isolated in the benz[*c*]acridine series.[24] The *trans* isomer **49** was converted to *trans*-8,9-dihydroxy-7-methyl-8,9-dihydrobenz[*c*]acridine (**51**) *via* a sequence similar to that used for **47**.[34]



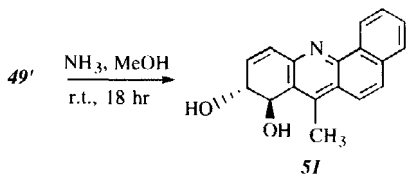
(16)

i) 1. *m*-CPBA, CH_2CH_2, 0°, 10 min 2. 5% NaOH *ii*) 1. AcOH, 25°, 17 hr 2. MeOH, conc.NH_4OH, 25°, 3 days



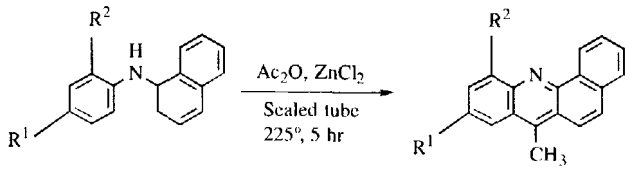
(17)

i) Ac_2O, pyridine*ii*) 1. NBS, AIBN, CCl_4, reflux, 35 min 2. DBU,CH_2CH_2, 35°, 1 hr



(18)

The Bernthsen reaction of *N*-(*p*-methoxyphenyl)-1-naphthylamine (**52**) and *N*-(*o*-methoxyphenyl)-1-naphthylamine (**53**) with Ac_2O and zinc chloride proceeded with concurrent cleavage of methyl ether groups to yield 9- (**54**) and 11-hydroxy-7-methylbenz[*c*]acridine (**55**) in 28% and 4% yield, respectively.[41]



(19)

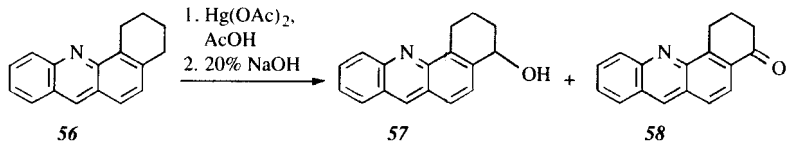
52: R^1 = OMe, R^2 = H
53: R^1 = H, R^2 = OMe
54: R^1 = OH, R^2 = H
55: R^1 = H, R^2 = OH

b) Syntheses of A-ring Oxygenated Benz[*c*]acridines

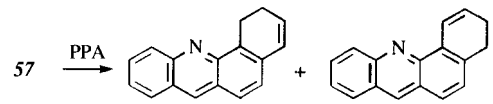
The most productive and effective route to the A-ring dihydrodiols of benz[*c*]acridines would be based on the introduction of oxygen functionality regiospecifically into the two different

benzylic positions in 1,2,3,4-tetrahydrobenz[*c*]acridine (**56**) followed by conversion to the alkene as the case described for the synthesis of the D-ring dihydrodiols of benz[*c*]acridines.

The starting material, **56**, was synthesized in quantity (86% based on benz[*c*]acridine) by the reduction of benz[*c*]acridine with sodium in refluxing amyl alcohol to 1,2,3,4,7,12-hexahydrobenz[*c*]acridine, followed by oxidation of the acridan to **56** with ferric chloride in concentrated hydrochloric acid.[24] Attempts to apply the *N*-oxide/acetic anhydride procedure to prepare 4-acetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine were unsuccessful, since ring opening of the heterocyclic ring occurred in the reaction of **56** with *m*-CPBA. However, successful oxidation of C-4 of **56** was achieved by the mercuric acetate/acetic acid method. Under these conditions a mixture of 4-acetoxy-, 4-hydroxy- (**57**), and 4-oxo-1,2,3,4-tetrahydrobenz[*c*]acridine (**58**) is produced which upon hydrolysis with a methanolic sodium hydroxide gave the 4-ol (**57**) in 70% yield based on recovered **56** and 4-oxo derivative (**58**, 10%), respectively. Dehydration of **57** at 100° in a biphasic mixture of PPA and xylene gave a high yield of 1,2-dihydrobenz[*c*]acridine (**59**), contaminated by a small amount (ca. 15%) of 3,4-dihydrobenz[*c*]acridine (**60**).

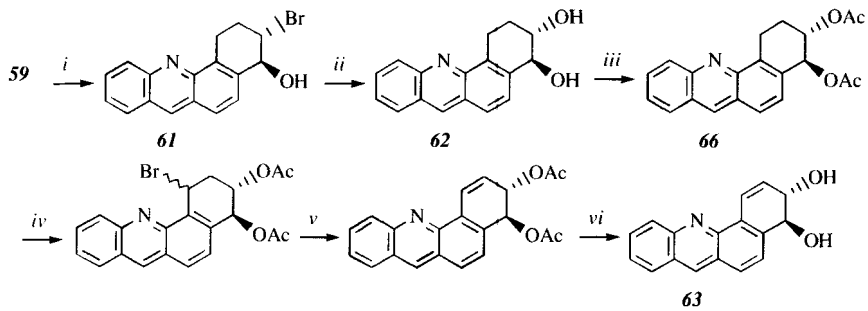


56 57 58 (20)



59 60 (21)

In order to introduce diols at 3- and 4- positions of 1,2-dihydrobenz[*c*]acridine (**59**), attempted epoxidation of **59** with *m*-CPBA was unsuccessful due to the formation of a complex mixture. However, *trans*-3,4-dihydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine (**62**) could be obtained by ring opening of the epoxide which was prepared through cyclization of the bromohydrin, *trans*-3-bromo-4-hydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine (**61**), formed from the reaction of **59** and NBS. *trans*-3,4-Diol (**62**)

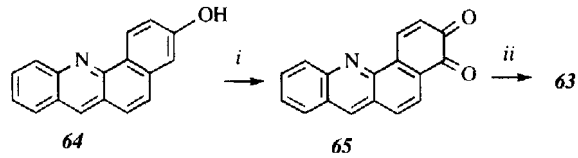


(22)

i) NBA, 47% *ii*) 1. 10% NaOH, acetone, r.t. 5 hr 2. 88% HCOOH, 70°, 90 min, 71%
iii) Ac_2O, pyridin,90% *iv*) NBS, AIBN, CCl_4, ca 70-75°, 30 min, 98%
v) Li_2CO_3, LiF, HMPA, 90-95°, 6 hr, 82% *vi*) NH_3, MeOH, r.t 2 hr, 85%

was converted in 62% overall yield to *trans*-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine (**63**) in the manner described for the synthesis of **31**.[24]

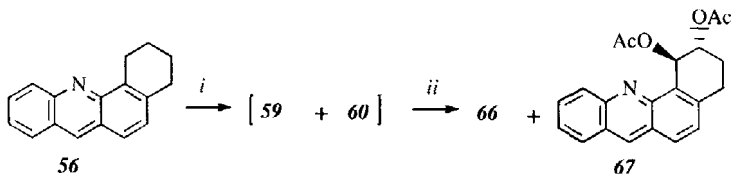
A more convenient synthesis to *trans*-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine (**63**) has been recently developed.[33] Thus, oxidation of 3-hydroxybenz[*c*]acridine (**64**) with Fremy's salt afforded 3,4-dioxo-3,4-dihydrobenz[*c*]acridine (**65**) in 85% yield, which was reduced by $NaBH_4$ to give **63** in 20% yield.[33]



(23)

i) 1. Fremy's salt,H_2O, 0.16MKH_2PO_4 buffer 2. MeOH, THF, in refrigerator for overnight
ii) $NaBH_4$, EtOH, r.t. 48 hr

The preparation of *trans*-1,2-dihydroxy-1,2-dihydrobenz[*c*]acridine (**69**) involved separation of the intermediate *trans*-1,2-diacetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (**67**) and *trans*-3,4,-diacetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (**66**). Thus, bromination (NBS) of **56** followed by dehydrobromination resulted in the formation of a mixture of **60** and **59**. While the Prévost reaction was unsatisfactory for the synthesis of **28**, its application to the mixture of **59** and **60** gave **66** and **67**, which were separated by column chromatography. The overall yield of **67** from **56** was 14%. Introduction of a double bond into **67** has been accomplished through bromination with NBS followed by base-catalyzed dehydrobromination to give *trans*-1,2-diacetoxy-1,2-dihydrobenz[*c*]acridine (**68**) in 59% two-step yield. Ammonolysis of **68** with methanolic NH_3 gave **69** in 64% yield.[24]



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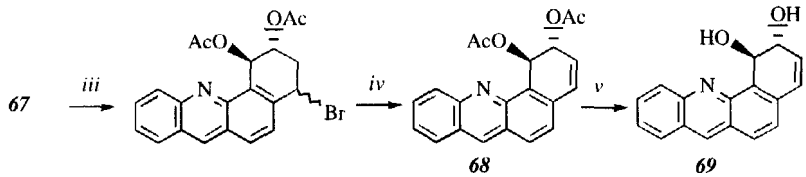


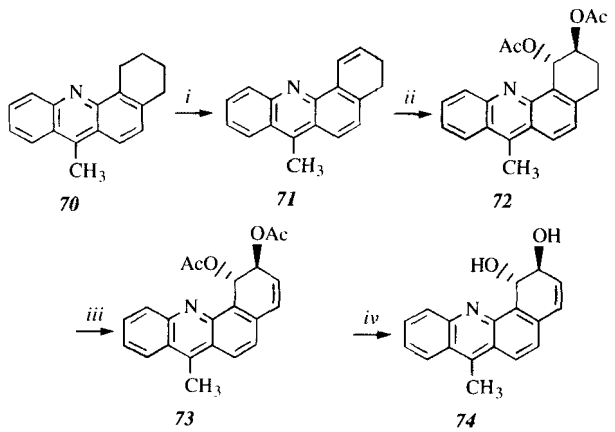
(25)

i) 1. NBS, AIBN, CCl_4, reflux, 3 hr 2.Li_2CO_3, LiF, HMPA, 100°, 3 hr
ii) I_2, AgOAc, r.t. 6 hr, reflux, 17 hr*iii*) NBS, AIBN, CCl_4, reflux, 3 hr, ca. 70-75°, 30 min, 70%
iv) DBN, THF, 0°, 24 hr, 84% *v*) NH_3, THF, MeOH, r.t., 20 hr, 64%

The procedure described above for the synthesis of **69** was readily adapted to the synthesis of analogous derivative (**74**) of **1** which was prepared from 3,4-dihydro-7-methylbenz[*c*]acridine (**71**) *via* the sequence of Prévost reaction, bromination, dehydrobromination, and hydrolysis.[34] In this case, 7-methyl-1,2,3,4-tetrahydrobenz[*c*]acridine (**70**) is the starting compound which had been prepared by

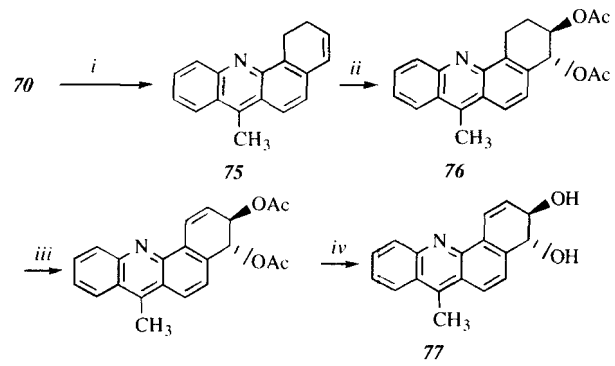
a previously reported method.[41]

Compound **70** was converted to **71** *via* bromination/dehydrobromination. The Prévost reaction of **71** using I_2 and silver benzoate afforded tetrahydrodiol dibenzoate which was converted to diacetate (**72**) *via* hydrolysis followed by acetylation of the resulting diol. Because the diacetates are better substrates for introduction of a double bond at the 8,9-position. Thus, **72** was converted to *trans*-dihydrodiol diacetate (**73**) by bromination with NBS followed by dehydrobromination. Hydrolysis of **73** afforded the required trans-dihydrodiol (**74**).[34,42] In like manner, 7-methyl-1,2-dihydrobenz[*c*]acridine (**75**) was converted to the *trans*-3,4-dihydroxy-7-methyl-3,4-dihydrobenz[*c*]acridine (**76**).[34,42] A more efficient route to **76** has been reported.[42] Thus, reduction of **1** with sodium in refluxing xylene/EtOH followed by reoxidation with CrO_3/HOAc afforded 7-methyl-1,4-dihydrobenz[*c*]acridine (**78**, 40%) and **70** (8%), respectively. The yield of **78** was increased to 64% by use of Na in liquid NH_3/EtOH. Isomerization of the isolated double bond of **78** by heating with sodium *tert*-butoxide in *tert*-butanol



(26)

i) 1. NBS, AIBN 2. DBU, 35° *ii*) 1. I_2, AgOBz 2. NaOH 3. Ac_2O, pyridine
iii) 1. NBS 2. DBU *iv*) NH_3, MeOH

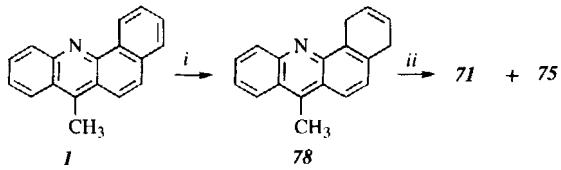


(27)

i) 1. NBS, AIBN 2. DBU, 35° *ii*) 1. I_2, AgOBz 2. NaOH 3. Ac_2O, pyridine
iii) 1. NBS, AIBN 2. Li_2CO_3, LiF, HMPA *iv*) NH_3, MeOH

gave 1,2-dihydro-7-methylbenz[*c*]acridine (**75**, 51%) and **71** (39%), respectively. The Prévost reaction with silver benzoate and I_2 of **75** led to 3,4-bis(dibenzoyloxy)-7-methyl-1,2,3,4-tetrahydrobenz[*c*]acri-

dine (**79**) which was hydrolyzed and acetylated to afford **76** in 18% overall yield from **1**.[42] This represents an improvement over the bromination/dehydrobromination sequence from **70** (3% from **70**).[34]



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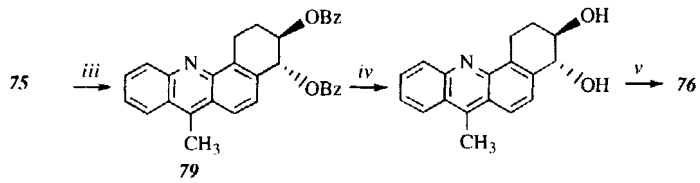
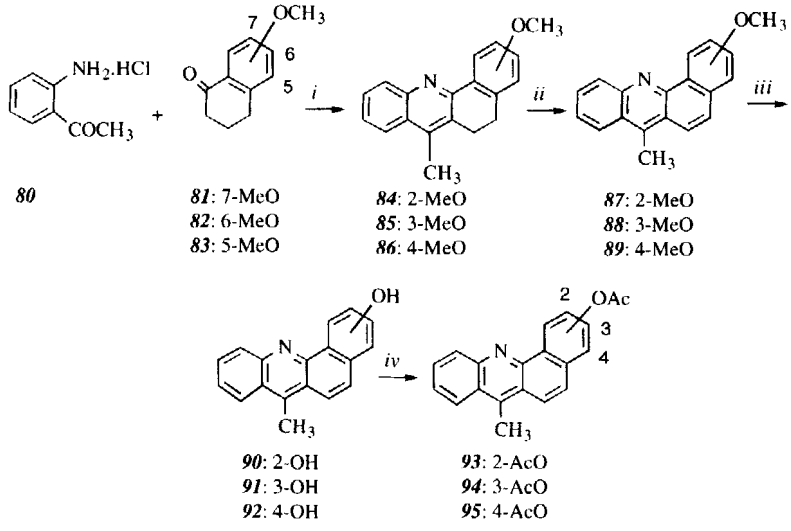


(29)

i) 1. Na, THF, liqNH$_3$, EtOH 2. CrO_3, AcOH *ii*) Na, *t*-BuOH
iii) I_2, AgOBz, r.t., 15 min, reflux, 2 h*iv*) Hydrolysis*v*) Ac_2O, pyridine

Heating a mixture of *o*-aminoacetophenone hydrochloride (**80**) and 7-methoxy-1-tetralone (**81**) at 140° for 10 min afforded 2-methoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (**84**). Compound **84** was subsequently dehydrogenated to 2-methoxy-7-methylbenz[*c*]acridine (**87**) by distillation on 5% Pd/C and chromatography on silica gel. Similar procedures of a mixture of **80** and 6-methoxy-1-tetralone (**82**), and a mixture of **80** and 5-methoxy-1-tetralone (**83**) gave 3-methoxy-7-methylbenz[*c*]acridine (**88**) *via* 3-methoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (**85**), and 4-methoxy-7-methylbenz[*c*]acridine (**89**) *via* 4-methoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (**86**), respectively.[20]



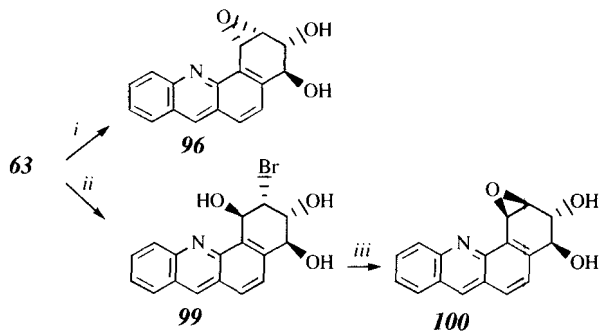
(30)

i) Friedlaender-Kempter synthesis,140°, 10 min *ii*) 5% Pd-C *iii*) HCl, pyridine,reflux *iv*) Ac_2O

Compound **87** was treated with a ten-fold excess of pyridinium chloride to afford 2-hydroxy-7-methylbenz[*c*]acridine (**90**) in 69% yield, which was acetylated to form 2-acetoxy-7-methylbenz[*c*]acridine (**93**) in 89% yield. The above similar procedure for **88** and **89** led to the isolation of 3-acetoxy-7-methylbenz[*c*]acridine (**94**) in 93% yield *via* 3-hydroxy-7-methylbenz[*c*]acridine (**91**,79%) and 4-acetoxy-7-methylbenz[*c*]acridine (**95**, 94%) *via* 4-hydroxy-7-methylbenz[*c*]acridine (**92**,81%), respectively.[20]

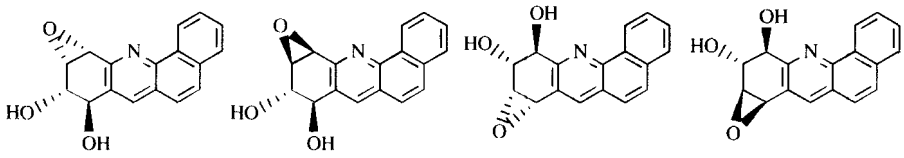
c) Syntheses of Non-K-region Epoxy Benz[*c*]acridines

Generally, the diol epoxides have been accessible from dihydrodiols through the methodology used for the preparation of PAHs.[18] Thus, direct epoxidation of **63** with a 10 molar excess of *m*-CPBA occurs stereospecifically to afford the single diastereomeric anti-diol epoxide, 3α,4β-dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (**96**), in 72% yield. No *N*-oxidation product was observed in the reaction due to the steric hindrance by the angular ring *peri* to the nitrogen.[43] Compounds prepared by this method include 8β,9α-dihydroxy-10α,11α-epoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (**97**), and 10α,11β-dihydroxy-8α,9α-epoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (**98**). In another two-step sequence, the *trans*-dihydrodiol (**63**) was converted to 1β,3α,4β-trihydroxy-2α-bromo-1,2,3,4-tetrahydrobenz[*c*]acridine (**99**), in 90% yield upon treatment with *N*-bromoacetamide (NBA) in aqueous acidic THF. The bromo triol (**99**) was then cyclized to the single diastereomeric *syn*-diol epoxide, 3α,4β-dihydroxy-1β,2β-epoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (**100**), in 66% yield.[24] Compounds **101** and **102** were prepared by this procedure from the dihydrodiols, **35** and **31**, respectively.[43]



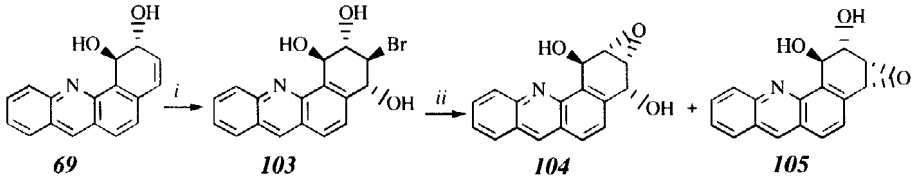
(31)

i) 1. ten-fold excess of reflux, 1-2 hr 72% *ii*) NBA, 90% *iii*) *t*-BuOK, anhyd.THF,66%



Reaction of **69** with *m*-CPBA did not give a diol epoxide but instead gave a complex reaction mixture. On the other hand, the reaction of **69** with NBA gave 1β,2α,4α-trihydroxy-3β-bromo-1,2,3,4-

tetrahydrobenz[*c*]acridine (**103**) in 27% yield. Treatment of **103** with *tert*-BuOK/anhyd. THF gave 1β,4α-dihydroxy-2α,3α-epoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (**104**) and a diol epoxide (**105**).[43]

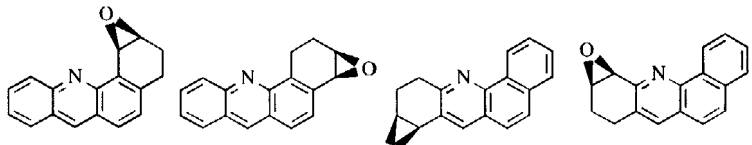


69 *103* *104* *105*

i) NBA *ii*) *t*-BuOK, anhyd.THF

(32)

Four tetrahydroepoxides, 1,2-epoxy-1,2,3,4- (**106**), 3,4-epoxy-1,2,3,4- (**107**), 8,9-epoxy-8,9,10,11- (**108**), and 10,11-epoxy-8,9,10,11-tetrahydrobenz[*c*]acridine (**27**), were synthesized in all cases by cyclization of the corresponding bromohydrins which were prepared by NBA in aqueous acidic THF in 11-45% two-step yields.[43]



106 *107* *108* *27*

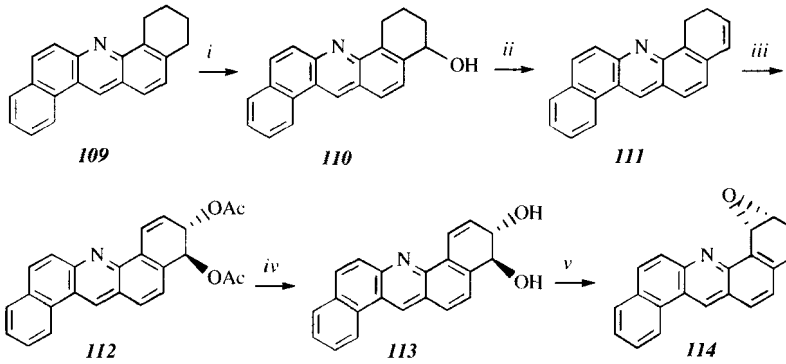
For the angular ring (A-ring) tetrahydroepoxides, **106** and **107**, attempted epoxidation of **60** and **59** with *m*-CPBA led to a complex mixture, in contrast to the formation of the D-ring tetrahydroepoxides, **27**,[24] **42**,[34] and **48**[34] from the corresponding dihydrobenz[*c*]acridines by the oxidation with *m*-CPBA.

II. SYNTHESES OF OXYGENATED DERIVATIVES OF DIBENZACRIDINES

1. Syntheses of Oxygenated Dibenz[*a,h*]acridines

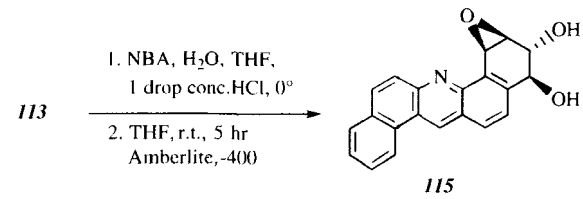
Recently, Krasnoshchekova *et al.* showed a correlation between the carcinogenicity of six 14-alkyl-dibenz[*a,h*]acridines and their protein binding ability.[44] Dibenz[*a,h*]acridines are found to be mutagenic and carcinogenic.[45] There is substantial evidence that they are metabolically activated to reactive diol epoxide intermediates that bind to DNA in vivo. The diastereomeric 10,11-diol-8,9-epoxide is 20-40 times more mutagenic than the related 3,4-diol-1,2-epoxide.[45,46] In a series of dibenz[*a,h*]acridines, all four dihydro diols, *trans*-10,11-dihydroxy-10,11-dihydrodibenz[*a,h*]acridine (**113**), *trans*-8,9-dihydroxy-8,9-dihydrodibenz[*a,h*]acridine (**116**), *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a,h*]acridine (**117**), and *trans*-1,2-dihydroxy-1,2-dihydrodibenz[*a,h*]acridine (**118**) were prepared by Kumar and co-workers.[47,48] The procedures described for the synthesis of various dihydrodiols and diol epoxides of benz[*c*]acridine and 7-methylbenz[*c*]acridines are readily adaptable to the synthesis of the analogous derivatives of dibenz[*a,h*]acridines. The conversion of 8,9,10,11-tetrahydrodibenz[*a,h*]acridine (**109**) to **113** was based on the method described for the synthesis of **59**. Thus, compound **109** was treated with mercuric acetate followed by PPA of the resulting alcohol **110** to give the olefin **111**. The olefin **111** is converted to 10,11-diacetate (**112**) *via* the sequence of Prévost

reaction, hydrolysis, acetylation, NBS bromination, and dehydrobromination.[47]



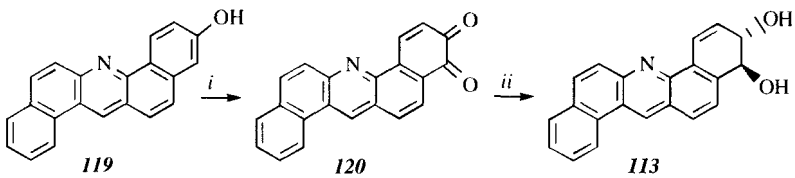
(33)

i) 1. $Hg(OAc)_2$, AcOH, reflux, 28 hr 2. 40% NaOH, THF, MeOH, r.t., 2 hr *ii*) PPA, xylene, 85-90°, 90 min *iii*) 1. I_2, AgOBz 2. 30% NaOH 3. Ac_2O, pyridine 4. NBS 5. Li_2CO_3, LiF, HMPA *iv*) NH_3, THF, MeOH *v*) *m*-CPBA, THF, r.t., 1 hr



(34)

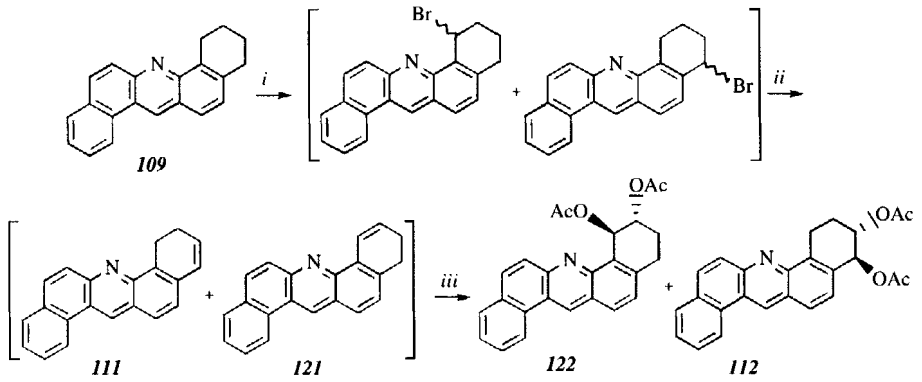
A convenient route to **113** was recently reported by Ray and co-workers.[49] Thus, 10-hydroxydibenz[*a,h*]acridine (**119**) synthesized by the originally developed method[49] was oxidized with Fremy's salt to give the *o*-quinone, 10,11-dioxo-10,11-dihydrodibenz[*a,h*]acridine (**120**), in 97% yield. Finally, reduction of **120** with $NaBH_4$ afforded **113** in 25% yield.[49]



(35)

i) Fremy's salt, 0.16M KH_2PO_4, HMPA, 5-7°, 2-2.5 hr *ii*) $NaBH_4$, EtOH, 25°, 48 hr

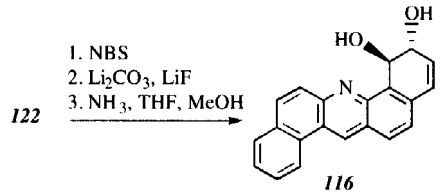
The route employed for the synthesis of **116** was similar to that previously described for the analogous derivatives of benz[*c*]acridine[24] using **109** as the starting material.[48] In this route, separation of 8,9-diacetate (**122**) and **112** by column chromatography on neutral alumina was necessary. Compound **112** was identical with that obtained by the $Hg(OAc)_2$ method.[47,48]



(36)

(a 1:2 mixture of *111* and *121*)

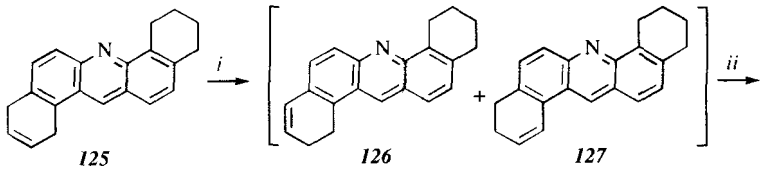
i) NBS, AIBN, CCl_4, 65-72°, 30 min *ii*) Li_2CO_3, LiF, HMPA, reflux, 3 hr, 80-85°
iii) 1. I_2, AgOBz 2. NaOH 3. Ac_2O, pyridine

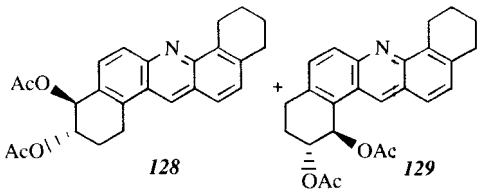


(37)

The methods used successfully to prepare the non-K-region dihydrodiols of benz[*c*]acridine[24,43] and 7-methylbenz[*c*]acridine[34] were not adaptable to the synthesis of *trans*-1,2-dihydroxy-1,2-dihydrodibenz[*a,h*]acridine (**118**) and *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a,h*]acridine (**117**) starting from 1,2,3,4-terahydrodibenz[*a,h*]acridine (**123**). This is due to the difficulty associated with the large scale synthesis of the starting compound **123**. Therefore, the use of 8,9,10,11-tetrahydrodibenz[*a,h*]acridine (**109**) as a starting point was investigated. Thus, Birch reduction of **109** yielded 7,8,9,10,11,14-hexahydro derivative which was again undergone the Birch reduction to give 1,4,7,8,9,10,11,14-octahydrodibenz[*a,h*]acridine (**124**). The crude product **124** was treated with *p*-chloranil and the resulting product was purified *via* its picrate to produce a 50% yield of pure 1,4,8,9,10,11-hexahydrodibenz[*a,h*]acridine (**125**). Isomerization of the isolated double bond of **125** with base produced a 2.5:1 mixture of 1,2,8,9,10,11-hexahydrodibenz[*a,h*]acridine (**126**) and 3,4,8,9,10,11-hexahydrodibenz[*a,h*]acridine (**127**) in quantitative yield. The mixture of the alkenes, **126** and **127**, was converted to a mixture of *trans*-3,4-diacetoxy-1,2,3,4,8,9,10,11-octahydrodibenz-[*a,h*]acridine (**128**) and *trans*-1,2-diacetoxy-1,2,3,4,8,9,10,11-octahydrodibenz[*a,h*]acridine (**129**) *via* the Prévost reaction followed by successive hydrolysis and acetylation of the resulting mixture of dibenzoates. At this stage, separation of **128** and **129** was readily achieved by column chromatography on silica gel. In this manner, **109** was converted to **128** and **129** in 26% and 6% overall yields, respectively. Aromatizations of **128** and **129** to *trans*-3,4-diacetoxy-1,2,3,4-tetrahydrodibenz[*a,h*]acridine (**130**) and *trans*-1,2-diacetoxy-1,2,3,4-tetrahydrodibenz[*a,h*]acridine (**131**)

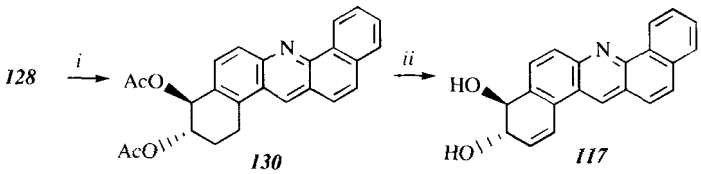
were achieved[48] by the previously reported DDQ oxidation.[50] Compounds **130** and **131** were converted to **117** and **118** as previously described.[48]





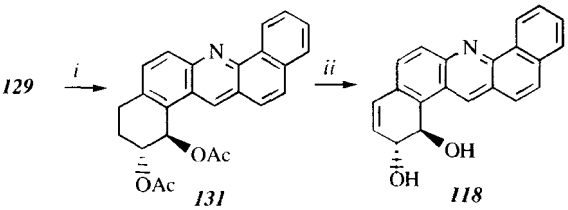
(38)

i) Na, EtOH, THF *ii*) 1. I_2, AgOBz 2. 20% NaOH, THF, MeOH 3. Ac_2O, pyridine



(39)

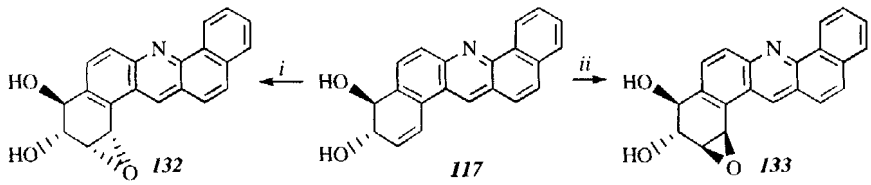
i) DDQ, benzene *ii*) 1. NBS 2. $LiCO_3$, LiF, HMPA 3. 20% NaOH



(40)

i) DDQ, benzene *ii*) 1. NBS 2. $LiCO_3$, LiF, HMPA 3. 20% NaOH

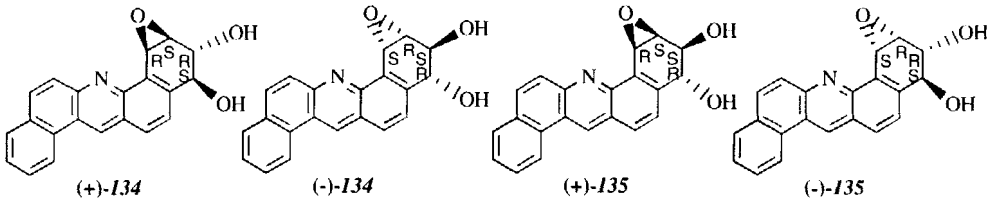
Treatment of **117** and **113** with *m*-CPBA produced the diastereomeric *anti*-diol epoxides, 3α,4β-dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrodibenz[*a,h*]acridine (**132**)[48] and (±)-10α,11β-dihydroxy-8α,9α-epoxy-8,9,10,11-tetrahydrodibenz[*a,h*]acridine (**114**)[47] in 67% and 48% yields, respectively. In another two-steps sequence, **117** and **113** were converted to the diastereomeric *syn*-diol epoxides, 3α,4β-dihydroxy-1β,2β-epoxy-1,2,3,4-tetrahydrodibenz[*a,h*]acridine (**133**)[48] and (±)-10α,11β-dihydroxy-8α,9β-epoxy-8,9,10,11-tetrahydrodibenz[*a,h*]acridine (**115**)[47] in good yields, *via* treatment with NBS in aqueous THF followed by cyclization of the resulting bromohydrin.



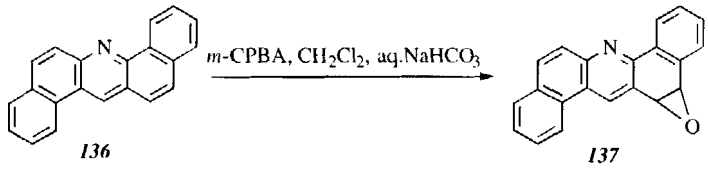
(41)

i) *m*-CPBA, THF *ii*) 1. NBA, 1 drop 4N HCl 2. Amberlite-400, THF

Recently, four enantiomerically pure, bay-region 10,11-diol 8,9-epoxide diastereomers ((+)-**134**, (-)-**134**, (+)-**135**, and (-)-**135**)) of dibenz[*a,h*]acridine were prepared.[51] Thus racemic *trans*-10,11-dihydroxy-10,11-dihydrobenz[*a,h*]acridine (**113**)[47] was resolved *via* its conversion to the diastereomeric *bis*((-)-menthyloxy)esters, separation of the diastereomers by short bed/continuous developing preparative TLC, and finally saponification of the individual diastereomers. In the manner described for racemic materials (**113**), the enantiomeric (-)-10,11-dihydro diol (**-)113** and (+)-10,11-dihydro diol **(+)113** were converted to the four stereoisomeric diol epoxides, (+)-**134**, (-)-**134**, (+)-**135**, and (-)-**135**. The comparative mutagenicity and tumorigenicity of those four stereoisomers are under current evaluation.[51]



Dibenz[*a,h*]acridine 12,13-oxide (**137**) was synthesized by the oxidation of dibenz[*a,h*]acridine (**136**) with *m*-CPBA in order to test this mutagenic activity.[52]

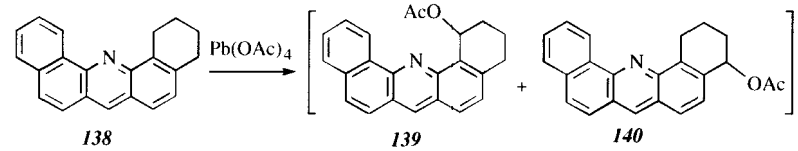


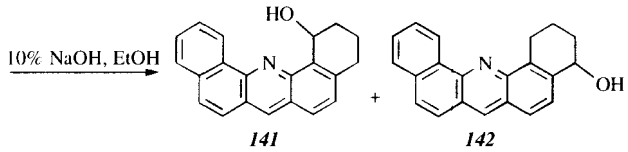
(42)

2. Syntheses of Oxygenated Dibenz[*c,h*]acridines

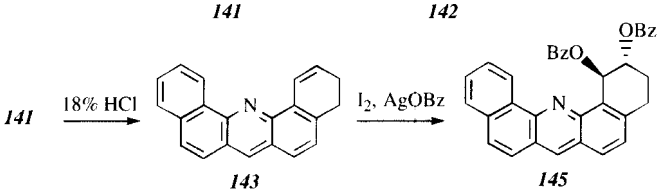
Dibenz[*c,h*]acridine is also found in tar, urban atmosphere, and tobacco smoke and is known to be carcinogenic. However, the K-region oxide, dibenz[*c,h*]acridine-5,6-oxide was not mutagenic in *Salmonella typhimurium* TA98 and TA100.[52] Therefore, bay-region diol epoxide, non-K-region dihydrodiols, and non-K-region oxides of dibenz[*c,h*]acridine, which are possible active metabolites of dibenz[*c,h*]acridine, were synthesized by two groups.[53,54]

Two routes to 3,4-dibenzoate, *trans*-1,2-*bis*(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**145**), and 1,2-dibenzoate, *trans*-3,4-*bis*(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**146**), from 1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**138**) were developed. Oxidation of **138** with lead tetraacetate afforded a mixture of 1-acetoxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**139**) and 4-acetoxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**140**) in 31% yield. The isomeric mixture was hydrolyzed with 10% NaOH and purified by column chromatography on silica gel to give 1-hydroxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**141**,65%) and 4-hydroxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**142**,22%). Acid catalyzed dehydration of the alcohols **141** and **142** led to 3,4-dihydrodibenz[*c,h*]acridine (**143**) and 1,2-dihydrodibenz[*c,h*]acridine (**144**) in 68% and 67% yield, respectively.[54] Prévost reaction of **143** gave **145** in 97% yield. Similarly, **146** was obtained from **144** in 84% yield.





(43)



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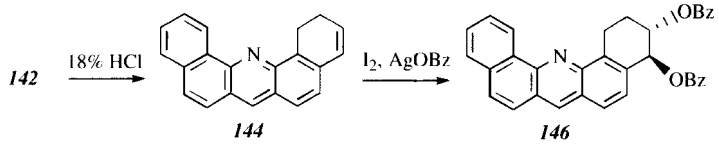
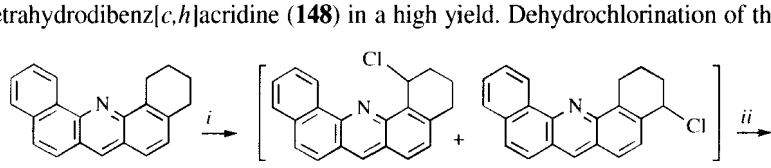


(45)

The second approach involves benzylic chlorination of **138** with *tert*-butyl hypochlorite in CCl_4 to give a 1:1 mixture of 1-chloro-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**147**) and 4-chloro-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**148**) in a high yield. Dehydrochlorination of the crude mixture



(46)

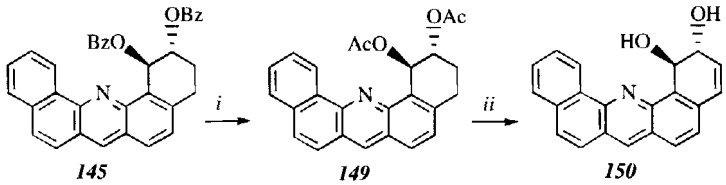
[*143* + *144*] $\xrightarrow{iii}$ *145* + *146*

(A 1:1 mixture of *143* and *144*)

i) *t*-BuOCl, AIBN, CCl_4 *ii*) Li_2CO_3, LiF, HMPA *iii*) I_2, AgOBz, benzene

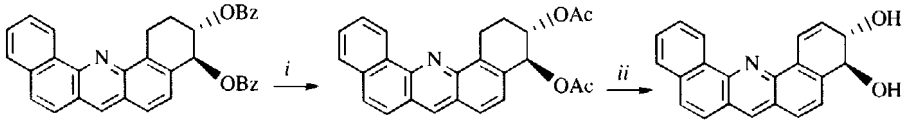
with LiF/$LiCO_3$ in HMPA yielded a mixture of **143** and **144** in good yield. Prévost reaction of the crude alkene mixture yielded a mixture of **145** and **146** which was separated by column chromatography.[53] The second route was superior to the first one in the overall yield.

The conversion of **145** and **146** to *trans*-1,2-dihydroxy-1,2-dihydrodibenz[*c*,*h*]acridine (**150**) and *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*c*,*h*]acridine (**151**) was accomplished[53] *via* the diacetoxy compound in a manner similar to that described for the synthesis of analogous derivatives of dibenz[*a*,*h*]acridine.[48] The overall conversion of **138** to pure 3,4-dihydrodiol (**151**) was 10%.[53]



145 **149** **150** (47)

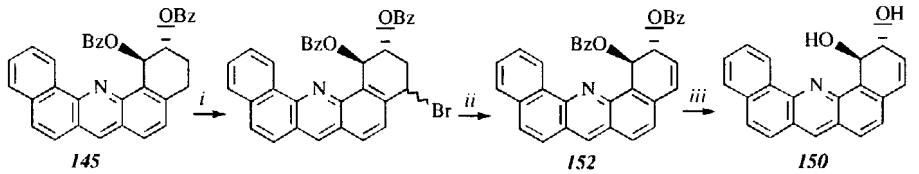
i) 1. 25% NaOH, MeOH, THF 2. Ac_2O, pyridine *ii*) 1. NBS, AIBN, CCl_4 2. DBN, THF 3. 40% NaOH, MeOH, THF



146 **151** (48)

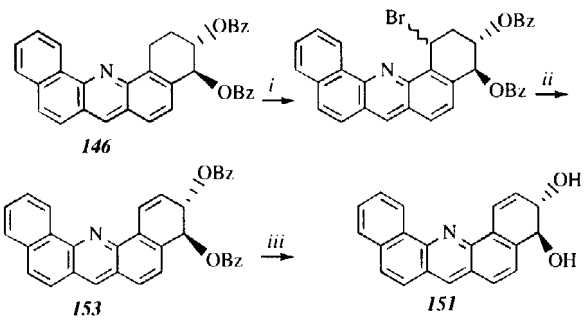
i) 1. 25% NaOH, MeOH, THF 2. Ac_2O, pyridine *ii*) 1. NBS, AIBN, CCl_4 2. $LiCO_3$, LiF, HMPA 3. NH_3, MeOH, THF

The *bis*(benzoyloxy) compounds, **145** and **146**, were subjected directly to the bromination and dehydrobromination reactions to afford *trans*-1,2-dibenzoxy-1,2-dihydrodibenz[*c*,*h*]acridine (**152**) and *trans*-3,4-dibenzoxy-3,4-dihydrodibenz[*c*,*h*]acridine (**153**) in good yields.[54]



145 **152** **150** (49)

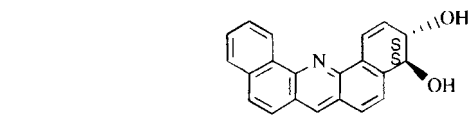
i) NBS, CCl_4 *ii*) DBN, THF *iii*) MeONa, MeOH, THF



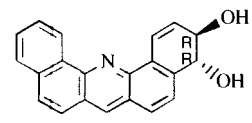
146 **153** **151** (50)

i) NBS, CCl_4 *ii*) DBN, THF *iii*) MeONa, MeOH, THF

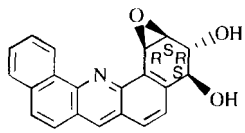
The four enantiomerically pure bay-region 3,4-diol 1,2-epoxide diastereomers [(+)-**154**, (-)-**154**, (+)-**155**, and (-)-**155**] of dibenz[*c,h*]acridine were synthesized from the corresponding pure *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*c,h*]acridine (**151**) enantiomers which were prepared by resolution of racemic **151** in a similar manner described for the synthesis of analogous derivatives of dibenz[*a,h*]acridine.[51] Racemic dihydrodiol (**151**) was resolved *via* conversion to the diastereomeric *bis*(-)-menthoxy esters, separation of the diastereomers by HPLC, and hydrolysis of the individual diastereomers.[53]



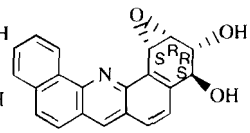
(+)-*151*



(-)-*151*



(+)-*154*



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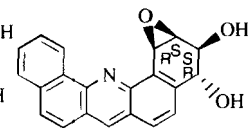
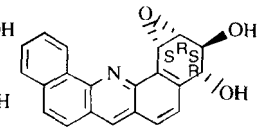
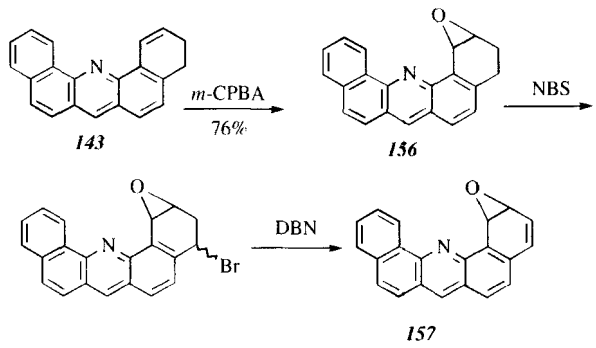


(+)-*155*



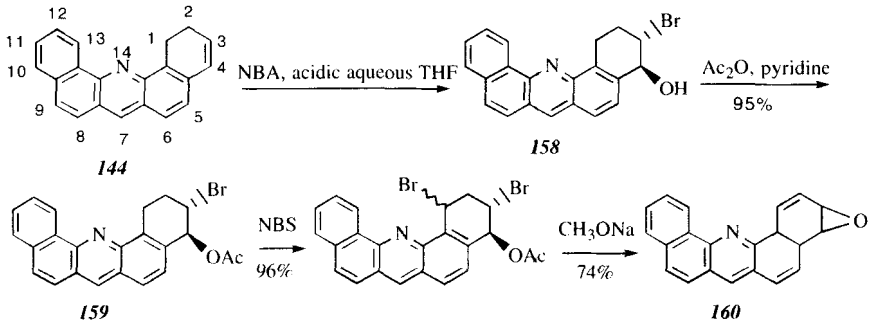
(-)-*154*

Two non-K-region epoxides, 1,2-dihydrodibenz[*c,h*]acridine-1,2-oxide (**157**) and 3,4-dihydrodibenz[*c,h*]acridine-3,4-oxide (**160**), were synthesized from **143** and **144**, respectively.[54]



143 *156* *157*

(51)



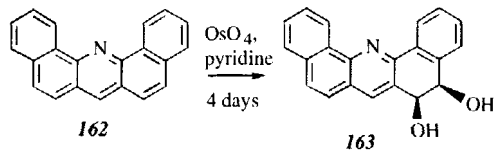
144 *158* *159* *160*

(52)

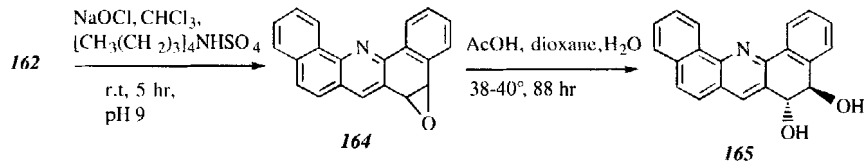
Epoxidation of **143** with *m*-CPBA afforded the corresponding epoxide, 1,2,3,4-tetrahydrodibenz[c,*h*]-

acridine-1,2-oxide (**156**), which was dehydrogenated *via* bromination followed by dehydrobromination to give the 1,2-epoxide **157**. On the other hand, this route could not be utilized for the synthesis of **160** because bromination of 3,4-epoxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**161**) was unsuccessful. Therefore, the epoxide **160** was prepared from **144** *via trans*-3-bromo-4-acetoxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**159**). Reaction of **144** with NBA in acidic aqueous THF afforded *trans*-3-bromo-4-hydroxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine (**158**) which was acetylated to give **159**. Bromination and base treatment of **159** led to **160**.[54]

K-region *cis*-5,6-Dihydroxy-5,6-dihydrodibenz[*c,h*]acridine (**163**) was prepared by the oxidation of dibenz[*c,h*]acridine (**162**) with OsO_4 in 40% yield.[53] On the other hand, the K-region *trans*-5,6-dihydroxy-5,6-dihydrodibenz[*c,h*]acridine (**165**) was obtained through epoxidation of **162** with NaOCl under phase-transfer conditions, followed by hydrolysis of 5,6-dihydrodibenz[*c,h*]acridine 5,6-oxide (**164**).[53]



162 *163* (53)



162 *164* *165* (54)

The epoxide **164** was also synthesized by the epoxidation of **162** with *m*-CPBA in 37% yield.[52]

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