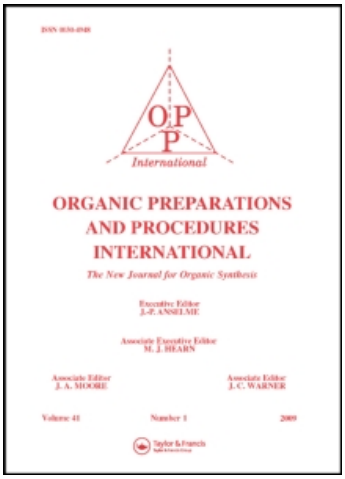

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SYNTHESIS OF CARCINOGENIC BENZ[*c*]ACRIDINES. A REVIEW

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SYNTHESIS OF CARCINOGENIC BENZ[*c*]ACRIDINES. A REVIEW

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INTRODUCTION

Methods for the syntheses of benz[*c*]acridines generally involve routes which are similar to those used in the synthesis of acridines.[1] This review summarizes the syntheses of potential carcinogenic benz[*c*]acridines. The synthetic methods may be grouped into two categories dependent upon whether they involve synthesis of the pyridine moiety or the constructions of the carbocyclic portion. The general nomenclature and numbering system employed for benz[*c*]acridines in this review is the same as that used in Chemical Abstracts (Fig. 1). In addition, methods for the syntheses of dibenzacridines and condensed benz[*c*]acridines have been included in the discussion. Chromatographic[2] and spectroscopic studies,[3] mutagenicity,[4] carcinogenicity,[5] and monooxygenase action[6] of these benz[*c*]acridines are not discussed here. The literature is covered up to the end of 1992.

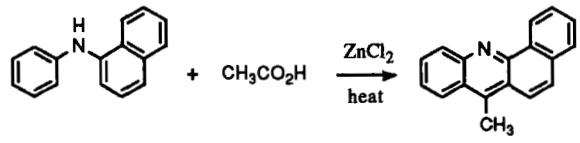
Benz[*c*]acridines have been found in coal tar,[7] shale oil,[4b,8] synthetic crude,[9] engine emissions,[10] ground water,[5c] meat,[11] and cigarettes.[12] For relevant biological studies the following references may be consulted: animal studies,[13,14] hepatocyte, and cultured cells,[13b,14b] and microsomal preparations.[14a,c,15,16]

I. SYNTHESES INVOLVING CONSTRUCTION OF THE PYRIDINE RING

Only a few synthetic methods of this type are suited for large scale preparation. These include the Bernthsen reaction,[17] cyclization of 2-carboxyphenylnaphthylamines,[18] the Ullmann-Fetvadjian reaction, and the Pfitzinger reaction. These four reactions are discussed in detail herein. Further information may be found in reference 1.

A. Bernthsen Reaction[1,19-24]

Many benz[*c*]acridines have been prepared by the Bernthsen reaction and its modifications.[25-31] In this reaction, *N*-phenyl-1-naphthylamine (**1**) is heated in the presence of an organic acid without a solvent to obtain the desired benz[*c*]acridines. Many organic acids have been used in these reactions. A typical example is the synthesis of 7-methylbenz[*c*]acridine (**2**).

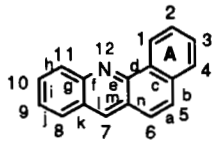


1 *2*

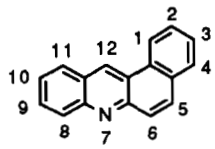
In the modified Bernthsen reaction, the organic acid anhydride[17,32,33,34,39] is used in the place of the acid along with a catalyst such as anhydrous zinc chloride ($ZnCl_2$), aluminum chloride ($AlCl_3$), or polyphosphoric acid (PPA) which often improves the yields. The use of PPA which serves both as a solvent and catalyst is referred to as Popp's modification,[23] gives improved yields in shorter reaction time. The combination of $ZnCl_2$ and $AlCl_3$ may also be used as a catalyst, but $ZnCl_2$ alone is not effective.[18] Heating of *N*-phenyl-1-naphtylamine (**1**), pivalic acid (2,2-dimethylpropionic acid) in the presence of $ZnCl_2$ gave benz[*c*]acridine (**3**).[17] An effect of the reaction temperature has also been studied.[1a,b]

The starting arylnaphthylamines are synthesized by the iodine-catalyzed condensation of anilines with naphthols or aminonaphthalenes (Knoevenagel method)[20b,40,41], or by the Ullmann condensation of aromatic halides and aromatic amines.[42-44] The Knoevenagel and Bernthsen reactions in the synthesis of 10-aminobenz[*c*]acridine (**6**) are compared. For example, 3-amino-*N*-phenyl-1-naphthylamine (**4**) is synthesized by the condensation of 1-naphthol and 1,3-phenylenediamine followed by cyclization in the presence of formic acid and 1 mole HCl. The cyclization is effected by heating the reaction mixture to 155° for 30 minutes, or followed by heating at 175° for 30 minutes.[1a,24] The reaction intermediate was suggested to be 2-formyl-5-amino-*N*-phenyl-1-naphthylamine (**5**) which upon cyclization followed by dehydration produces the benz[*c*]acridine (**6**).[1a]

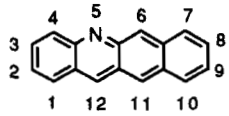
1. Benzacridines



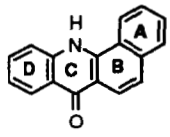
benz[*c*]acridine
(1:2-benzacridine)



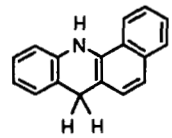
benz[*a*]acridine
(3:4-benzacridine)



benz[*b*]acridine

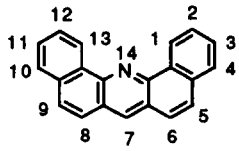


7(12)-benz[*c*]acridone

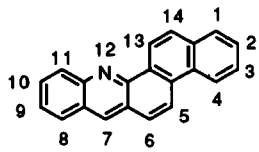


benz[*c*] acridan

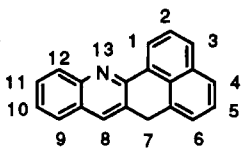
2. Dibenzacridines



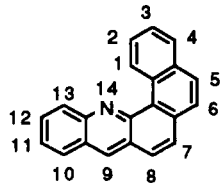
dibenz[*c,h*]acridine
(α-naphthacridine;
α-N-α-dinaphthacridine)



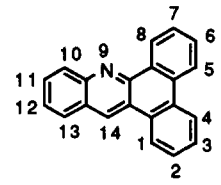
naphth[1,2-*c*]acridine



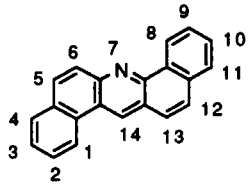
7(H)-naphth[1,8-*b,c*]-
acridine



naphth[2,1-*c*]acridine
(phenanthroacridine)



dibenz[*a,c*]acridine
(phenophenanthracridine)



dibenz[*a,h*]acridine
(α-N-β-dinaphth-
acridine)

3. Indolo[2,3-*j*]benz[*c*]acridines

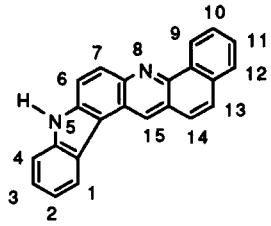
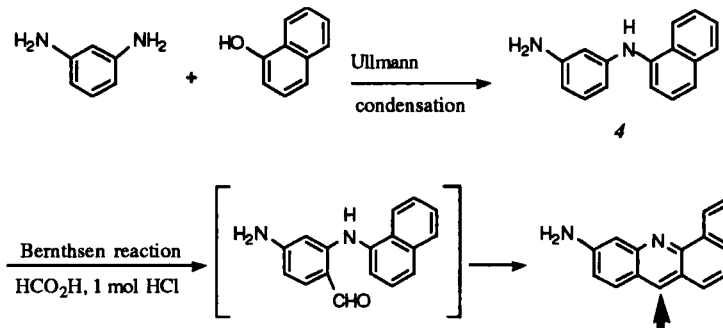


Figure 1. Benzacridines, dibenzacridines and indolo[2,3-*j*]benz[*c*]acridines.



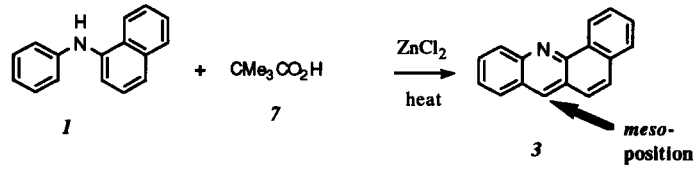
4

5

6

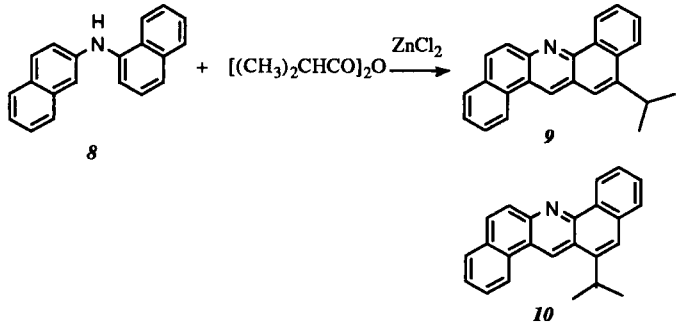
Steric hindrance near the *meso*-region (at the 7-position) of benz[*c*]acridine ring can prevent the side-reaction or it can affect the yield by inhibition of the cyclization of the intermediate.[17,33] Thus, benz[*c*]acridines bearing bulky substituents at the *meso* position could not be synthesized by the

Bernthsen method[17,30] (*meso*-effect). While benz[*c*]acridines with substituents at other locations could be easily synthesized.[17] The loss (cleavage) of the *t*-butyl group in the non-substituted benz[*c*]acridine (**3**) syntheses from *N*-phenyl-1-naphthylamine (**1**) with pivalic acid (**7**) was attributed to the steric effect in the *meso*-position.[17]



1 *7* *3*

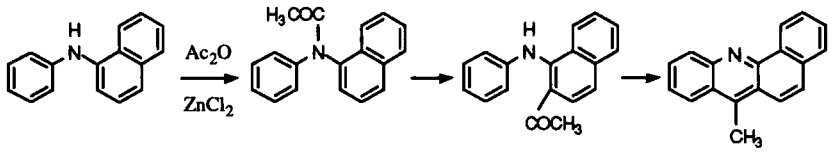
Recently, it is reported that alkyl migration has been occured during the Bernthsen reaction between *N*-1-naphthyl-2-naphthylamine (**8**) and 2-methylbutanoic acid and its anhydride at 200-230° for seven hours. In this reaction, 5- (**9**) or 6-s-butyldibenz[*a,h*]acridine (**10**) was obtained in 1-2% yield, instead of the expected 14-isomer.[45] It is suggested that alkyl migration may have occured in some cases where the Bernthsen reaction was conducted at high temperature and for the long reaction time.[45]



8 *9* *10*

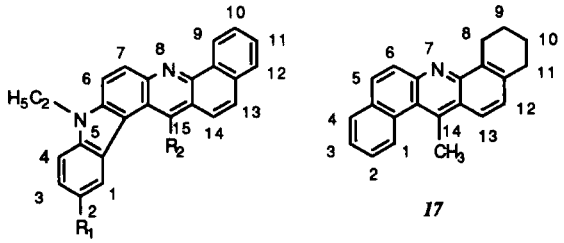
Isolation has shown that aminoketones may be the intermediates in the modified Bernthsen reaction.[1b] Aminoketones may also be cyclized by processes of the $AlCl_3$-catalyzed Friedel-Crafts type reaction. Effects of pH, substituents, and other reaction parameters can be exploited for optimizing the yield.[1a,46,47]

The mechanism of the Bernthsen synthesis has been investigated. Thus, the two possible intermediates, *N*-acetyl-*N*-phenyl-1-naphthylamine (**11**) and *N*-phenyl-2-acetyl-1-naphthylamine (**12**), were demonstrated.[48] Both acetic anhydride-1-^{14}C and deuteroacetic anhydride-2-$^{2}H_6$ [$(CD_3CO)_2O$] were employed. The cyclization was effected by $ZnCl_2$, phosphorus pentoxide (P_2O_5) or PPA. Both **11** and **12** were converted to 7-methylbenz[*c*]acridine (**2**) in the presence of anhydrous $ZnCl_2$. The products of the reaction were 7-methylbenz[*c*]acridine-7-^{14}C (**13**) or deuterated 7-methylbenz[*c*]acridine (**14**), and an isotopic exchange of deuterium was observed when deuterated acetic anhydride was used. Furthermore, the effects of catalysts, reaction time and the volume of acetic anhydride on the yield were studied, and the yield of 7-methylbenz[*c*]acridine (**2**) could be increased to 69% when these factors were optimized.



1 *11* *12* *2 (13,14)*

Angular dibenzacridines were also prepared by this method. Examples include 5-ethyl-15-methyl-5H-indolo[2,3-*j*]benz[*c*]acridine (**15**), 5-ethyl-2-methyl-5H-indolo[2,3-*j*]benz[*c*]acridine (**16**),[49] and 14-methyl-8,9,10,11-tetrahydrodibenz[*a,h*]acridine (**17**).[50] Table 1 shows benz[*c*]acridines synthesized by the Bernthsen method.[17,18,22,26,27,30,32,33,51a,52-55]

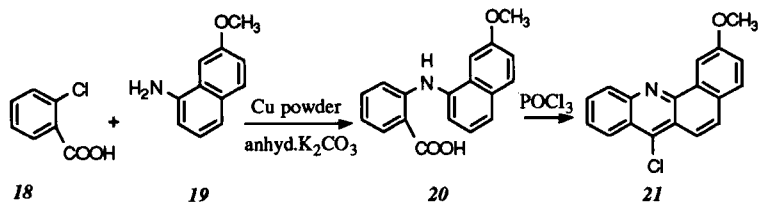


17

15 : R_1=H, R_2=CH_3
16 : R_1=CH_3, R_2=H

B. Cyclization of 2-Carboxyphenylnaphthylamines[56]

The cyclization products of 2-carboxyphenylnaphthylamines with $POCl_3$ are 7-chlorobenz[*c*]acridines. For example, Ullmann condensation of 2-chlorobenzoic acid (**18**) with 7-methoxy-1-naphthylamine (**19**) gave 2-(7-methoxy-1-naphthy)-anthranilic acid (**20**), which was converted into 7-chloro-2-methoxybenz[*c*]acridine (**21**) by treatment with $POCl_3$.[56]



18 *19* *20* *21*

2-Bromo-3-nitrobenzoic acid (**22**) condensed readily with 1-naphthylamine to give 2-(1-naphthyl)-3-nitroanthranilic acid (**23**), which was smoothly cyclized with $POCl_3$ to 11-nitro-7(12)-benz[*c*]acridone (**24**). Reaction of **24** with stannous chloride dihydrate ($SnCl_2$. $2H_2O$) gave 11-amino-7(12)-benz[*c*]acridone (**25**), which was then reduced to 11-aminobenz[*c*]acridine (**26**) by aluminum amalgam (foil) with 10% ferric chloride.[57]

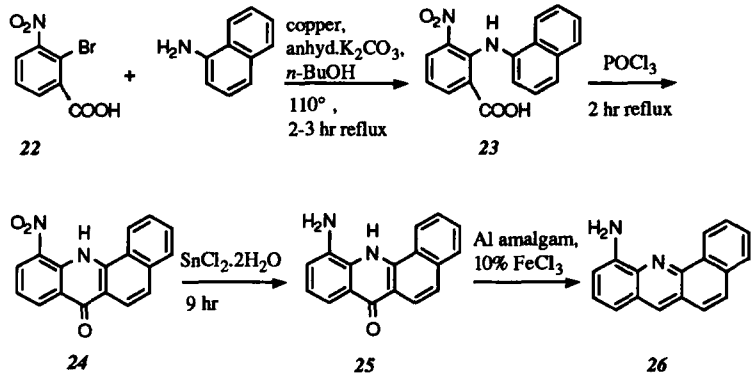
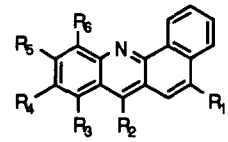


TABLE 1. Benz[*c*]acridines *via* Bernthsen or Modified Bernthsen Reaction



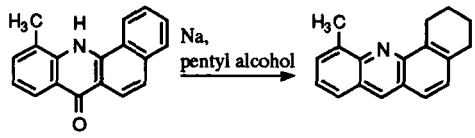
R_1	R_2	R_3	R_4	R_5	R_6	mp. (°C)	Ref
H	Ph	H	H	H	H	140	51a
H	Me	H	H	H	H	144 (126)	26(51a)
H	*n*-octyl	H	H	H	H	48	51a
H	*n*-amyl	H	H	H	H	84	51a
H	*n*-heptyl	H	H	H	H	60	51a
H	*n*-nonyl	H	H	H	H	51	51a
H	*n*-heptadecyl	H	H	H	H	82	51a
H	isobutyl	H	H	H	H	107	51a
H	4-heptyl	H	H	H	H	79	51a
H	H	H	H	Me	H	148	51a
H	Me	H	Me	H	Me	167	51a
H	benzyl	H	H	H	H	145	51a
H	*n*-propyl	H	H	H	H	87	51a
H	Me	H	H	Me	Me	166	51a
Me	Me	H	H	H	Me	127-128	51a
H	Me	Me	H	H	Me	140	51a
H	Me	H	Me	Me	H	144	51a
Me	Me	H	H	H	H	167	51a
H	Me	H	H	Cl	Me	173	33
H	Et	H	H	Cl	Me	134	33
H	Et	H	Me	Me	H	143	33

TABLE 1. Continued

R_1	R_2	R_3	R_4	R_5	R_6	mp.(°C)	Ref
H	Et	H	F	H	H	118	27
H	propyl	H	F	H	H	93	27
H	pentyl	H	F	H	H	105	27
H	benzyl	H	F	H	H	145	27
Me	Me	H	H	Me	Me	170	52[a]
Me	Me	H	Me	H	Me	183	52[a]
Me	Me	Me	H	H	Me	184	52[a]
Me	Me	H	Me	Me	H	206	52[a]
H	Me	H	H	H	H	139	26
H	Me	H	Et	H	Et	87	51b
H	Et	H	Et	H	Et	oil[b]	51b
F	Me	H	H	Me	H	173-175	54
F	Me	H	H	Me	H	175	18
F	Me	H	Me	H	H	174	18
H	Ph	H	cyclohexyl	H	H	148	55[a]
H	H	H	SMe	H	H	119	17[a]
Me	H	H	SMe	H	H	135	17[a]
H	Me	H	H	CF_3	H	150	30
H	Et	H	H	CF_3	H	142	30
H	propyl	H	H	CF_3	H	145	30
H	Et	H	H	Me	Me	95	33
H	Me	H	H	Me	H	141	32
H	Me	H	H	H	Me	133	32
H	Me	H	H	H	H	162	32
H	Me	H	H	H	Me	164-165	32
H	Et	H	Me	H	H	139	26
H	Et	H	Me	H	H	149	33
H	Et	H	H	Me	H	85	33
H	Et	H	H	H	Me	83	33
Me	Et	H	Me	Me	H	193	52
H	Et	Me	Me	H	Me	125	33
H	Me	H	*n*-butyl	H	H	104	22
H	Me	H	OH	H	H	240-257	53[c]
H	Me	H	H	H	OH	169-172	53[c]

a) The Knovenagel failed in this case but the Ullmann-Fetvadjian was succesful. b) bp. 283°/20 mmHg. c) Decomposed

Benz[*c*]acridones can be reduced to the corresponding tetrahydrobenz[*c*]acridines by sodium in pentyl alcohol.[58]



27 *28*

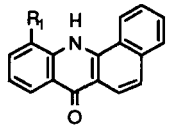
Benz[*c*]acridones can be also converted to the corresponding benz[*c*]acridines by Zn, or to 7-chlorobenz[*c*]acridines by $POCl_3$ and phosphorus pentachloride (PCl_5).[1a,b]

7-Chlorobenz[*c*]acridines are useful starting materials for the synthesis of 7-substitued benz[*c*]acridines such as 7-(3-octylaminopropylamino)-benz[*c*]acridine (PAA 2056) and related 7-(alkyl- and aralkyl-amino-alkyl-amino)-benz[*c*]acridines,[59] and 7-benz[*c*]acridinemethanols and 5,6-dihydro-7-benz[*c*]acridinemethanols.[60] 7-(3-Octylaminopropyl-amino)-benz[*c*]acridine (PAA 2056) and related 7-(alkyl- and aralkyl-amino-alkyl-amino)-benz[*c*]acridines are effective antiamebicidal agents.[61] 7-Benz[*c*]acridinemethanols and 5,6-dihydro-7-benz[*c*]acridinemethanols are effective as antimalarial agents.[60]

7-Substitued benz[*c*]acridines can be used in the syntheses of 7-nitrogen half-mustard benz[*c*]acridines. They have some antitumor activities for Ehrlich ascites tumor EF.[57]

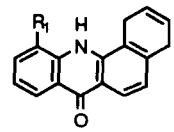
Tables 2-5 show the 7(12)-benz[*c*]acridones,[29,57,58,63] chlorobenz[*c*]acridines,[56-58,64,65] and benz[*c*]acridines,[57,58] formed by the cyclization of various naphthylanthranilic acids.

TABLE 2. 7(12)-Benz[*c*]acridones *via* Cyclization of Naphthylanthranilic Acids.



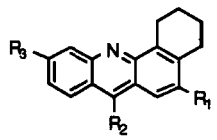
R_1	mp (° C)	Ref.
H	>360	63
NH_2	325-326	57
Me	275	58

TABLE 3. 1,4-Dihydro-7(12)-benz[*c*]acridones *via* Cyclization of Naphthylanthranilic Acids.



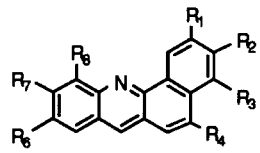
R_1	mp (° C)	Ref.
H	298-302	29
Me	64	58

TABLE 4. 1,2,3,4-Tetrahydrobenz[*c*]acridines *via* Cyclization of Naphthylanthranilic Acids.



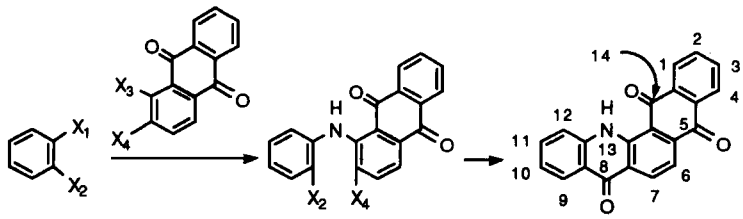
R_1	R_2	R_3	Yield (%)	mp (° C)	Ref.
H	Cl	H	50	107-108	53
OMe	Cl	Cl	39	190-191	64

TABLE 5. Chlorobenz[*c*]acridines *via* Cyclization of Naphthylanthranilic Acids.



R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Yield (%)	mp (° C)	Ref.
H	H	H	H	Cl	H	H	H	87	144-145	56
H	H	H	H	Cl	OMe	H	H	69	200-201	56
H	H	H	H	Cl	H	Cl	H	79	201-202	56
H	H	H	H	Cl	H	H	NO_2	65	252.5-253.5	57
H	H	OMe	H	Cl	H	H	H	53	196-197	56
H	OMe	H	H	Cl	H	H	H	91	171-172	56
OMe	H	H	H	Cl	H	H	H	94	152-153	56
H	H	OMe	H	Cl	H	Cl	H	50	236.5-237	56
H	H	H	H	Cl	H	H	Me	57	156.5	58
H	H	H	OMe	Cl	H	Cl	H	80	194	65
H	H	H	OMe	Cl	H	Cl	H	46	199-200	64

Phthaloylacridones have also been synthesized by the anthranilic acid cyclization method. For example, 5,14-dihydronaphth[2,3-*c*]acridan-5,8,14-trione (**29**) was synthesized by this method.[66,67]

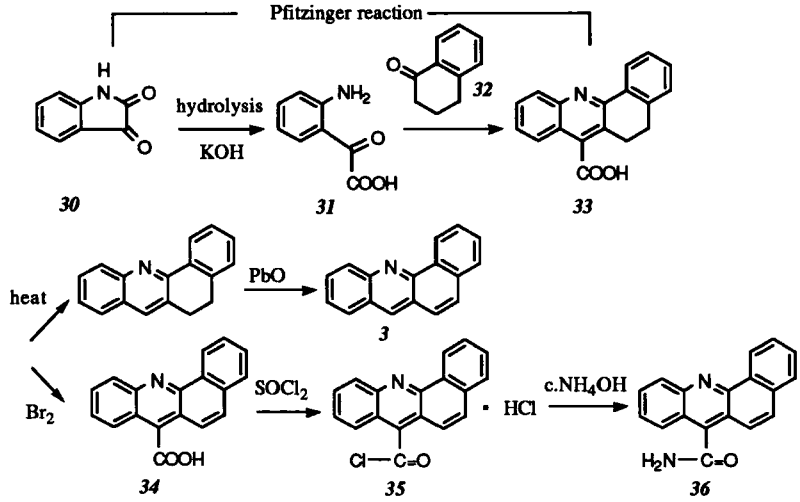


29

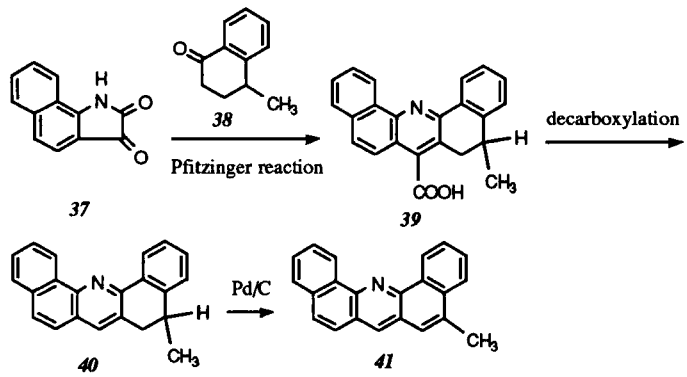
X_1	X_2	X_3	X_4	Ref.
NH_2	CO_2H	Cl	H	66,67
Cl	CO_2H	NH_2	H	66,67

C. Pfitzinger Reaction[60,68]

Isatin (**30**) is hydrolyzed in basic media (potassium hydroxide) to isatoic acid (**31**), which is condensed with α-tetralones (**32**) (as well as other cyclic ketones) to give 7-carboxyl-5,6-dihydrobenz[*c*]acridines (atophans (tetraphan)) (**33**).[28,60,69-74] These compounds are normally decarboxylated followed by dehydrogenation to afford the 7-unsubstituted benz[*c*]acridines (**3**).[68-70,75] Oxidation of **33** with bromine led to 7-carboxyl-benz[*c*]acridines (**34**) which were converted to a variety of benz[*c*]acridine-7-carboxamides (**36**) *via* the acid chloride (**35**).[69]



The Pfitzinger reaction fails or gives very poor yields of benz[*c*]acridines if the sterically hindered isatins or cyclohexanones are used as starting materials.[60,68,76,77] For example, α- and β-naphthisatins do not react with cyclohexanone[76,78,79] or α-acenaphthisatin.[76] 5,8-Dimethyltetralone has also failed to condense with 4,7-, 5,6-, 5,7-, or 6,7-dimethylisatin.[68] 4–Methyl-1-oxo-1,2,3,4-tetrahydronaphthalene (**38**) and α-naphthisatin (**37**) were reacted to obtain 7-carboxyl-5-methyl-5,6-dihydrodibenz[*c*,*h*]acridine (tetraphan **39**). After their decarboxylation, 5,6-dihydro-5-methyldibenz[*c*,*h*]-acridine (**40**) was obtained, which was dehydrogenated over palladium-charcoal to yield 5-methyldibenz[*c*,*h*]acridine(**41**).[77]



Derivatives of naphth[1,2-*c*]acridine (**42**),[80] 7H-naphth[1,8-*b*,*c*]acridine (**43**),[81] and naphth[2,1-*c*]acridine (**44**) are also synthesized by the same method as compound **41**.[81]

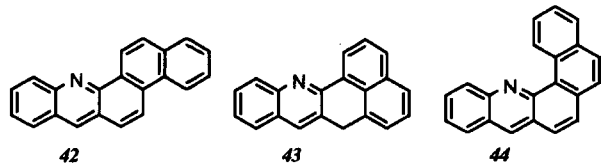
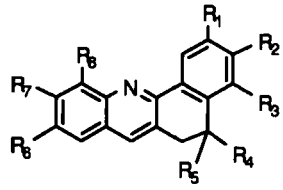


Table 6 shows benz[*c*]acridine synthesized by the Pfitzinger method.[68,70,71,82,83]

TABLE 6. 5,6-Dihydrobenz[*c*]acridines Prepared by Pfitzinger Reaction

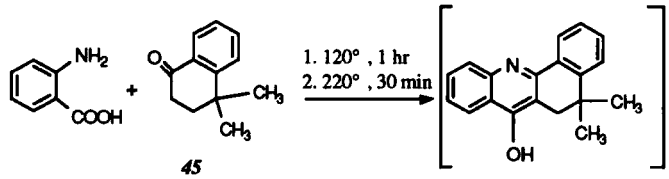


R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Yield (%)	mp (° C)	Ref.
Me	Me	H	H	H	Me	Me	H	-	215	68
Me	H	Me	H	H	Me	Me	H	-	135	68
Me	Me	H	H	H	H	Me	Me	-	131	68
Me	H	Me	H	H	H	Me	Me	-	104	68
Me	Me	H	H	H	Me	H	Me	-	134	68
Me	H	Me	H	H	Me	H	Me	-	102	68
Me	Me	H	H	H	F	H	H	-	139	68
H	H	H	H	H	F	H	H	-	97	68
H	H	H	H	H	H	H	Me	-	93-94	70
H	H	H	H	H	Br	H	H	-	168	70
H	H	H	H	H	Cl	H	H	-	102	70
H	H	H	Me	H	H	H	H	-	178(picrate)	71
H	H	H	Me	Me	Cl	H	H	92	147-148	83
Cl	H	H	H	H	H	H	H	-	124	82

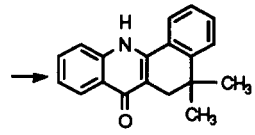
D. Reactions Related to the Pfitzinger Reaction

Benz[*c*]acridines have also been synthesized by condensation of cyclohexanones with the various reactants. The condensation of anthranilic acid with 4,4-dimethyl-1-tetralone (**45**) produced 5,5-dimethyl-5,6-dihydro-7(12)-benz[*c*]acridone (**46**) in 50% yield.[84]

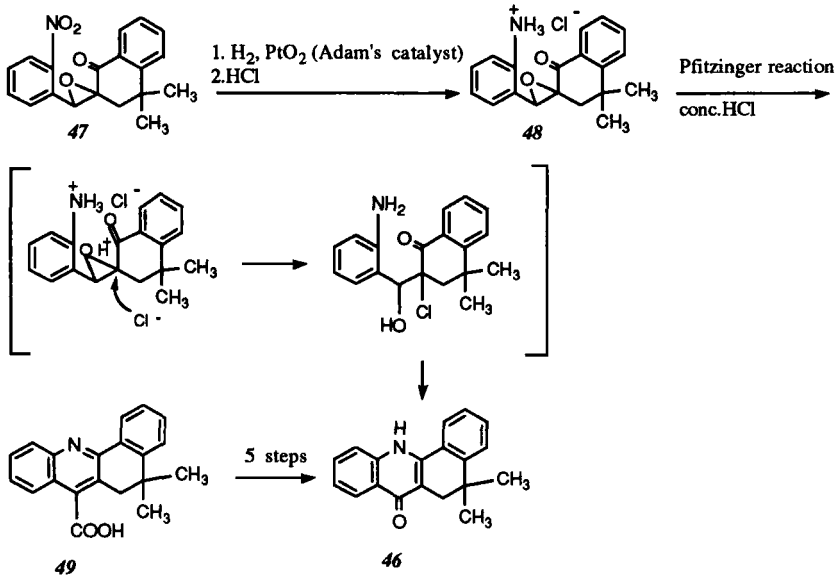
Compound **46** was also obtained from 2-(*o*-aminobenzal)-4,4-dimethyl-1-tetralone oxide hydrochloride (**48**) or 7-carboxy-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (**49**) in five steps.[84]



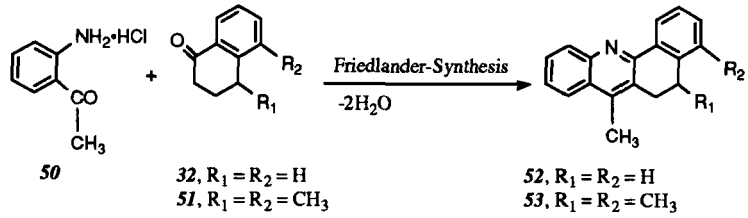
45



46



In a modification of the Friedlander reaction, *o*-aminoacetophenone hydrochloride (**50**) reacts with 1-tetralone (**32**) or 4,5-dimethyl-1-tetralone (**51**) to give the corresponding 7-methyl-5,6-dihydrobenz[*c*]acridine (**52**)[85] and 4,5,7-trimethyl-5,6-dihydrobenz[*c*]acridine (**53**) in 52% and 68% yields, respectively.[86]

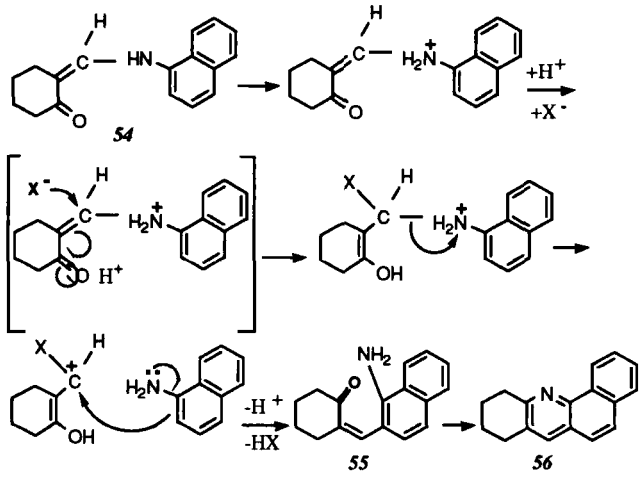


32, $R_1 = R_2 = H$
51, $R_1 = R_2 = CH_3$

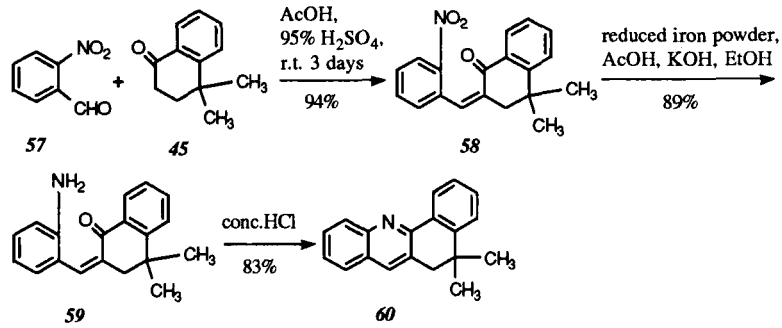
52, $R_1 = R_2 = H$
53, $R_1 = R_2 = CH_3$

On the other hand, reaction of 2-tetralone with anthranilic acid gives 5,6-dihydrobenz[*a*]-acridone in 86% yield.[87]

The following mechanism of synthesis of 8,9,10,11-tetrahydrobenz[*c*]acridine (**56**) involving the intermediate (**55**) was provided to explain the outcome of such reactions.[87] In this case, the product, 8,9,10,11-tetrahydrobenz[*c*]acridine (**56**), was obtained from 2-(1-naphthylaminomethylene)-cyclohexanone (**54**) in 17% yield.[88,89]

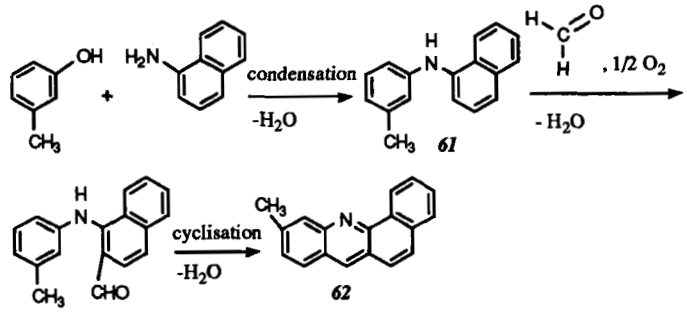


In a related reaction, 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (**60**) was obtained from *o*-nitrobenzaldehyde (**57**) and 4,4-dimethyl-1-tetralone in a good yield (the three steps yield is 69%).[90] The intermediate, 4,4-dimethyl-2-(*o*-nitrobenzal)-1-tetralone (**58**), furnished 4,4-dimethyl-2-(*o*-aminobenzal)-1-tetralone (**59**) which is similar to intermediate **55**.[90] Other similar reactions leading to benz[*c*]acridines have also been described.[83,90-92]

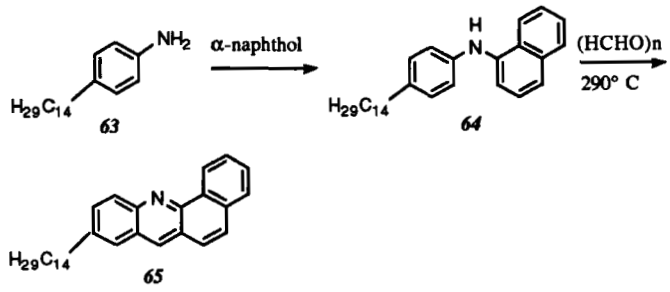


E. Ullmann-Fetvadjian Reaction[42-44,51,93]

The Ullmann-Fetvadjian reaction (condensation of paraformaldehyde with a heated mixture of a naphthol and primary arylamine)[43] is also a convenient method for benz[*c*]acridine syntheses. In this method, aromatic amines such as aniline and 1-naphthylamine are first reacted with naphthols (phenols) and the reaction product is then cyclized in the presence of an aldehyde (paraformaldehyde).[33,43,93-98] 1-Naphthylamine, *m*-toluidine, and formaldehyde have reacted to give 10-methylbenz[*c*]acridine (**62**).[22]



Katritzky et al[99] have prepared the benz[*c*]acridine (**65**) with C_{14} alkyl side chain at position 9 in the hope of increasing their solubility in hydrocarbon solvent, using the method of Buu-Hoi and co-workers.[22] In this case, a one-pot cyclization with formaldehyde resulted in the formation of tarry materials. Therefore, the amine (**64**) was isolated and condensed with formaldehyde at 290° to give the desired benz[*c*]acridine (**65**) in 32% yield.



Dibenz[*c*]acridine (**66**) can also be synthesized through reaction of 2 mol of 1-naphthylamine and 1 mol of methylene iodide[42] or 2 mol of 1-naphthylamine and 1 mol of methylene chloride[100,101] in the presence of alkali, e.g. potassium carbonate and concentrated aqueous potassium hydrochloride.[42,100,101] Methylene iodide,[42,102,103] and methylene chloride,[100,101,103] have replaced formaldehyde in other similar reactions.

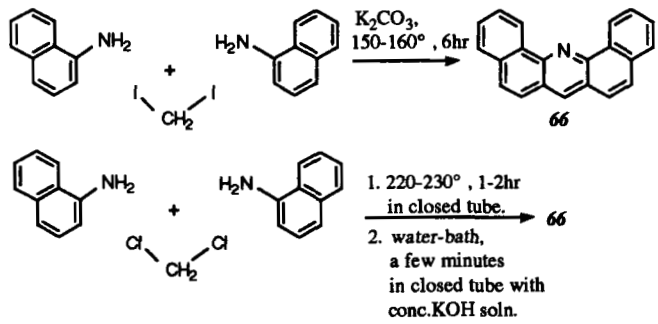
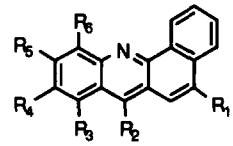


Table 7 shows the benz[*c*]acridines formed by the Ullmann-Fetvadjian reaction.[17,22,33,51a,70,96,102,104,105]

Dibenz[*a,h*]acridine,[42-44,93,100] and many condensed benzacridines have also been synthesized

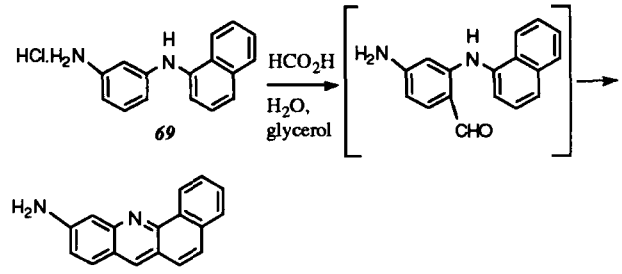
TABLE 7. Syntheses of Benz[*c*]acridines through Ullmann-Fetvadjian Reaction



R_1	R_2	R_3	R_4	R_5	R_6	mp (° C)	Ref.
H	H	H	*t*-amyl	H	H	98	33
H	H	H	*n*-butyl	H	H	70	22
H	H	Me	H	H	Me	122.5	105
H	H	H	Me	H	Me	155	105
H	H	H	*n*-heptyl	H	H	60	22
H	H	H	Me	H	H	131-132	104
H	Me	H	Me	Me	H	144	51a
Me	Me	H	H	H	H	167	51a
Me	Me	H	H	H	Me	127-128	51a
H	H	H	H	Me	Me	96-97	51a
H	H	H	SMe	H	H	119	17
Me	H	H	SMe	H	H	135	17
H	H	H	Ph	H	H	163	51a
H	H	H	H	Me	Me	96-97	51a
H	H	H	H	H	Me	107	51a,70
H	Me	H	*n*-butyl	H	H	104	22
H	H	H	H	Me	H	148	22,51a
H	H	Me	H	H	H	136	22
H	H	Me	Me	H	Me	160	96,102

by the Ullmann-Fetvadjian reaction.[40,44,93,106] For example, benzo[*c*]naphth-[2,3-*h*]acridine (**68**) was synthesized from 1-naphthol and 1-aminoanthracene (**67**) in the presence of paraformaldehyde (Table 8).[44] More examples can be found in Table 8.[40,44,50,51b,93,107]

For the syntheses of aminobenz[*c*]acridines by the Ullmann-Fetvadjian reaction, *m*-phenylenediamine (diarylamines) and formic acid are used directly. 10-Aminobenz[*c*]acridine (**6**) was obtained by treatment of *N*-(3-aminophenyl)-1-naphthylamine hydrochloride (1-naphthyl-*m*-phenylenediamine hydrochloride) (**69**) with formic acid.[108]



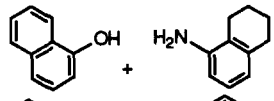
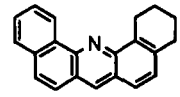
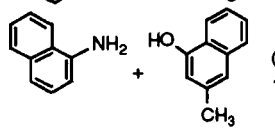
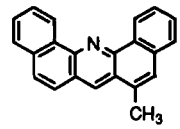
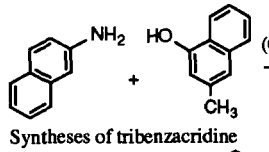
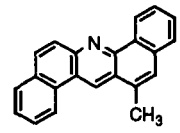
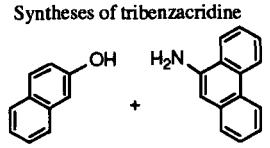
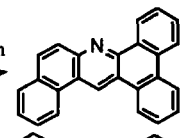
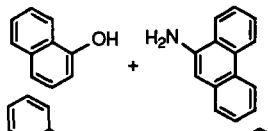
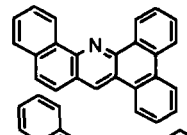
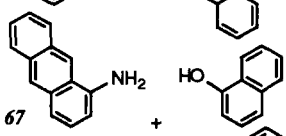
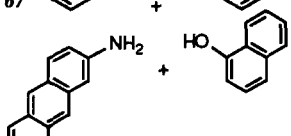
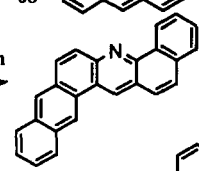
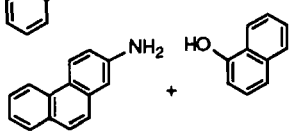
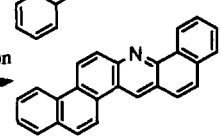
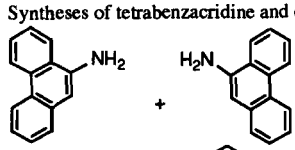
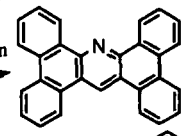
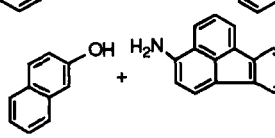
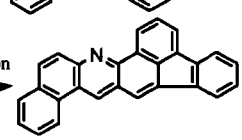
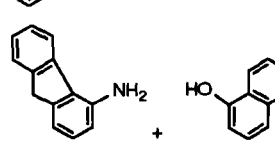
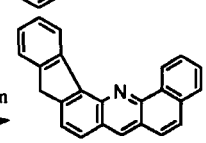
69

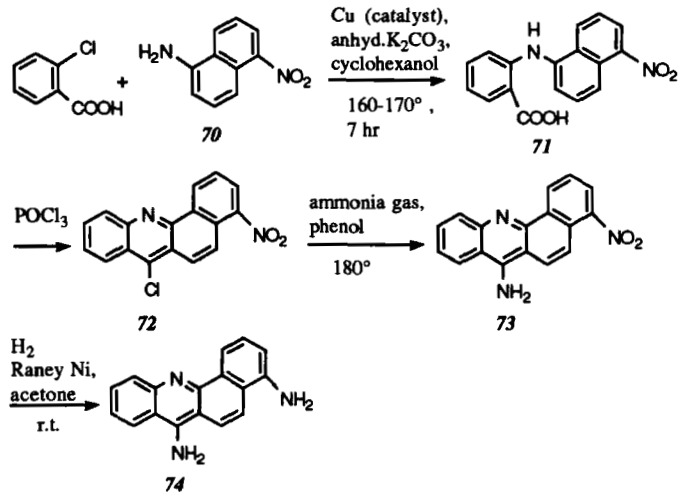
6

4-Nitro-7-chloro-benz[*c*]acridine (**72**) was converted into 4-nitro-7-aminobenz[*c*]acridine (**73**) by passing a stream of ammonia through the solution in phenol at 180°; the nitro-product was hydrogenated in acetone at atmospheric temperature and pressure using Raney nickel to provide

4,7-diaminobenz[*c*]acridine (**74**).[24,57,109]

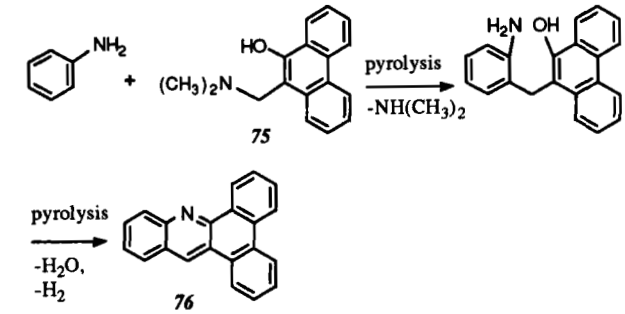
TABLE 8. Ullmann-Fetvadjian Syntheses of Angular Benzacridines containing Benz[*c*]acridine Moiety

Starting material	Angular benzacridine	Ref.
Syntheses of dibenzacridine		
		50
		51b
		51b
Syntheses of tribenzacridine		
		93
		93
 *67* *68*		44
		44
		93
Syntheses of tetrabenzacridine and other condensed benzacridines		
		93, 107
		40
		93

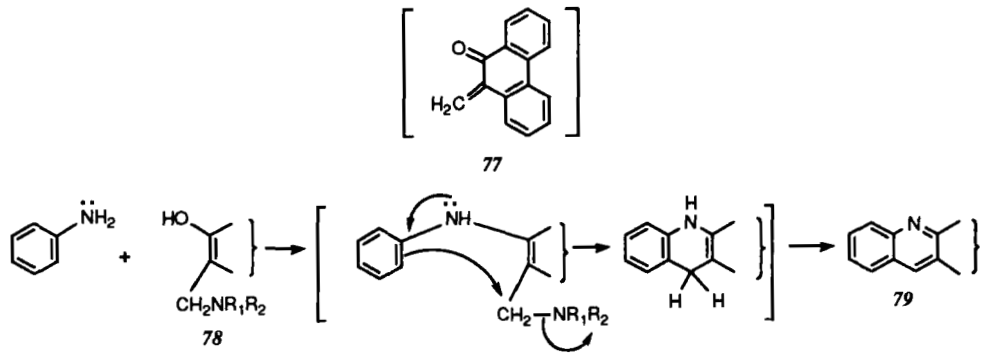


F. Reaction of Mannich Bases and Aniline

The condensation reaction of the Mannich base 10-(*N,N*-dimethylaminomethyl)-9-phenanthrol (**75**) with aniline yielded dibenz[*a,c*]acridine (phenophenanthracridine, **76**) in 62% yield.[110]



Although compound **75** may potentially produce a quinone methide (**77**) as the Diels-Alder type intermediate, the evidence obtained did not support such an intermediate. The mechanism proposed entailed initial attack by aniline on compound **78** and then an intramolecular process leads to the elimination of the dimethylamine and formation of the benz[*c*]acridines (**79**).[110,111]



G. Ullmann-La Torre Reaction[51a,112]

Diarylamines (*o*-tolyl-1-naphthylamine. **80**) are heated with lead oxide (PbO) at a high temperature (350°) to give the benz[*c*]acridines (**3**). Table 9 shows the benz[*c*]acridines obtained by this method.[51a,112]

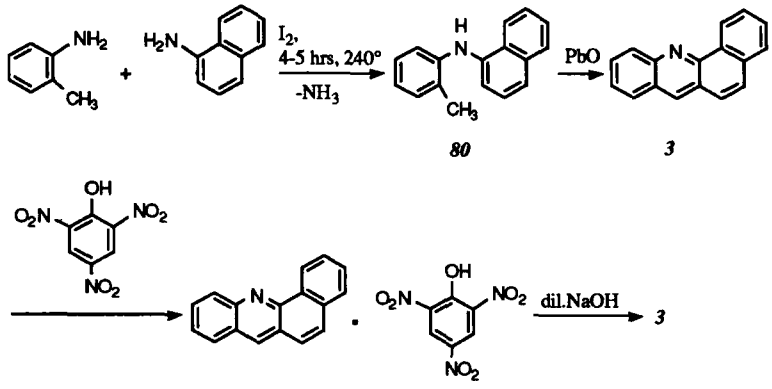
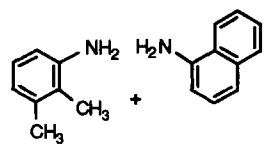
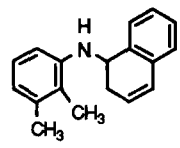
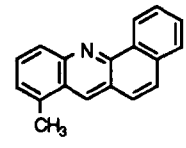
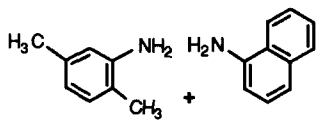
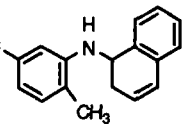
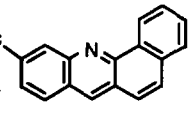
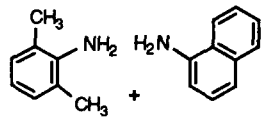
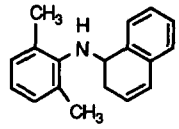
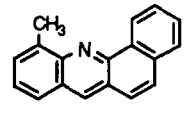
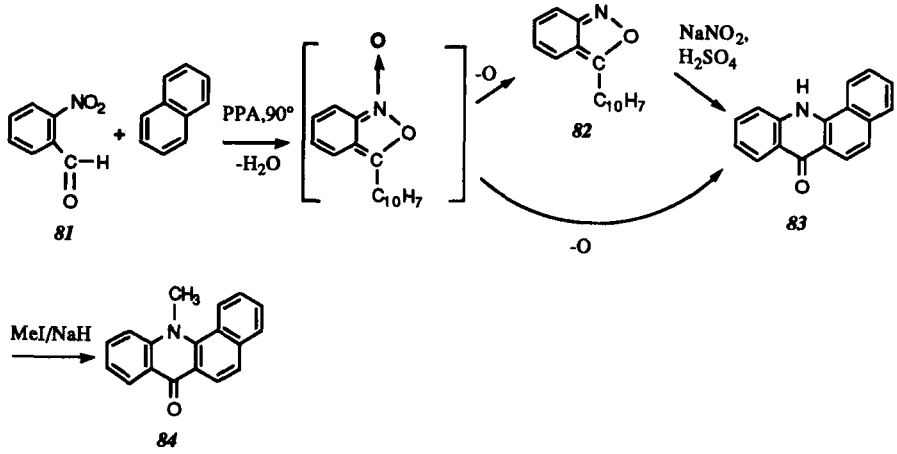


TABLE 9. Benz[*c*]acridines *via* Ullmann-La Torre Reaction.

Starting material	Diarylamine	Benz[*c*]acridine	Ref.
			51a
			51a
			51a, 112

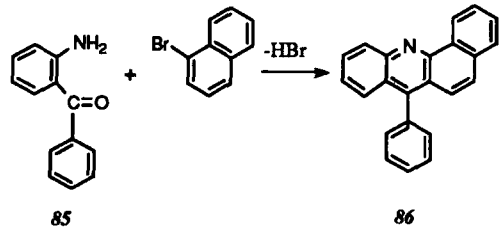
H. Tanasescu Reaction[92,113]

Tanasescu et al. reported the synthesis of benz[*c*]acridine by the reaction of 2-nitrobenzaldehyde (**81**) and naphthalene in the presence of PPA.[92,113] The products were 7(12)-benz[*c*]acridone (**83**) and 5-naphthylbenzo[*c*]isoxazole (**82**). Compound **82** could be converted to **83** by treatment with sodium nitrite and sulfuric acid. The posturated reaction path is shown.[113] The reaction had failed when concentrated sulfuric acid was used as a catalyst.

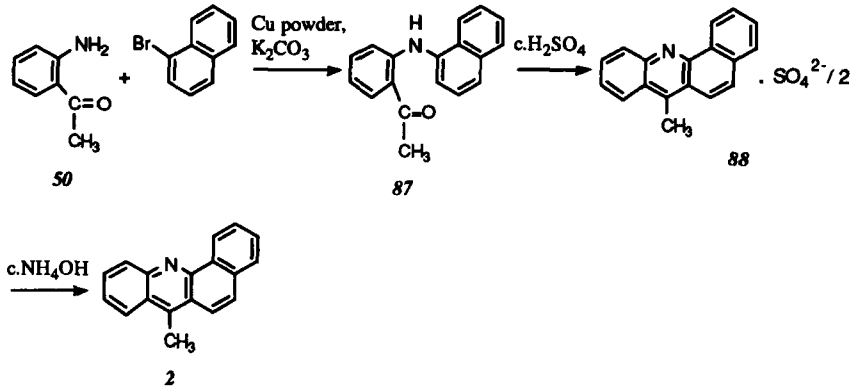


I. Cyclization of N-Naphthylphenylamine-2-ketones or Aldehydes[114-116]

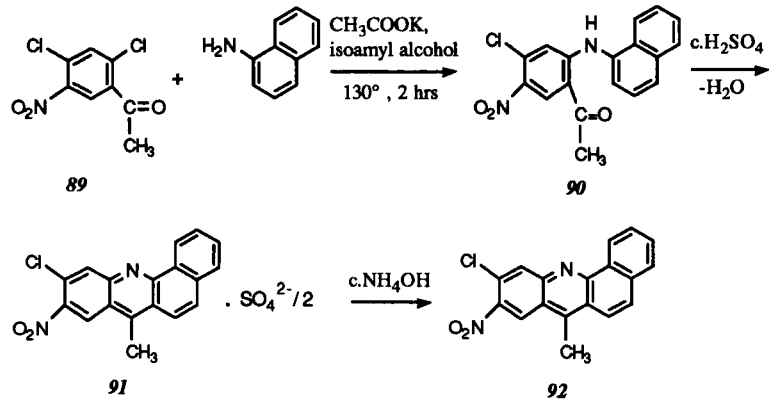
7-Phenylbenz[*c*]acridine (**86**) has been synthesized from 1-bromonaphthalene and 2-aminobenzophenone (**85**).[114] This reaction has probably involved a Ullmann type condensation as a first step and is followed by the cyclization of the resulting Bernthsen-like intermediate.[114]



A mixture of 2-aminoacetophenone (**50**), 1-bromonaphthalene, potassium carbonate, and copper powder was refluxed in nitrobenzene and 2-(1-naphthylamino)-acetophenone (**87**) was obtained. Compound **87** was dissolved in glacial acetic acid containing concentrated sulfuric acid, and the mixture was heated on the steam-bath. The yellow 7-methylbenz[*c*]acridine sulfate (**88**) precipitated immediately. On addition of concentrated ammonia, 7-methylbenz[*c*]acridine (**2**) was obtained.[115]



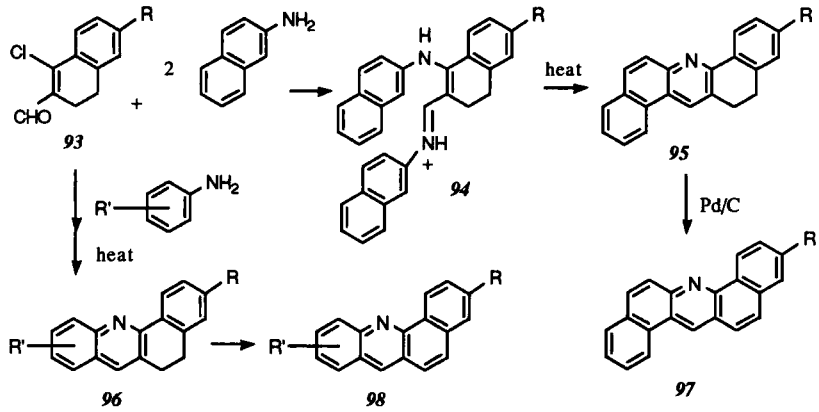
Additional application of this reaction can be seen from the preparation of 7-methyl-9-nitro-10-chlorobenz[*c*]acridine (**92**).[116]



89 90 91 92

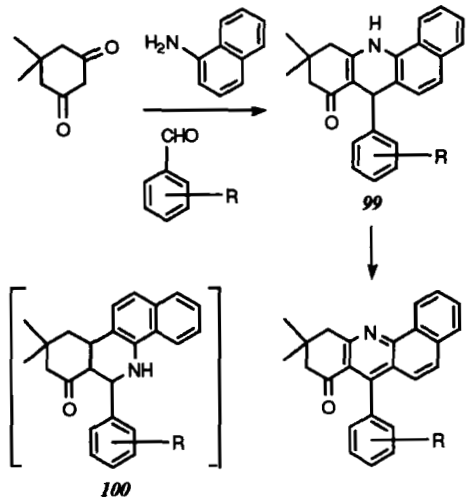
J. Other Methods

Recently, Ray *et al.* have synthesized dihydroacridine derivatives such as 12,13-dihydrodibenz[*a*,*h*]acridines (**95**)[117,118] and 5,6-dihydrobenz[*c*]acridines (**96**)[119,120], by utilizing of the thermal cyclization of anil derivatives (**94**) which have been prepared from the chloroaldehydes (**93**) and aromatic amines. The aromatization of the dihydro compounds by heating with Pd/C in *p*-cymene produced dibenz[*a*,*h*]acridines (**97**)[117] and benz[*c*]acridines (**98**)[119] in high yields, respectively. Thus, this method is found to be superior in yield, availability of starting materials, and technical simplicity to earlier methods and also represents the syntheses of dihydrodiols of benzacridines which are proximate and ultimate carcinogenic compounds.[117,119]



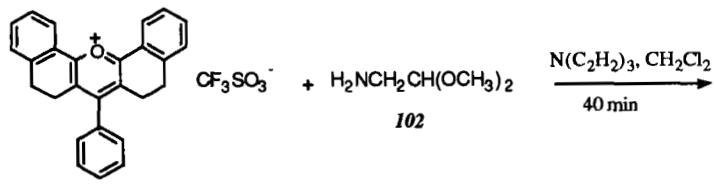
93 94 95 96 97 98

Condensation of dimedone, α-naphthylamine, and aromatic aldehydes has been reported to yield the acridones (**99**),[121] instead of benzo[*c*]phenanthridines (**100**) whose structures had been erroniously assigned.[122]

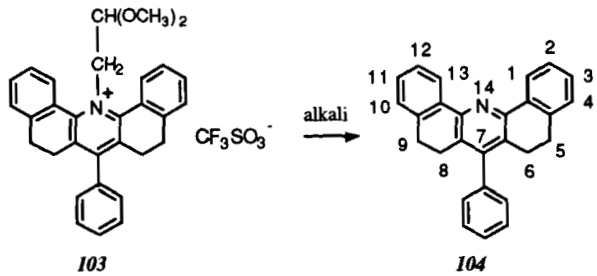


100

By replacing the oxygen atom in the pyrylium ion (pentacyclic pyrylium trifluoromethanesulphonate, **101**) with a nitrogen atom, the symmetric benz[*c*]acridine (**103**) was obtained.[123a,b] In 1st step, 2,2-dimethoxyethylamine (**102**) in triethylamine reacted with **101** in suspended dichloromethane to give acridinium salt (**103**) in a good yield. Compound **103** was converted to 7-phenyl-5,6,8,9-tetrahydrodibenz[*c*,*h*]acridine (**104**).[123a,b] Penta- and nonacyclic compounds of the type have been obtained in the syntheses of the azaarene systems.[124]

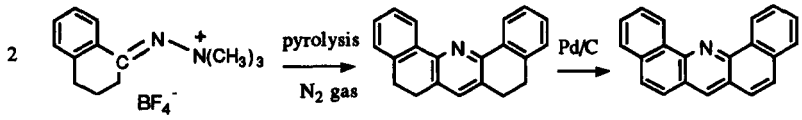


101 *102*



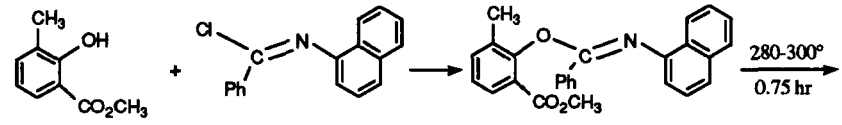
103 *104*

Dibenz[*c*,*h*]acridine (**66**) was obtained by the pyrolysis of 2 mol of ketone *N*,*N*,*N*-trimethylhydrazonium fluoborate salt (**105**) synthesized from tetralones or cyclohexanones via a dehydration of compound **106**.[125]

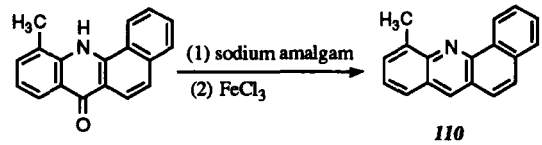


105 *106* *66*

The condensation of *N*-1-naphthylbenzimidoyl chloride (**108**) with the sodium salt of 2-hydroxy-3-methyl-methyl benzoate (**107**) gave 6-methoxycarbonyl-2-methylphenyl-*N*-1-naphthyl-benzimidate (**109**) which rearranged and cyclized smoothly to 11-methyl-7(12)-benz[*c*]acridone (**27**) in 72% yield.[58]

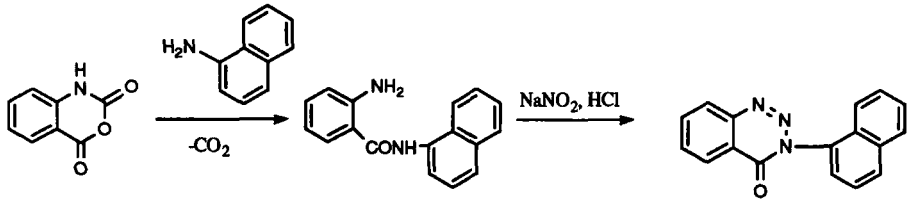


107 *108* *109*

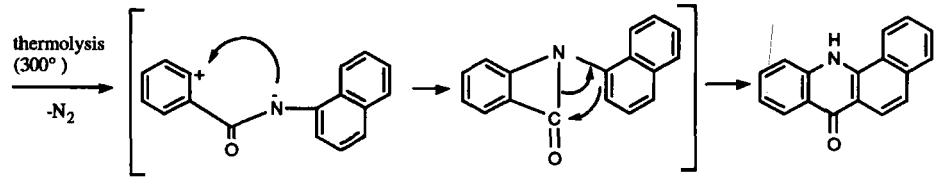


27 *110*

A 17% yield of benz[*c*]acridone-7-one (**83**) was obtained when 3-(1-naphthyl)-1,2,3-benzotriazin-4(3H)-one (**111**) was heated at 300°.[126] The reaction suggests the involvement of the benzazetinone intermediate (**112**) formed *via* the zwitterion or *via* a radical pathway.[126]

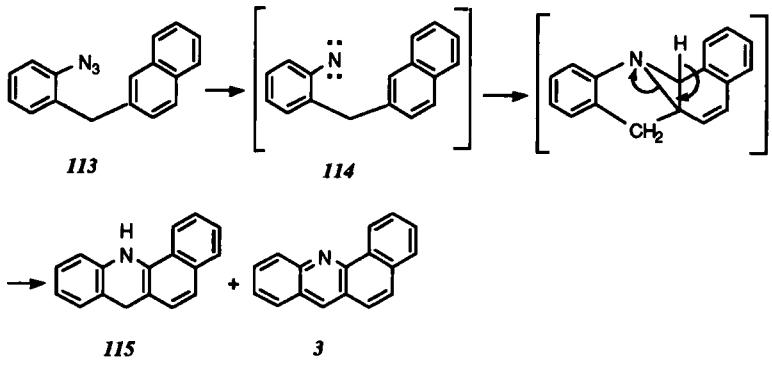


111



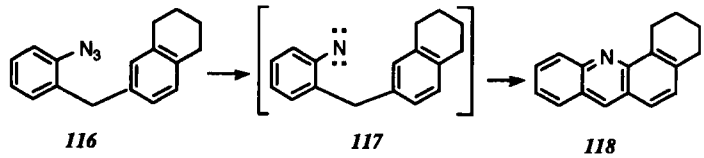
112 *83*

The intramolecular nitrene (**114**) insertions into the naphthalene double bonds can also lead to benz[*c*]acridines. Thus, thermal decomposition of 2-(2-azidobenzyl)naphthalene (**113**) gives, by nitrene insertion, mixtures of benz[*c*]acridan (**115**) and benz[*c*]acridine (**3**) in 38.5% and 36% yield, respectively.[127]



113 *114* *115* *3*

By this method, 1,2,3,4-tetrahydrobenz[*c*]acridine (**118**) was also synthesized from 2-(2-azidobenzyl)tetralin (**116**).[127]

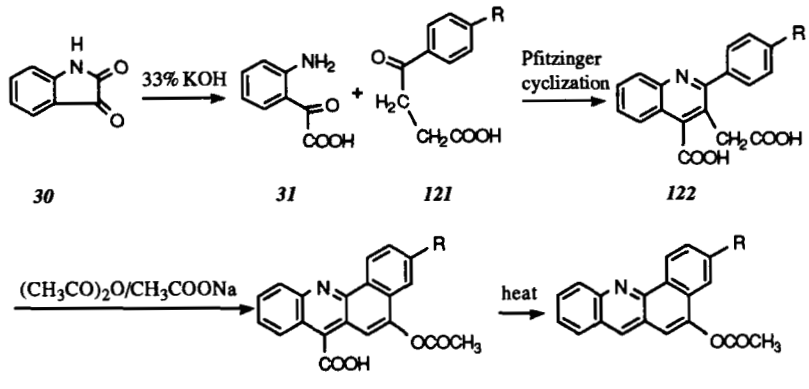


116 *117* *118*

Thermal electrocyclization of *o*-quinone methanide *N*-methoxyimines (**119**), easily prepared from 10-(methoxyimino)phenanthren-9-one, affords dibenz[*a*,*c*]acridines (**120**) in good yields, *via* a thermal *cis-trans*-isomerization of **119** .[128,129]

II. SYNTHESES BASED ON PRECURSORS CONTAINING A PYRIDINE RING

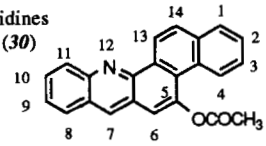
Figure 2 shows an example of benz[*c*]acridine synthesis without the pyridine ring construction in the steps of the synthetic pathway. Therefore, examples have been placed in a second category of the benz[*c*]acridine synthesis. β-Aroylpropionic acids (**121**) are condensed with isatin (**30**) under Pfitzinger conditions to give the corresponding 2-aryl-3-carboxylmethylcinchoninic acids (**122**). The acids **122** were converted into their 3-substituted-5-acetoxybenz[*c*]acridines (**124**) by usual methods.[41b]



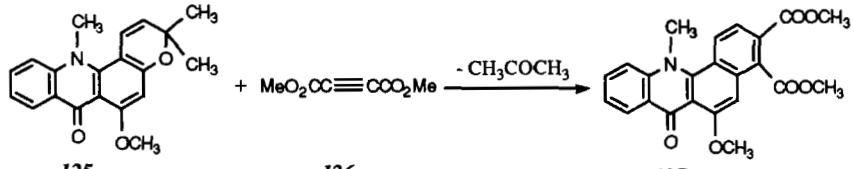
30 31 121 122 123 124

Compd No.	R	Yield (%)	mp (° C)
124a	H	47	298-300
124b	CH_3	40	310
124c	Br	54	335-337
124d	C_6H_5	41	355-357
124e (5-acetoxynaphth[1,2-*c*]acridine)		50	325-326

FIGURE 2. Synthesis of 3-substituted-5-acetoxybenz[*c*]acridines (*124a-e*) by Pfitzinger reaction of isatic acid (*31*) from isatin (*30*) with β-aroylpropionic acids (*121*)



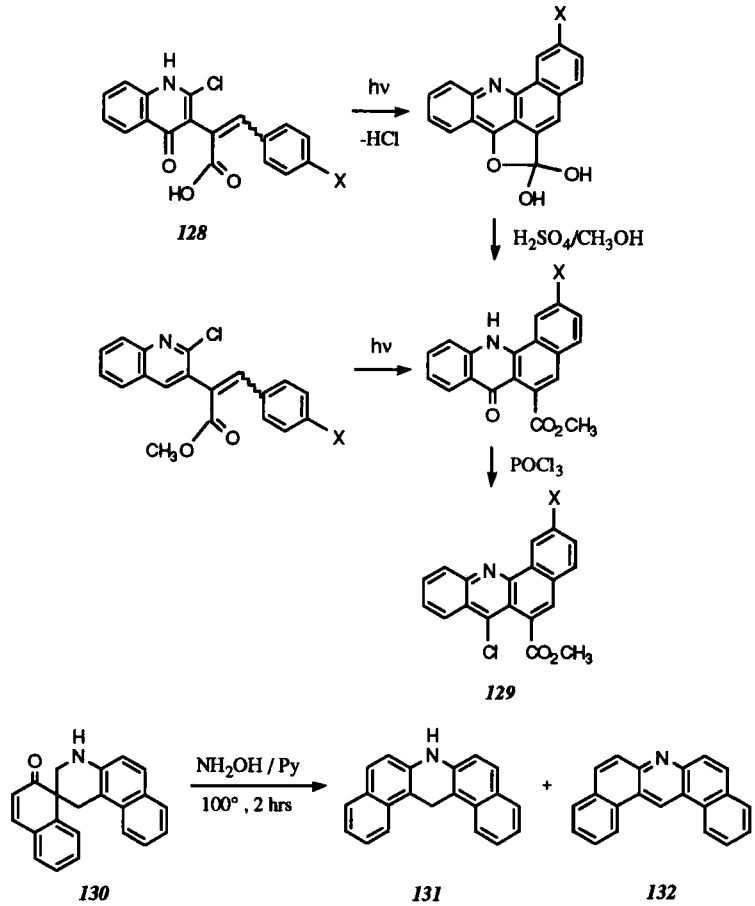
A second example belonging to this category has been described with the use of a Diels-Alder type reaction. In the reaction, acronycine (**125**) is heated with dimethyl acetylenedicarboxylate (**126**) at an elevated temperature to obtain a low yield of 3,4-dicarboxy-6-methoxy-12-methylbenz[*c*]acridine-7-one (**127**).[113]



125 126 127

A photolytical *peri*-ring closure of 3-styryl-4-quinolinones (**128**) is reported to give the benz[*c*]acridine system (**129**) in good yields.[130]

2 Mmol of spiro[(1,2,3,4-tetrahydro-benzo[*f*]quinoline)-2,1'-(1'H-naphthalene-2'-one] (**130**) and 3 mmol of hydroxyamine hydrochloride in pyridine was heated for 2 hrs at 100° to give a 1:1 mixture of 7,14-dihydro-dibenz[*a,j*]acridine (**131**) and dibenz[*a,j*]acridine (**132**) in 76% yield.[131]



128 *129* *130* *131* *132*

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