Azachrysene Preparation

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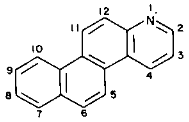
I. Introduction.

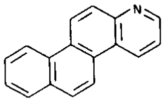
Azachrysenes are tetracyclic compounds containing nitrogen in any one of six symmetry-distinct positions in the molecule. The basic structure is described as a benzophenanthridine or naphthoquinoline. Historically the azachrysenes have been important to the drug and dye industries, and several eminent chemists devoted much time to the elucidation of their exact structures by unambiguous synthesis. More recently, their occurrence in liquified coal products and shale oil has prompted renewed interest in their chemistry and physiological effects. Several natural products found primarily in the plant parts of the poppy family, *Papaveraceae*, are 5-azachrysene derivatives (1a-e).



The azachrysenes are structurally unique as precursors to and intermediates in the preparation of azasteroids, and much of the literature on these compounds is steroid related. In addition, azachrysenes possess a varied group of physiological effects, functions of the six possible positions of the nitrogen in the chrysene skeleton and the variety of reactive groups the molecule can accommodate. These compounds are known to inhibit leukemia (2-4) and tumor formation (5-10) as well as fungal and bacterial growth (11-19). They also are anti-inflammatory agents (20,21) and muscle relaxants (22-27) and exhibit cardiotonic activity (28,29). Sanguinarine, a naturally occurring alkaloid isolated from bloodroot, is used to induce glaucoma in laboratory animals for medicinal research (30).

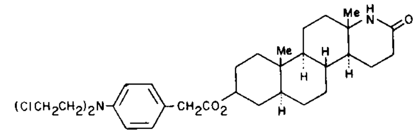
The preparation of azachrysene derivatives is a significant challenge. The recent proliferation of literature references citing successful methods is indicative of the rising interest in further research of their physiological powers. We limit the scope of this review to a discussion of the synthetic procedures developed for preparation of the azachrysene skeleton from 1950 through 1979. The literature of azachrysenes prior to 1950 has been thoroughly reviewed (31a,b).

II. 1-Azachrysene, Naphtho[2,1-*f*]quinoline.

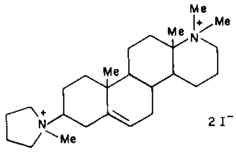


A. Physiological Interest.

The majority of 1-azachrysene derivatives fall under the category of 17a-azasteroids, and very much research has been directed at their synthesis and use as medicinals (32a-c). Nitrogen containing steroids are thought to have an effect on membranes causing fluctuations in ATP levels or in dehydrogenase activity in the mitochondria (32d). A series of recent papers by Catsoulacos and co-workers (5-10a) has shown the homo-azasteroidal ester of (*p*-(bis-(2-chloroethyl)amino)phenyl)acetic acid to be a very promising antitumor agent with no apparent mutagenic or carcinogenic activity and low mammalian toxicity. This compound also inhibits DNA synthesis and mitosis in normal lymphocyte cultures (33) and appears to be the first steroidal alkylating agent to have shown *in vivo* activity in L1210 leukemia in mice (2a).

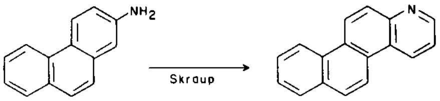


Chandonium iodide, a bisquaternary 17a-azasteroid analog, is an effective short-acting neuromuscular blocking agent (22-27), acting selectively at acetylcholine receptors (26). 1-Azachrysene derivatives may also be used as intermediates in the synthesis of hormones such as cortisone (34), aldosterone (35-37), 17-azaprogesterone (38,39) and pregnane (40a,b).



B. Synthetic Methods. General.

Prior to 1950, the Skraup cyclization of 2-aminophenanthrene gave the highest yield (80-90%) of unsubstituted 1-azachrysene, and this continues to be a convenient high-yield pathway to that compound today (43c).



Kaufman (41a) dehydrogenated the 17a-lactam of dehydroisoandrosterone over selenium metal at 350° to produce 1-azachrysene in low yield. Cambell and Temple

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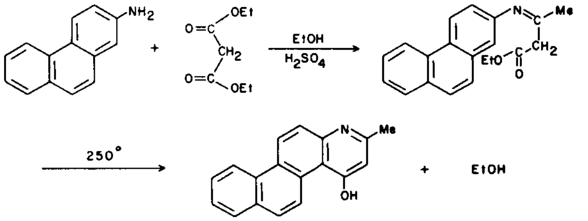
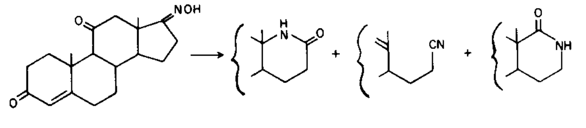
(42) used a modified Skraup reaction to afford 69% of the compound. The simple disubstituted 4-hydroxy-2-methyl-1-azachrysene was prepared (43a) from the Conrad-Limpach reaction of 2-aminophenanthrene with ethyl acetoacetate. Cyclodehydration techniques have found application in the preparation of this ring system (43b).



C. Synthetic Methods. Azasteroids.

Application of the Skraup reaction to substituted 1-aminophenanthrenes provides a ready route to 17a-azasteroid analogs. Much of the work done on the 17a-azasteroids, however, involves expansion of the five-membered D ring to a six-membered ring containing nitrogen. Conversion of 17-oximino steroids to the corresponding 17a-D-homolactams *via* Beckmann rearrangement is the most frequently used method for this enlargement (15,34-37,40,41a-d,45-52a,53-59). In addition to the 17a-lactam as the major product of this reaction, several researchers have identified the presence of minor products. Nagata and co-workers (37) carried out the rearrangement of the 17-oxime **1** of adrenosterone using 4-acetamidobenzenesulfonyl chloride in pyridine to give the 17a-lactam **2** in 91% yield plus 6% of the seconitrile **3**.

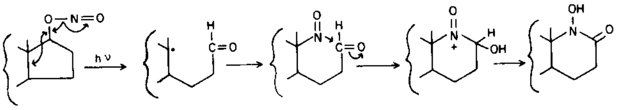


1 2 3 4

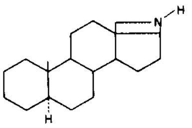
Similar results with various steroids have been described by Shoppee and Killick (54), Catsoulacos and Boutis (5), and Fenselau, Hamamura and Moffatt (53). Mechanisms for these reactions were presented by the latter. Matkovics and co-workers (59) report the seconitrile **3** as well as the unexpected formation of the 17-lactam **4** (58,59). More recently, photo-induced Beckmann rearrangements have been attempted, resulting in low yields of the 17a-D-homolactam (60), accompanied in some cases by the 17-D-homolactam isomer (61a,b).

Schmidt conditions transform 17-ketosteroids to a nearly equimolar mixture of 17a- and 17-D-homolactams (59,62a) Estrone, dehydroepiandrosterone and their respective derivatives were used in these studies. Further application of the Schmidt reaction to azasteroid preparation has been made (62b).

Successful insertion of nitrogen into the 17a-position of the D ring has been accomplished by two other novel photochemical transformations. Photolysis of steroidal 17-nitrite esters (63-66) yields 17a-hydroxamic acids *via* homolytic carbon-carbon bond cleavage to an alkoxy radical intermediate (63a). In a related mechanistic investigation of the photochemical preparation of 1-azachrysenes, Suginome and co-workers found that the photolysis of the nitrite in benzene with monochromatic light (372 ± 4 nm) afforded both C-13 epimers, confirming that the cyclization of the nitroso aldehyde does not take place from an excited species (63b). Direct irradiation of the 17-diacetyl hydrazone of androsterone gives 11% of *O*-acetyl-D-homo-17a-aza-5α-androsterone and 19% of its



Benezra and Lusinchi (68) report a unique approach to the formation of the D ring heterocycle. Under Ruschig conditions, 18(*N*)-cyclo-17β-amino-5α-androstane **5** rearranges to give 18(*N*)-cyclo-17ε-methoxy-17a-aza-D-homo-5α-androstane **6**. Hydrogenolysis of **6**, followed by formylation, gives *N*-formyl-17a-aza-D-homo-5α-androstane **7**.



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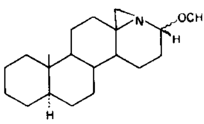

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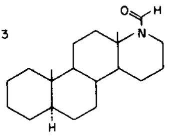

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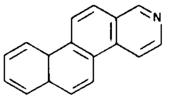
Once the 1-azachrysene skeleton is prepared, substituent groups may be added to the nitrogen. Methods for the synthesis of steroidal nitroxides (69-71), tetrazolo-(72,73), *N*-hydroxy (74), and *N*-amino- (75a) 17a-aza-D-homosteroids have been discussed. Chromophoric aza-homosteroids, including *N,N*-dimethylammonium perchlorate salts, have been prepared (75b). Quaternization methods have been developed (75c).

Steroidal lactams react with Vilsmeier reagent (76-78) and form carbamates in good yields; initially prepared as possible alkylating agents, these in fact exhibit no significant antitumor activity (79). Oxo acids or oxo acid esters of steroids form 3-oxo-4-aza-Δ^5-steroidal derivatives when heated with a source of ammonia or primary amine (80,81).

III. 2-Azachrysene, Naphth[2,1-*f*]isoquinoline.

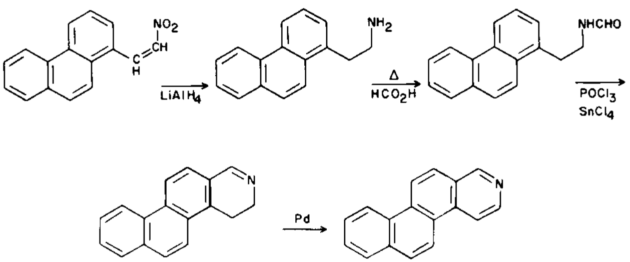


A. Physiological Interest

17-Aza-D-homocholestenol, as prepared by Hayazu (28), produces cardiotonic effects.

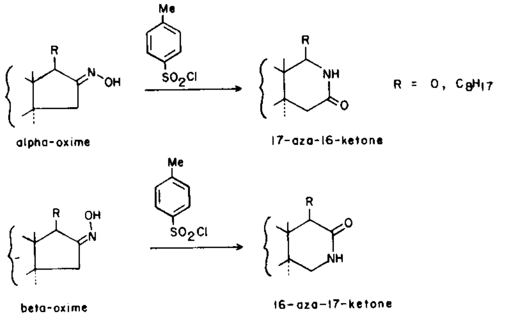
B. Synthetic Methods.

Whaley and Meadow (82b) provide the first documented preparation of unsubstituted 2-azachrysene **12**. Their procedure begins with conversion of 1-phenanthrenecarboxaldehyde to 1-(β-nitrovinyl)-phenanthrene **8** by the Henry addition reaction. Compound **8** is then reduced with lithium aluminum hydride to give β-(1-phenanthryl)ethylamine **9**, which is formylated to yield β-(1-phenanthryl)-ethylformamide **10**. 3,4-Dihydro-2-azachrysene **11** is next formed by cyclization of **10** with phosphorus oxychloride and stannic chloride in nitrobenzene. Dehydrogenation of **11** over palladium dispersed on charcoal gives **12** in 34% yield.

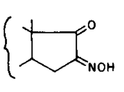


11 12

Beckmann rearrangement is a convenient method for the preparation of 17-aza-16-oxo-D-homosteroids from the corresponding 16-hydroxylamino derivatives (83,84). It appears necessary, however, to work only with the α-oxime, since the β-oxime will yield the 16-aza-17-oxo configuration, *i.e.*, a 3-azachrysene derivative (85,86).



Excellent yields of 16,17-secoimide steroid derivatives **14** are obtained from two methods described by Tuba and Bor (87,88). Compound **14** may be produced by treatment of a 16,17-dioxo 16-oxime **13** with acetic acid and aqueous sulfuric acid or by cyclization of a methyl 16,17-seco-15-amid-17-oate **15** with sodium methoxide in methanol. The products are useful as intermediates for bacteriocidal compounds. The D ring structure **14** has also been formed as 10% of the product mixture from the reaction of **16** with sodium metal in liquid ammonia-diethyl ether (89). Interestingly, irradiation of **14** in tetrahydrofuran gives the related ring-opened methylene compound, presumably the result of intramolecular hydride transfer (90).



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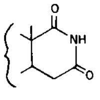

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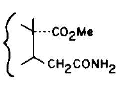

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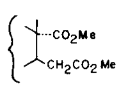

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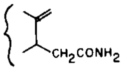
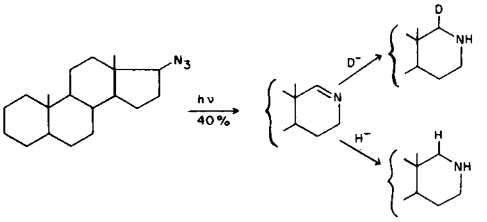
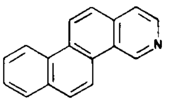


17-Azido steroids undergo photochemical rearrangement to form the 2-azachrysene skeleton (91a,b).



IV. 3-Azachrysene, Naphth[1,2-*h*]isoquinoline.

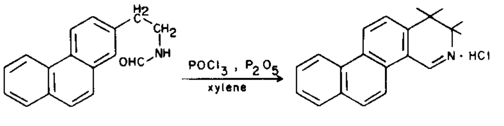


A. Physiological Interest.

3-Azachrysene has received the least attention of any of the isomers during the past thirty years. Tetrahydro-3-azachrysene was first synthesized in 1938, when the isoquinolines were of interest for their structural relationships to morphine (31a). More recently a derivative cited in the literature for its pharmacological value has been 16-aza-D-homocholestenol, claimed to have cardiotonic activity as an inhibitor of arrythmia (28).

B. Synthetic Methods.

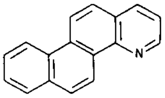
The hydrochloride of 1,2-dihydro-3-azachrysene **18** has been prepared by Whaley and Meadow (82b). They formylated β-(2-phenanthryl)ethyl amine to β-(2-phenanthryl)-ethylformamide **17** and used Bischler-Napieralski conditions to accomplish cyclization.



17 18

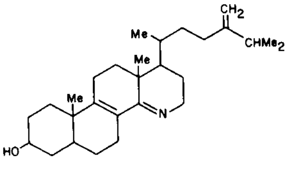
As mentioned in conjuction with the 2-azachrysene analog, a steroid β-oxime converts to the 16-aza-17-ketone *via* a Beckman rearrangement (85).

V. 4-Azachrysene, Naphtho[1,2-*h*]quinoline.



A. Physiological Interest.

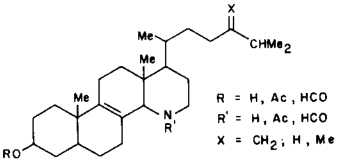
The newly isolated naturally-occurring antibiotic A25822B is proven to be a powerful fungicide against dermatophytes and has some antibacterial activity as well (12-19). Antibiotic A25822B, 24-methylene-15-aza-D-homocholesta-8,14-dien-3β-ol, is produced by culturing *Geotrichum flavo-brunneum* under submerged aerobic fermentation conditions and isolated by extraction (15).



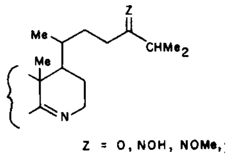
The 15-aza-D-homocholestanol described by Hayazu (29) also has antiarrythmic activity.

B. Synthetic Methods.

Several antifungal azahomocholestadiene derivatives have been prepared by Jones (16,18).

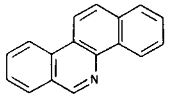


R = H, Ac, HCO
R' = H, Ac, HCO
X = CH_2; H, Me



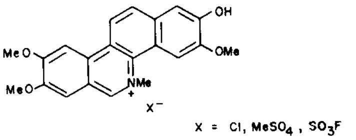
Z = O, NOH, NOMe, NOAc

VI. 5-Azachrysene, Benzo[*c*]phenanthridine.



A. Physiological Interest.

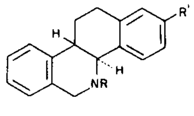
Intense interest in the medicinal applications of 5-azachrysenes has arisen from the isolation and total synthesis of the antileukemic and antitumor alkaloid fagaronine, an alkoxy benzo[*c*]phenanthridinium salt (3,4,92,93a-d). This



X = Cl, $MeSO_4$, SO_3F

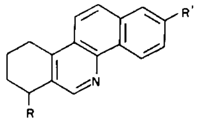
compound is known to be active against leukemias L1210 and P388 in mice, and some derivatives are effective against Lewis lung carcinoma (4). Moreover, Sethi (94a) has recently observed that fagaronine chloride and nitidine chloride, a related 5-azachrysene alkaloid (*vide infra*), inhibit nucleic acid polymerases by a specific interaction with the adenine:thymine base pairs of templates. Structure-activity correlations have been formulated (94b).

Benzo[*c*]phenanthridine derivatives **19** and **20** below have impressive anti-inflammatory activity (20,21), resembling that of hydrocortisone. Both drugs strongly inhibit hindpaw edema in rats, and **19** is particularly potent against acute inflammation and leukocyte migration (21).



19 R = Me, R' = H
20 R = CH_2Ph, R' = OMe

When tested for activity against thirty-three bacterial strains, 7,8,9,10-tetrahydro-7-oxo-2-methoxybenzo[c]phenanthridine **21** successfully inhibited growth in a substantial portion of the organisms. Kessar and co-workers (95) attribute this activity to the specific locations of the methoxy and keto functional groups. Close structural analogs **22** and **23** have been shown to exhibit antiandrogenic action in immature castrated rats (96).

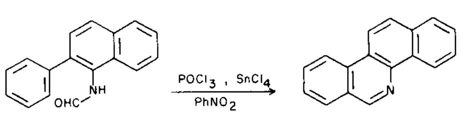


21 R = O, R' = OMe
22 R = R' = H
23 R = OH, R' = H

Sanguinarine, present in the common bloodroot, proves useful in the production and research of experimental glaucoma. For an interesting account of the historical background to this discovery and general procedures for the isolation of the alkaloid, the reader is referred to the review by Hakim, Mijovic and Walker (30). Authur and coworkers (97) report the local use of the related benzo[*c*]phenanthridine alkaloid avicine (*Zanthoxylum avicennae*) against jaundice in Kuala Lampur.

B. Synthetic Methods.

In search of practical high yield procedures for the preparation of 5-azachrysenes, investigators have shown particular creativity in the variety of approaches taken (**82a**). Techniques involving condensation and cyclization of naphthalene and isoquinoline derivatives are most predominant in the literature. Whaley and Meadow (82b) present a straightforward and highly effective synthesis of unsubstituted benzo[*c*]phenanthridine starting with the nitration of 2-phenylnaphthalene and subsequent reduction to 2-phenyl-1-naphthylamine. Formylation of this last compound affords 1-formamido-2-phenylnaphthalene **24**, which is then easily cyclized to the desired product in 60% yield via treatment with phosphorus oxychloride, stannic chloride and reflux in nitrobenzene. Boyer and Patel (98a) have since reported an 86% yield of **25** from **24** using similar reagents.



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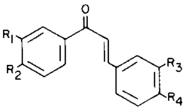
In preparative work on 5-azachrysene alkaloids based on the earlier findings of Robinson (148,149). Gopinath and co-workers (99a) synthesized four new compounds **31a-d** closely related to the naturally occurring structures. With chalcone **26** as starting material, they performed successive reactions of hydrocyanation to the ketonitrile **27**, hydrolysis to the corresponding benzoylpropionic acid **28**, hydrogenation and cyclization to give tetralone **29**, Leuckart reaction with acetamide and aromatization to the amide **30**. Cyclization with phosphorus oxychloride led to the benzo[*c*]phenanthridine derivative **31**. This approach has resulted in the successful synthesis of the alkaloid oxyavicine (99b).



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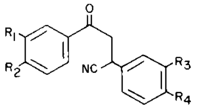

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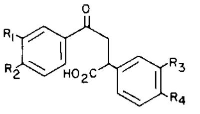

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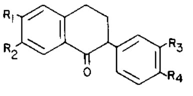

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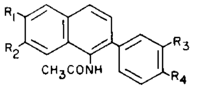

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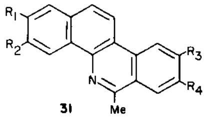
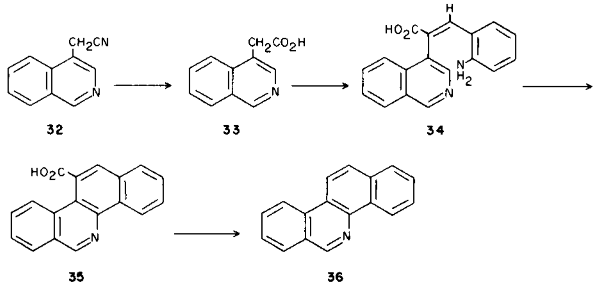
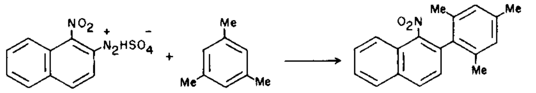


31

	R_1	R_2	R_3	R_4
a	OMe	OMe	H	OMe
b	OMe	OMe	OMe	H
c	CH_2O_2		H	OMe
d	CH_2O_2		OMe	H

Abramovitch and Tertzakian (100) elegantly prepared 5-azachrysene by effecting internuclear cyclization onto a pyridine ring. The nitrile **32** was hydrolyzed to an amide which formed **33** in nitric acid. Condensation of **33** with nitrobenzaldehyde and subsequent reduction gave *trans*-α-(4-isoquinolyl)-*o*-aminocinnamic acid **34**. Pschorr cyclization of **34** produced benzo[*c*]phenanthridine-11-carboxylic acid **35**, which readily decarboxylated to 5-azachrysene **36**. In the same vein, these investigators (101) achieved the synthesis of the 8,10-dimethyl derivative **38** by heating 2-mesityl-1-nitronaphthalene **37** with ferrous oxalate and granulated lead. Some 1-amino-2-mesitylnaphthalene 39 was also isolated.





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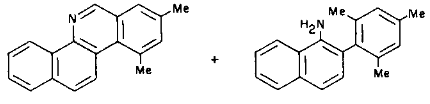
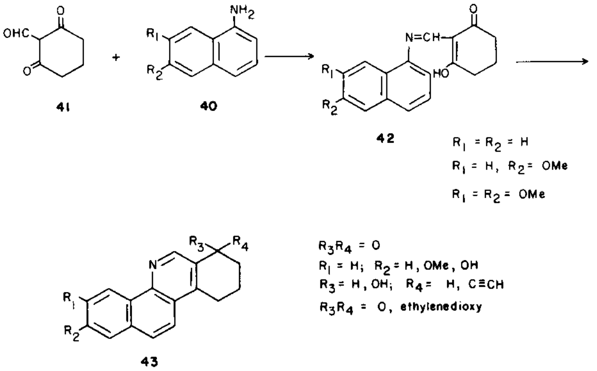


38 39

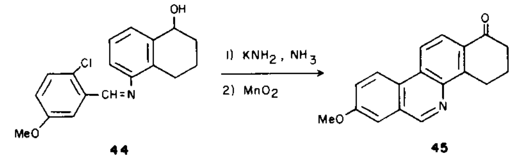
Cyclodehydration as performed by Kessar (102,103) is a convenient route to the 7,8,9,10-tetrahydro-7-oxobenzo[*c*]phenanthridines. Room temperature condensation of 1-naphthylamines **40** with 2-formyl-1,3-cyclohexanedione **41** gives the corresponding anils **42**, which cyclize readily in polyphosphoric acid to form the tetrahydro-oxo derivatives **43** in optimal yield.



$R_1 = R_2 = H$
$R_1 = H,\ R_2 = OMe$
$R_1 = R_2 = OMe$

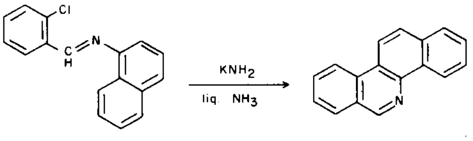
$R_3R_4 = O$
$R_1 = H;\ R_2 = H, OMe, OH$
$R_3 = H, OH;\ R_4 = H,\ C{\equiv}CH$
$R_3R_4 = O$, ethylenedioxy

In a cyclization procedure which is mechanistically quite different, reaction of 2-chloro-5-methoxybenzaldehyde with 5-amino-1,2,3,4-tetrahydro-1-naphthol yields the 1-naphthol anil **44**. On benzyne cyclization and oxidation, this compound is converted cleanly to 3,4-dihydro-8-methoxybenzo[*c*]phenanthridin-1-(2*H*)one **45** (104).



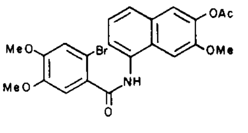
44 45

Using the benzyne procedure Kessar and Singh (105) have prepared the parent 5-azachrysene **36** in 35% yield. Thus, *N*-(chlorobenzilidene)naphthylamine **46** cyclized with potassium amide in liquid ammonia to give **36**.

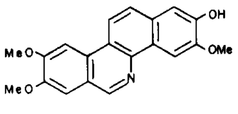


46 36

The antineoplastic alkaloid fagaronine may be synthesized by the Kessar benzyne cyclization (92), as well as the method elucidated by Gopinath and co-workers (4,93). *N*-Demethylfagaronine **48** is formed by irradiation of the naphthalide **47** in triethylamine, followed by treatment with phosphorus trichloride and hydrogenation over palladized charcoal and potassium hydroxide (106).

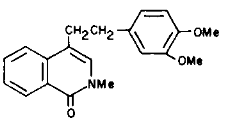


47



48

Formic acid ring closure of 2-(naphthylaminomethylene)cyclohexanones leads to the preparation of tetrahydrobenzo[*c*]phenanthridines (107). Reduction of isocarbostyril **49** with lithium aluminum hydride, followed by heating with concentrated hydrochloric acid, gives further 5-azachrysenes **50, 51** and **52** (108).



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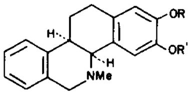
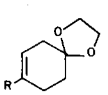


50 R = R' = Me
51 R = H, R' = Me
52 R = Me, R' = H

Sharma and co-workers (109) provide an unusual pathway to the dichloro derivative **56**. The morpholino enamine **53** condenses with α-naphthylisocyanate **54** to give the compound **55**. The amide is treated with phosphorus oxychloride, affording thereby the dichloro benzo[*c*]phenanthridine **56**.



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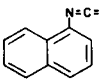

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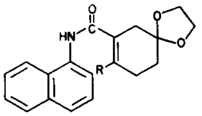

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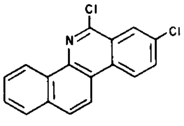
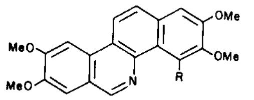


56

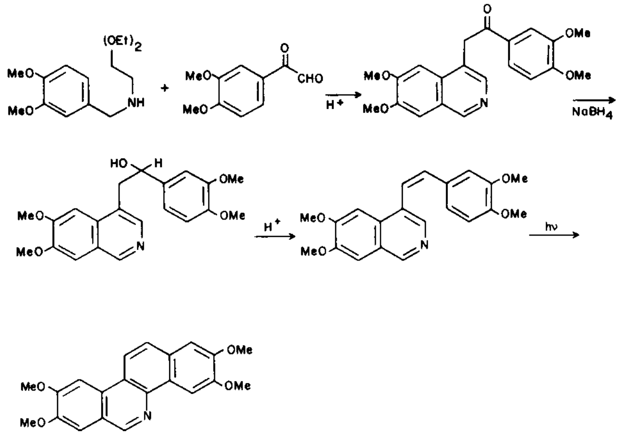
R = morpholino

A recent effort in chemical cyclization provides the synthesis of 2,3,8,9-tetramethoxy-5-azachrysene derivatives (110). Condensation of 6,7-dimethoxy-1-naphthylamine with 3,4-dimethoxybenzaldehyde and treatment of the intermediate imine with vanadium oxyfluoride in a mixture of trifluoroacetic acid and methylene chloride gave 30% **57**. Reaction of the same imine and vanadium oxyfluoride in a mixture of trifluoroacetic anhydride and methylene chloride produced 20% of **58**.

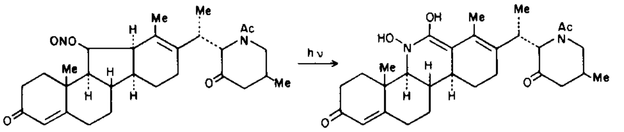


57 R = H
58 R = CF_3CO

Several groups have had notable success with photochemical ring closure procedures. Dyke and Sainsbury (111) sought a photochemical route to the 5-azachrysene skeleton as an alternative to the Pschorr cyclization technique. They formulated the unambiguous pathway outlined below.

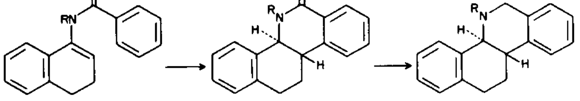


In a rearrangement reaction unprecedented in this series, Suginome, Masamune and co-workers (112) photolyzed the nitrite of *N*-acetyl-22,27-imino-12α-jerv-4,13-(17)-dien-11-β-ol-3,23-dione **59**, a fused five-membered ring alcohol, under Barton conditions to form the hydroxynitrone **60**.



59 60

Ninomiya and co-workers (20,113-117) photocyclized the *N*-benzoyl enamines of α-tetralone **61** to 5-azachrysene *trans*-lactams **62** in good yields. Quantitative reduction of **62** and **63** is possible with lithium aluminum hydride, and heating **62** with selenium metal at 250° affords the *cis*-isomer of **62**.

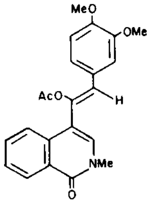


61 62 63

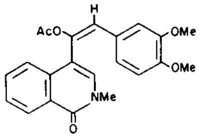
R = $PhCH_2$, Me

In pursuit of an 11-oxygenated 5-azachrysene to be used in preparing derivatives of the major alkaloid chelidonine, Onda, Harigaya and Suzuki (118,119) used photochemical means to cyclize the isocarbostyril enol acetates **64** and **65** to the 11-acetoxybenzo[*c*]phenanthridines **66** and **67**;

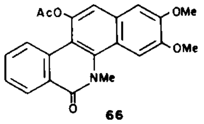
essentially the same mixtre (**66**:**67**/3:2) was formed no matter whether the starting olefin was of *E* or *Z* character. Hydrolysis and oxidation of **66** give the quinone **68**.



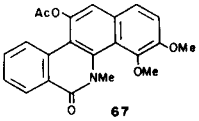
64



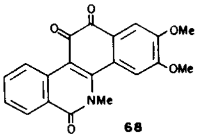
65



66

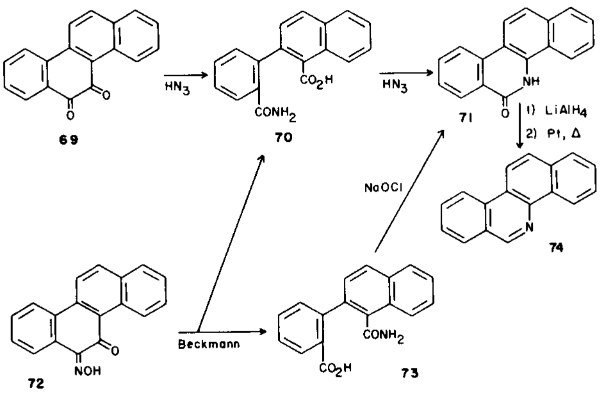


67

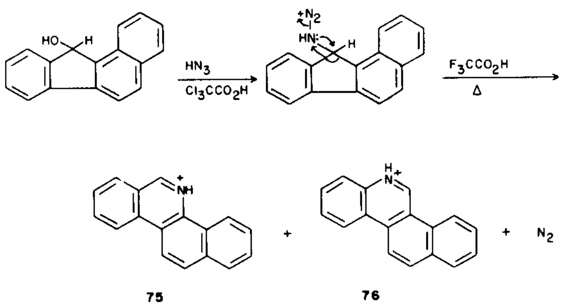


68

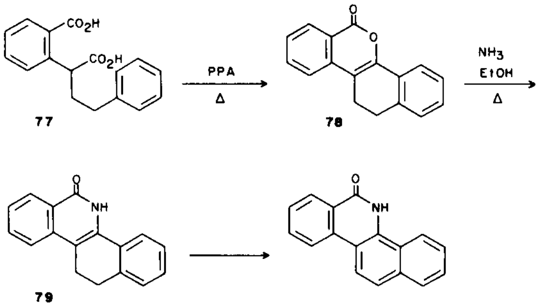
Many researchers have constructed the 5-azachrysene framework by processes other than the standard direct cyclization approach. Insertion of a nitrogen into the 5-position of an existing tetracycle can be accomplished by several methods. Chrysenequinone **69** is transformed into benzo[*c*]phenanthridine **71** upon reaction with excess hydrazoic acid. One mole of hydrazoic acid forms the intermediate amido acid **70**, which converts to **71** with additional reagent. Beckmann rearrangement of the chrysenequinone mono oxime **72** yields the two amido acids **70** and **73**, which react further with hydrazoic acid and sodium hypochlorite, respectively, to give **71**. Reduction of **71** with lithium aluminum hydride, followed by dehydrogenation over platinized asbestos gives a 95% yield of unsubstituted benzo[*c*]phenanthridine **74** (120).



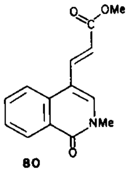
A mixture of 5- and 6-azachrysenes **75** and **76** in a ratio of 2.9:1 results from the following ring expansion with hydrazoic acid and trifluoroacetic acid (121).



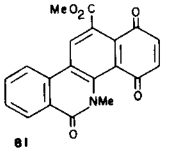
Chatterjea (122) made the dihydronaphthoisocarbostyril **79** by a direct substitution of nitrogen for oxygen in the isocoumarin **78**. Compound **78** was originally formed by heating α-(*o*-carboxyphenyl)-γ-phenylbutyric acid **77** with polyphosphoric acid.



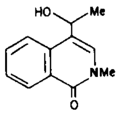
Internuclear condensation of two or three appropriate cyclic compounds has proven to be another practical route to the 5-azachrysenes. Dyke and his group (123) combined the diene ester **80** with excess *p*-benzoquinone in boiling glacial acetic acid to yield 60% of product **81**. They also found that heating compound **82** with *p*-benzoquinone in acetonitrile led to 67% of the benzo[*c*]phenanthridine trione **83**.



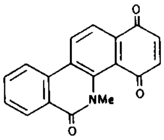
80



81

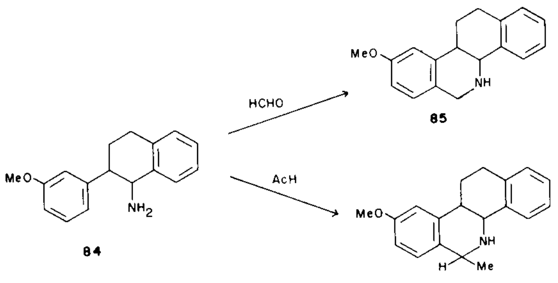


82



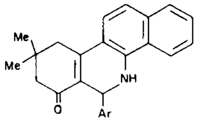
83

Kametani and co-workers (124) employed the Mannich reaction in treating *trans*-1-amino-1,2,3,4-tetrahydro-2-(3-methoxyphenyl)naphthalene **84** with formalin and acetaldehyde to produce 5-azachrysenes **85** and **86**, respectively.

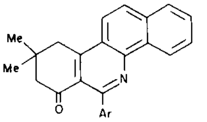


84 85 86

The addition of various aromatic aldehydes to equivalent amounts of α-naphthylamine and dimedone gives the desired adduct **87** in the yields listed (125). Compound **87** may be oxidized to **88** in chromium trioxide and acetic acid.



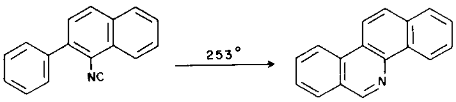
87



88

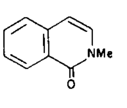
Ar	% Yield
phenyl	48
p-nitrophenyl	51
m-nitrophenyl	32
p-methoxyphenyl	43
o-methoxyphenyl	56
p-dimethylaminophenyl	42
o-iodophenyl	29

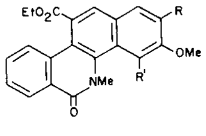
The literature contains two unique syntheses of 5-azachrysenes involving the use of carbenes. Boyer and Patel (126a,b) suggest that the thermal isomerization of 1-isocyano-2-phenylnaphthalene **89** to yield 31% benzo[*c*]phenanthridine **90** takes place *via* a ground state electrophilic carbenoid insertion reaction. 1-Cyano-2-phenylnaphthalene and benzo[*g*]cyclohept[*b*]indole were also present in the reaction mixture in 35% and 3% yields, respectively.



89 90

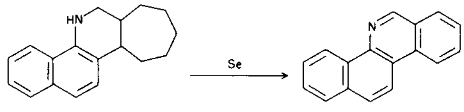
Treatment of 2-methyl-1-isoquinolone with the carbene derived from ethyl diazoacetate and subsequent thermal rearrangement, alkylation, oxidation and cyclization gave structures **90a** and **90b** in 85% overall yield (127).





90a R = OMe, R' = H
90b R = H, R' = OMe

Another procedure is unique in relation to previous discussion in that it involves transformation of a fused cycloheptane to a six-membered ring. Bhargava and Saharia (128) have noted that selenium dehydrogenation of 11-aza-1,2,3,4,11,12,13,14,15,16,17,18-dodecahydrocycloheptaphenanthrene **91** results in the appearance of benzo[*c*]phenanthridine.

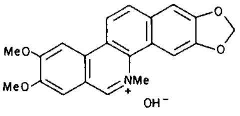


91

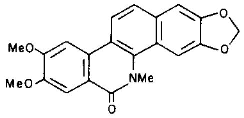
C. Alkaloids.

Improved extraction and separation techniques have made possible the isolation and characterization of a number of new 5-azachrysene natural products since 1950, when only chelidonine, α-homochelidonine, sanguinarine and chelerythrine were well known (31a). Several sources review these alkaloid isolation procedures (30,129,130).

Structures were assigned to nitidine **92** and oxynitidine **93** by Arthur and co-workers (131) in 1958. These compounds were extracted from *Zanthoxylum nitidum* and are substituted in the 2,3,8,9-positions, unusual for alkaloids in this class (132). The genus *Zanthoxylum* is a member of the *rutaceae* family of flowering shrubs which are native to Southeast Asia and parts of North America (133).

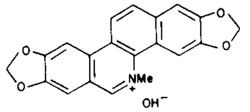


92

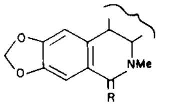


93

A year later, avicine **94** was isolated from *Z. avicennae* as a crude quatenary salt. Basification of its aqueous solution produced a mixture of oxyavicine **95** and dihydroavicine **96**, but there is no evidence that the former occurs naturally in the root bark (97).

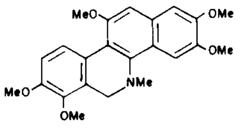


94

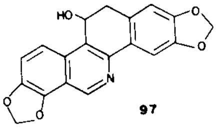


95 R = O
96 R = H₂

In 1975 Kim and Stermitz (134) reported the structure of dihydrosanguilutine, extracted from *Sanguinaria canadensis*. The structure has subsequently been revised (140a). On the basis of independent synthetic work, Ishii (140c-e) has demonstrated that the oxygenation pattern of the fully aromatized O_5-benzo[*c*]phenanthridine alkaloids in the papaverous plants is 2,3,7,8,10, *viz.*, as shown in **103** and **104**.

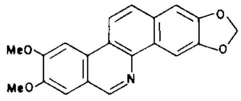


Recently Castedo and co-workers (135) isolated luguine **97** from *Glaucium flavum,* together with the known materials norsanguinarine, oxysanguinarine and (+)-*N*-methyllindcarpine.



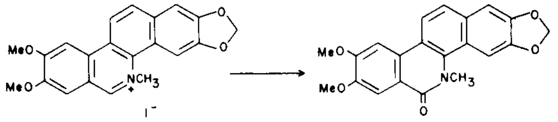
97

Much synthetic effort has been made on these newly discovered alkaloids, with most of the attention devoted to the nitidines. Dyke, Sainsbury and Moon (136a) describe total syntheses of oxyavicine and 2,3-dimethoxy-8,9-methylenedioxobenzo[c]phenanthridine **98**, a close structural analog of nitidine.

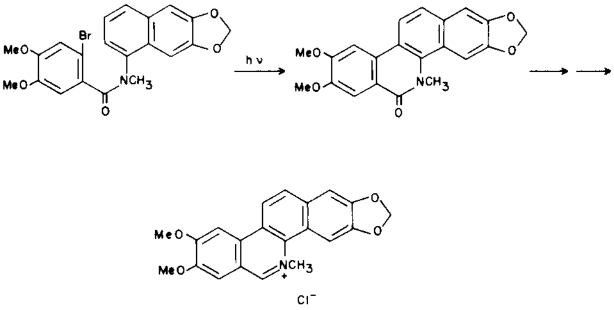


98

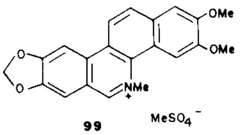
Two syntheses of dihydronitidine have been reported by Gopinath (136b), while Arthur separately prepared the compound at the same time (136c). Kametani (136d-f) prepared nitidine and converted it to oxynitidine *via* oxidation with potassium ferricyanide in base.



Photochemical ring closure was a feature of the recent synthesis of nitidine chloride by Begley and Grimshaw (136g).



Allonitidine **99** and nitidine methylsulfate **100** were prepared by Zee-Cheng and Cheng (137,138). A biomimetic synthesis of nitidine has also been reported by Kametani (139).



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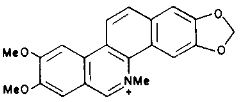
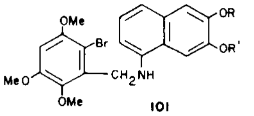


100

In the construction of singuilutine **103** and chelilutine **104** (140a), the crucial point in the five-step course from the initial 2,3,5-trimethoxybenzaldehyde is the photocyclization of the benzylnaphthylamines **101** to the benzophenanthridines **102** (140b).



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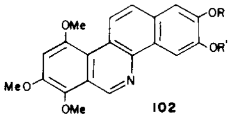

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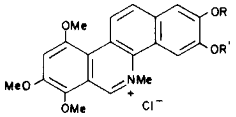
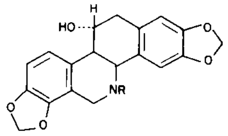


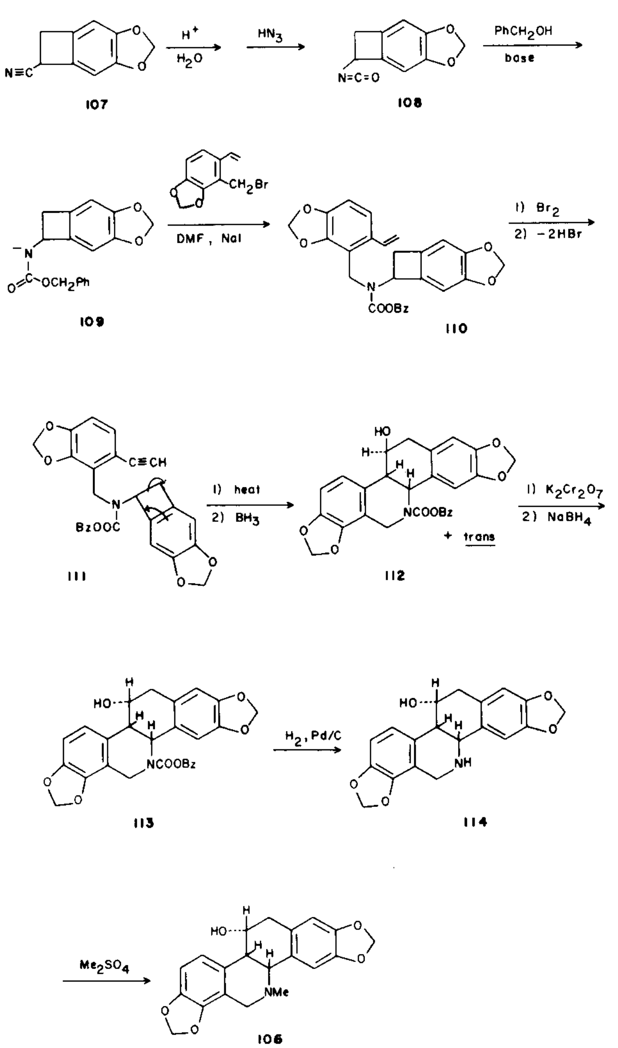
103 R = R' = Me
104 R = R' = CH_2

Close biosynthetic interrelationships exist between the four major chelidonium group natural products chelidonine, α-homochelidonine, sanguinarine and chelerythrine (141a-j). Robinson (141k) and Dalton (142a) supply detailed discussions of the biosyntheses of these isoquinoline alkaloids. In recent years, researchers have made significant contributions to futher specific synthetic techniques necessary for their preparation as well (142b-f). Thus, the first total synthesis of *dl*-norchelidonine **105** and *dl*-chelidonine **106** was provided by Oppolzer and Keller (143), using 1-cyano-4,5-methylenedioxybenzocyclobutene and 2,3-methylenedioxybenzaldehyde as starting materials. An intramolecular *ortho*-quinodimethane cycloaddition is the key step to the procedure.

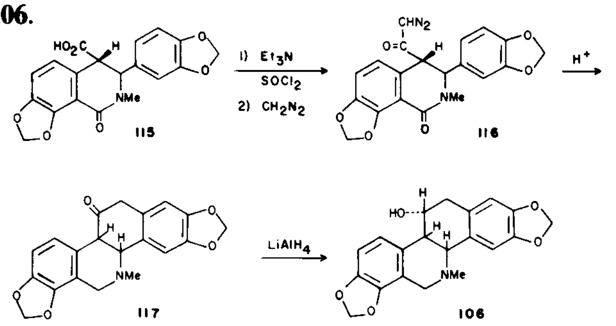


105 R = H
106 R = Me

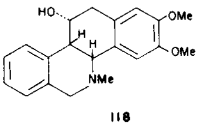
Dalton (142) cites and comments on another total synthesis by the same authors (143) which also requires 1-cyano-4,5-methylenedioxybenzocyclobutene **107** at the initial step (See Figure). Acid hydrolysis of the nitrile gives the amide, which on Curtius rearrangement is converted to the isocyanate **108**. Treatment of **108** with benzyl alcohol and base yields the secondary carbamate anion **109**, which reacts with the benzyl bromide in dimethylformamide with a catalytic amount of sodium iodide to form the tertiary carbamate **110**. Bromination followed by two-fold dehydrohalogenation changes **110** to the alkyne **111**, which undergoes thermal rearrangement and oxidative hydroboration yielding *cis* and *trans* alcohols **112**. To invert the stereochemistry of the hydroxyl group, the *cis* isomer is oxidized with potassium dichromate to the ketone and then selectively reduced to **113** by sodium borohydride. Hydrogenolysis of the carbamate group gives *dl*-norchelidonine **114**. Chelidonine **106** is readily derived from **114** by methylation of the nitrogen.



Another elegant route to *dl*-chelidonine was recently reported by Cushman (144). His starting material was the isoquinoline **115** formed by condensation of the Schiff base piperonylidenemethylamine with 3,4-methylenedioxyhomophthalic anhydride. In triethylamine buffer, the carboxyl group of **115** was converted to the acid chloride, followed by reaction with diazomethane to give **116**. The diazo ketone **116** underwent ring closure to **117**. The ketone **117** was stereospecificially reduced by excess lithium aluminum hydride to generate the final product **106**.



Ninomiya and co-workers (145a) prepared **118** as a chelidonine and homochelidonine model compound by a method entailing photochemical cyclization of the enamide **119** (145c-g). Homochelidonine was synthesized by these researchers using the enamide photocyclization (145b). Other photocyclization techniques have found application in the preparation of the 5-azachrysene alkaloids (145h-j).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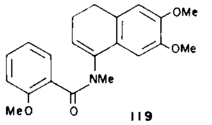
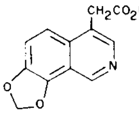

119

Dyke, Moon and Sainsbury are responsible for much of the synthetic activity on sanguinarine (146). In preparing this compound they first constructed the acetoxyisoquinoline **120** by reductive condensation of 2,3-methylenedioxybenzaldehyde with aminoacetaldehyde dimethylacetal and further reaction with glyoxylic acid in dilute hydrochloric acid. Then, **120** was condensed with 6-nitropiperonal, the adduct was reduced and cyclized under Pschorr conditions, and after decarboxylation sanguinarine **121** was isolated.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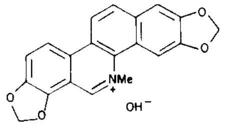
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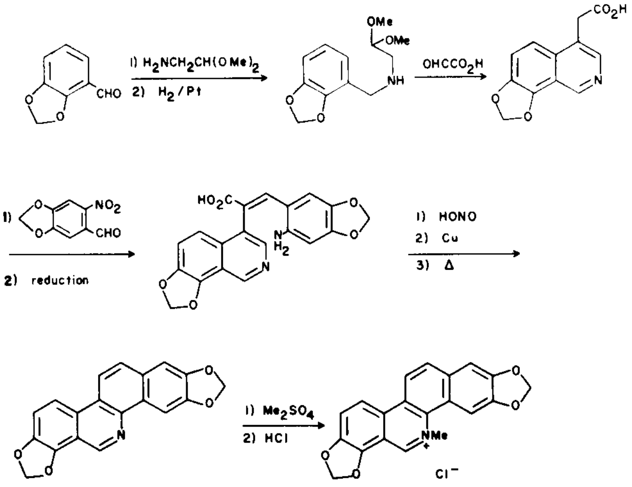
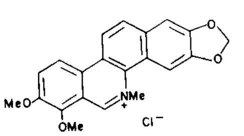
Two years later, the same team reported the first synthesis of sanguinarine chloride, 2,3:7,8-bismethylenedioxybenzo[*c*]phenanthridine methochloride (147a).

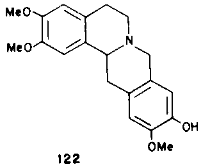


Onda (147b) demonstrated a protopine-sanguinarine conversion *via* photochemical ring closure.

Bailey (148-152) published a series of papers in the 1950's which finally elucidated a complete synthetic pathway to chelerythrine chloride.



It has been shown that a biogenetic link exists between the protoberberine and benzophenanthridine alkaloids. Kametani (153a) demonstrated a biomimetic approach to the benzo[*c*]phenanthridine **124** by transforming 10-hydroxy-2,3,11-trimethylberbine **122** into **124** through the intermediate methine base **123**. Onda has as well commented on the interconversion of phthalide isoquinoline and benzophenanthridine systems (153b).



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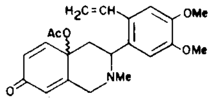

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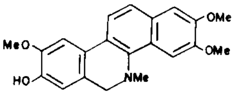

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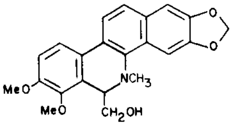
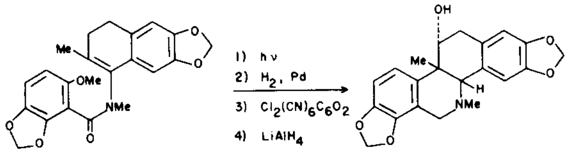
The photochemical addition of alcohols to benzophenanthridines has recently increased the scope of synthetic methods in the alkaloid series. Thus irradiation of chelerythrine in the presence of methanol leads to the formation of the adduct "bocconoline" (154a).

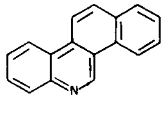


Synthesis within the corynoline group has been much enhanced by use of photochemical methods (154c). Corynoline and epicorynoline have been prepared (154d-i).



In view of their comparatively abundant availability from plant sources some of the benzophenanthridine alkaloids themselves serve as useful starting materials for further alkaloid synthesis (155a-e).

VII. 6-Azachrysene, Benzo[*i*]phenanthridine.

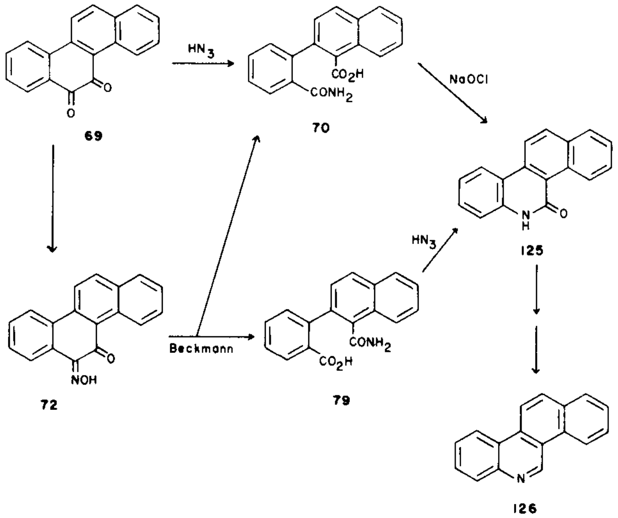


A. Physiological Interest.

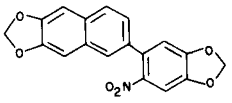
6-Azachrysene derivatives are known for their activity as anti-inflammatory agents, sex hormones and anticancer drugs (156,157).

B. Synthetic Methods.

Application of the Schmidt reaction and Beckmann rearrangement to the preparation of unsubstituted 6-azachrysene is analogous to that of the 5-azachrysene system (120). Chrysenequinone **69** reacts with one mole of hydrazoic acid to yield 2-*o*-benzamido-1-naphthoic acid **70**. Beckmann rearrangement of chrysenequinone mono oxime **72** generates **70** and 2-*o*-carboxyphenyl-1-naphthamide **73**. Compound **73** is cyclized to **125** upon addition of one mole of hydrazoic acid. The final product **126** is formed in quantitative yield in the following way: (i) the preparation of 6-chlorobenzo[*i*]phenanthridine *via* reaction of **125** with phosphorus oxychloride in dimethylaniline; (ii) reduction of the 6-chloro compound with lithium aluminum hydride; and (iii) dehydrogenation over platinized asbestos.



As was true for the 5-azachrysenes, specific cyclization techniques are most useful when constructing the 6-azachrysene skeleton (126b). Gopinath (158) describes a simple and effective approach, beginning with nitration at the 6′-position of 2,3-methylenedioxy-6-(3,4-methylenedioxyphenyl)naphthalene to give **127**. The acetyl derivative of the corresponding amine is then cyclized to the benzo[*i*]phenanthridine **128**.



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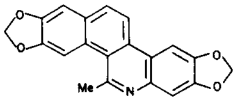
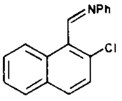


128

Kessar and co-workers (159,160) extended their benzyne cyclization procedure (*vide supra*) to accomodate 6-azachrysene preparation. Thus benzo[*i*]phenanthridine **130** was obtained in 35% yield by naphthyne cyclization of the chloro anil **129**.



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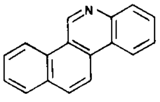
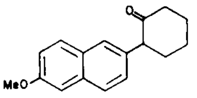


130

By a different approach, Kessar (161) prepared 7-hydroxy-2-methoxy-7,8,9,10-tetrahydrobenzo[*i*]phenanthridine **134**. Leuckart reaction of the starting ketone **131** led to the amide **132**, which cyclized in the presence of phosphorus pentachloride to the 2-methoxy-tetrahydro derivative **133**. Subsequent partial dehydrogenation, rearrangement and esterification *in situ* of the *N*-oxide, followed by hydrolysis, gave the product **134**.



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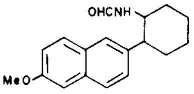

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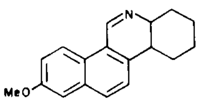

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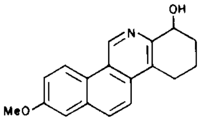
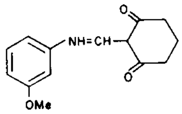


134

For the synthesis of 6-azasteroidal compounds, Sunthankar and Mehendale (162,163) devised the following method involving chemical cyclization of enamines. 1,3-Cyclohexanedione, *m*-anisidine and ethyl orthoformate condensed to the anil **135**, which formed **136** upon cyclodehydration in polyphosphoric acid. Under alkaline conditions, methyl vinyl ketone condensed with **136** to give the azaestrahexaenone **137**.



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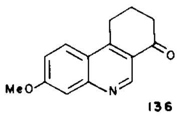

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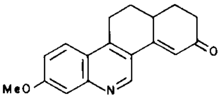
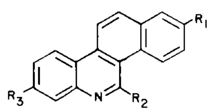


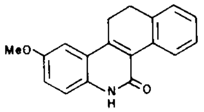
137

Various derivatives of 6-azachrysene substituted in the 2,5,8-positions have been prepared by Arumugam (164) using the Bruckner procedure. Initial addition of dinitrogen tetroxide to a substituted 2-naphthylcyclohexene and successive lithium aluminum hydride reduction, treatment with acyl chlorides, cyclization and dehydrogenation over palladized charcoal gave compounds **138-143** in yields of about 50%.

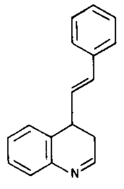


138 $R_1 = R_3 = H$, $R_2 = Me$
139 $R_1 = R_3 = H$, $R_2 = Ph$
140 $R_1 = H$, $R_2 = Ph$, $R_3 = Me$
141 $R_1 = H$, $R_2 = R_3 = Me$
142 $R_1 = OMe$, $R_2 = Me$, $R_3 = H$
143 $R_1 = OMe$, $R_2 = R_3 = Me$

Sharma and Rani (165) report the synthesis of 2-methoxy-5,6,9,10-tetrahydrobenzo[*i*]phenanthridone *via* condensation of the enamine of tetralone with *p*-methoxyphenylisocyanate, followed by cyclization in phenylhydrazine and acetic acid.



Photoinduced transformation of 4-styrilquinoline **144** by slow cyclization in cyclohexane affords 25% of benzo[*i*]phenanthridine **130** as described by Loader, Sargent and Timmons (166,167).



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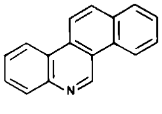
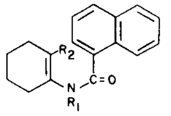


130

Extensive research has also been conducted by Suginome, Masamune and co-workers (168-173) on the photochemical rearrangement of jervine nitrites to 6-azachrysene nitrone derivatives.

Ninomiya (157,174,175) reports a highly useful photochemical ring closure, whereby various *N*-cyclohexenyl-1-naphthamides **145** are cyclized to the benzo[*i*]phenanthridinones **146**.



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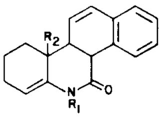

146

(R_1 and R_2 lower alkyls)

VIII. Conclusion.

It is clear that the past thirty years have witnessed an intensifying interest in this class of very useful compounds, necessitating the development of new and imaginative approaches to preparation of the azachrysene skeleton. With the diversity of this class encompassing classical coal tar derivatives, natural products, steroids and other medicinal agents, exciting further developments can continue to be expected.

Acknowledgement.

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