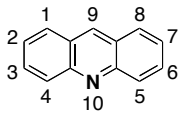
"...the step from the laboratory to the patient's bedside...is extraordinarily arduous and fraught with danger." Paul Ehrlich

Baran Group Meeting

Acridine Alkaloids

Jonathan Lockner

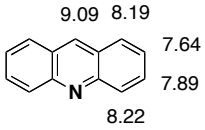


acridine
dibenzo(b,e)pyridine
2,3,5,6-dibenzopyridine
2,3-benzoquinoline
10-azaanthracene

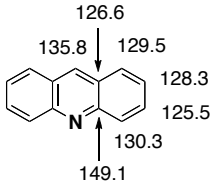
3,6,9 are the important positions of acridine drugs

flat (planar) aromatic, hydrophobic, pKa 5.6
colorless to light yellow crystals (mp 107-110 °C)
chromatography on basic alumina
irritating odor, lachrymator, carcinogenic, mutagenic
→ Bruce N. Ames (UC Berkeley) studied carcinogenesis/mutagenesis by chemicals, including acridines (*Science* **1972**, *176*, 47)

^{1}H NMR:



^{13}C NMR:

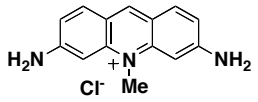


1870 → **acridine** isolated from coal tar (Carl Grabe & Heinrich Caro, BASF, Germany)
Grabe introduced "ortho", "meta", "para" nomenclature
1895 → "Orange Dye" patent; acridines being used as fabric dyes & biological staining agents
1912 → Ehrlich & Benda proposed use of acridines as antimicrobials (**acriflavine**/Trypaflavin/Gonoflavin)
Ehrlich (of Salvarsan "606" fame) first introduced idea of synthetic chemotherapy
1913 → Carl Browning identified **proflavine**, the neutral (non-methylated) version of acriflavine
1914-1918 → WWI; acridines as wound antiseptics in base hospitals on Western Front
1917-1946 → widespread clinical use of acridines as antibacterials during "antibacterial gap"
1939-1945 → WWII; **quinacrine** used in eastern theatres, in absence of quinine from Japanese-held Java
1946 → end of WWII, penicillins eclipse acridines
1970s → **nitracrine**/Ledarkin; **amsacrine**/Amsidyl for cancer treatment
present → anticancer, anti-AChE, antiprion, antinociceptive

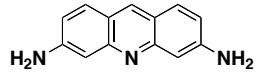
Dyes to Drugs:

Orange Dye
U.S. Patent 537723 A, April 16, 1895 (Swiss chemists)

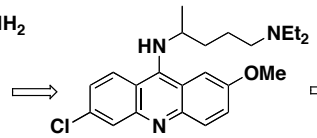
Cancer Treatment Using Specific 3,6,9-Substituted Acridines
WO2006095139, September 14, 2006 (Neidle et al)



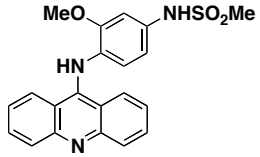
acriflavine



proflavine



quinacrine/Mepacrine/Atebrin
(antimalarial)



amsacrine/Amsidyl
(antileukemia)

"There is no exaggeration that [the availabiilty of quinacrine] probably changed the course of history."
L. J. Bruce-Chwatt



Female Voluntary Non-surgical Sterilization:
The Quinacrine Sterilization Method



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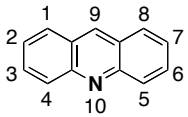
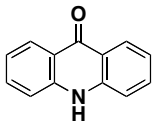


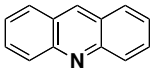
Acridine Alkaloids

Jonathan Lockner

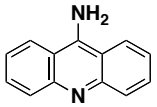
Commercial Availability of Acridines:



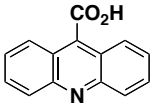
9(10H)-acridanone
$18.84/g
mp >300 °C



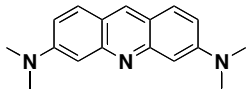
acridine
$3.23/g
mp 107-110 °C



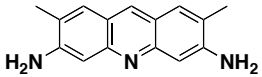
9-aminoacridine
$1.19/g



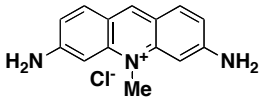
9-acridinecarboxylic acid
$21/g



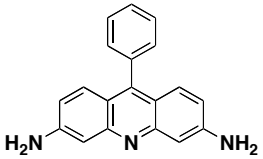
acridine orange (AO)
$2.56/g



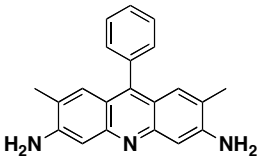
acridine yellow (AY)
$2.19/g



Acriflavine (Trypaflavin)
$0.87/g

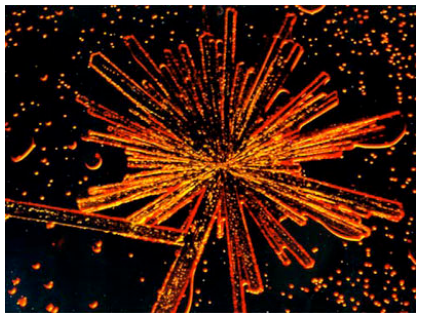


chrysaniline ("phospin")
dyes silk & wool yellow



benzoflavin
$25.91/g

staining with AO:

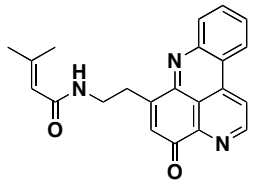




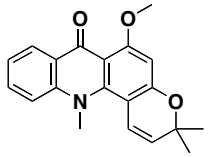
Acridine Isolation:

marine:
a) tunicates & ascidians
b) sponges
c) sea anemones

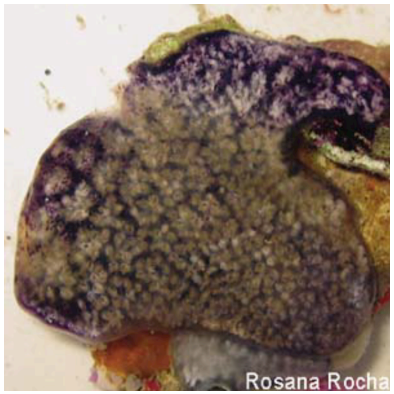
plant:
a) bark of Australian scrub ash tree



cystodytin A

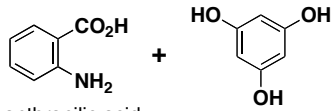


acronycine



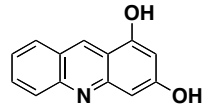


Acridine Biosynthesis:



anthranilic acid
(or equiv)

phloroglucinol
(or equiv)



2,4-dihydroxyacridine

Chem. Rev. **1993**, *93*, 1825
Adv. Het. Nat. Prod. Syn. **1992**, *2*, 377
Die Pharmazie **1970**, *25*, 777
Australian J. Sci. Research **1951**, 423

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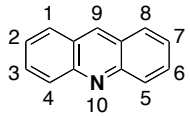
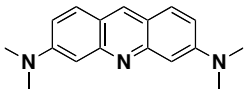


Acridine Alkaloids

Jonathan Lockner

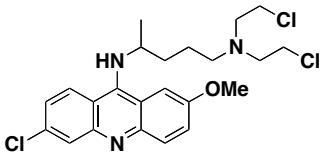
Using Acridine Dyes to Study Cellular Processes:



acridine orange (AO)
nucleic acid selective fluorescent dye

absorption: 440-480 nm (blue)
emission: 520-650 nm (green-red)
"metachromatic fluorochrome"

Useful for cell cycle determination: stain nucleic acids; flow cytometry
Hydrophobic → quickly diffuses into cell membrane, then complexes with DNA (green fluorescence) and RNA (red fluorescence)
AO/EDTA mixture used for 1) denaturing dsRNA, and 2) binding ssRNA
Darzynkiewicz, Z. *Methods in Cell Biology* **1990**, *33*, 285
Jaroszeski, M. J. *Methods in Molecular Biology* **1998**, *91*, 10



quinacrine mustard
fluorescence studies of plant, animal, human chromosomes
Science **1970**, *170*, 762

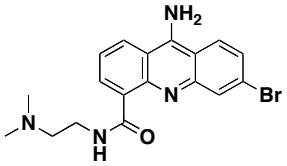
Interaction of Acridines with DNA:

"Single action": 9-aminoacridine; quinacrine; acridine orange
1) intercalate DNA

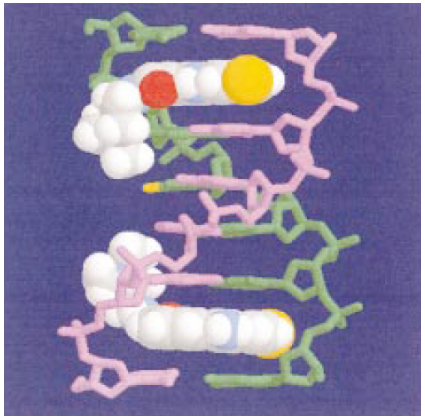
"Dual action": quinacrine mustard
1) intercalate DNA
2) form covalent bond with DNA

Intercalative activity (and thus mutagenicity) can be 'designed out' of the aminoacridine profile → Appropriately substituted acridines maintain anticancer potency by instead interfering with topoisomerase II enzyme (e.g. amsacrine stabilizes DNA/topo II "cleavable complex")

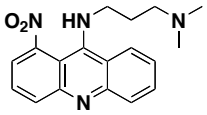
Lerman, L. S. *Proceedings of the National Academy of Sciences* **1963**, *49*, 94
J. Antimicrobial Chemotherapy **2001**, *47*, 1
Current Med. Chem. **2002**, *9*, 1655



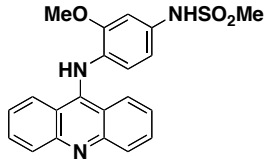
9-amino-6-bromo-DACA



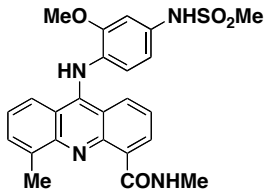
J. Med. Chem. **1999**, *42*, 536
acridinecarboxamide complexed with hexanucleotide $d(CG(5\text{-}BrU)ACG)_2$
(CG-preferential behavior associated with acridine chromophore)



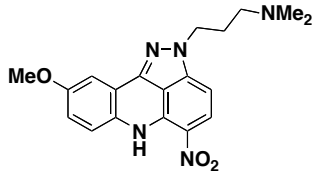
nitracrine/Ledakrin
(antitumor)
J. Med. Chem. **1992**, *35*, 4832



amsacrine/Amsidyl
(antileukemia)
J. Med. Chem. **1974**, *17*, 922



asulacrine/amsalog/CI-921
(anticancer)
J. Het. Chem. **1989**, *26*, 1469



PZA/pyrazoloacridine
(antitumor)
J. Med. Chem. **1992**, *35*, 4770

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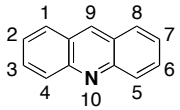
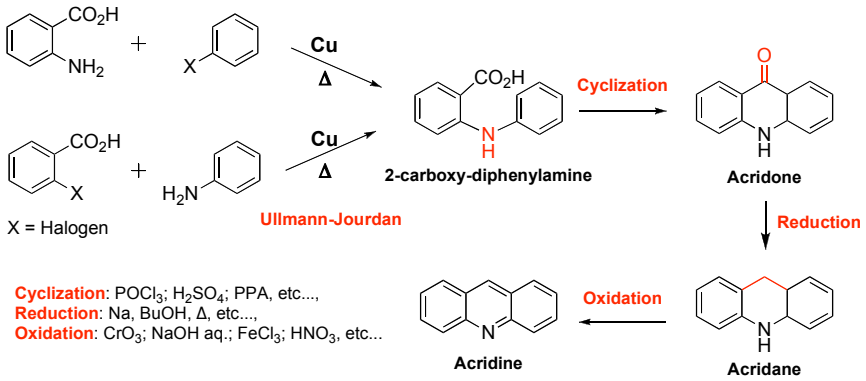


Acridine Alkaloids

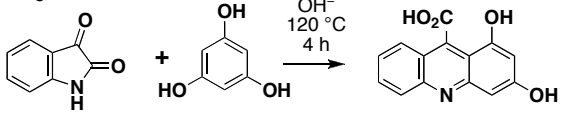
Prager, R. H.; Williams, C. M. *Science of Synthesis* **2004**, *15*, 988
Demeunynck. M. *Expert Opin. Ther. Patents* **2004**, *14*, 55
Chiron, J.; Galy, J.-P. *Synthesis* **2004** 313
Albert, A. *The Acridines*, 2nd ed.; Edward Arnold Ltd: London, **1966**

Jonathan Lockner

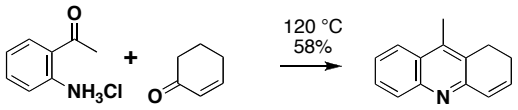
Usual Acridine Synthesis Methodology:



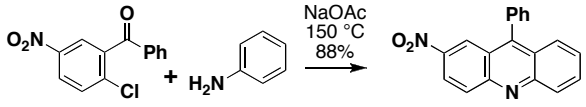
Pfitzinger 1886:

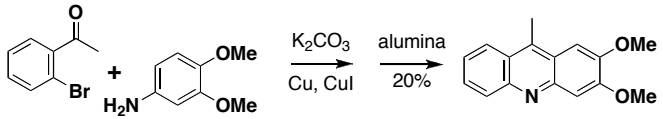


Friedländer:

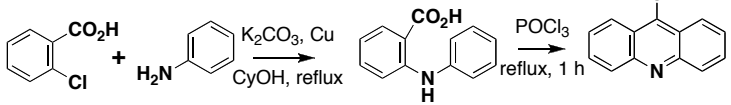


Ullman 1906:

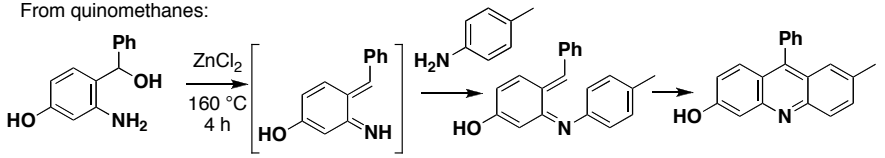




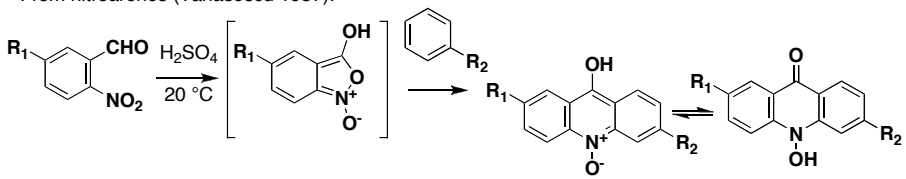
Goldberg:



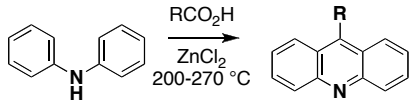
From quinomethanes:



From nitroarenes (Tanasescu 1937):

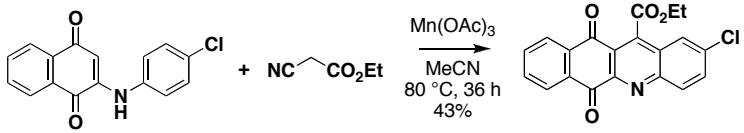


From diphenylamines and carboxylic acids (Bernthsen 1884):

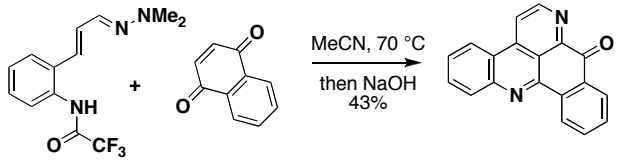


improved by μW
(J. A. Seijas, M. P. Vazquez-Tato)

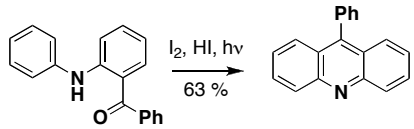
Via radical reactions of quinones (Chuang 1990):



Via aza-Diels–Alder (del Mar Blanco 2000):



From acylated diphenylamines:



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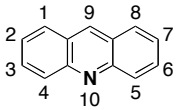
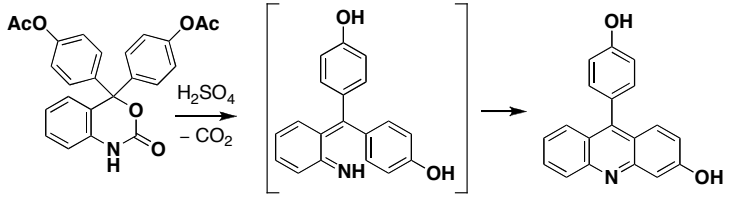


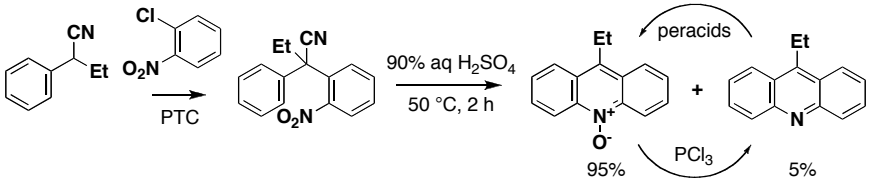
Acridine Alkaloids

Jonathan Lockner

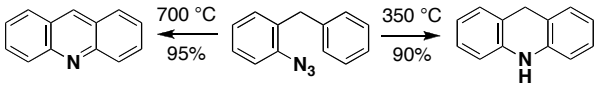
Electrocyclizations:



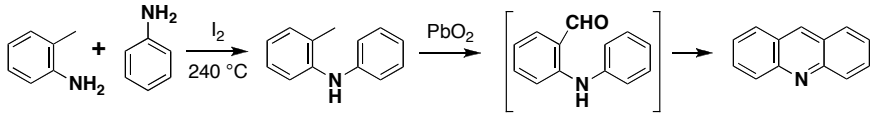
Via arylation of phenylacetonitriles (Makosza 1973):



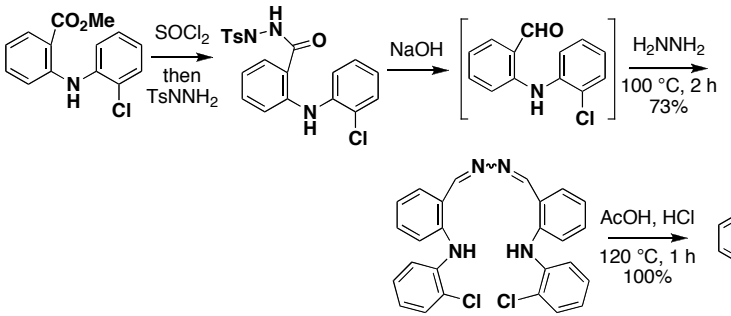
Photolysis or pyrolysis of aryl azides:



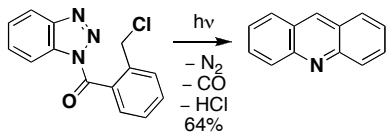
From diarylamines (this example also shows that carbonyl can be generated *after* N-arylation):



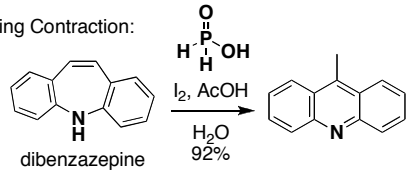
Via the McFadyen–Stevens Reaction:



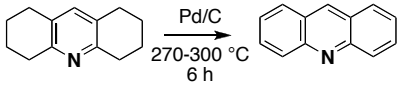
Ring Expansion:



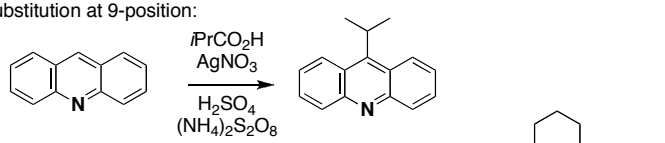
Ring Contraction:

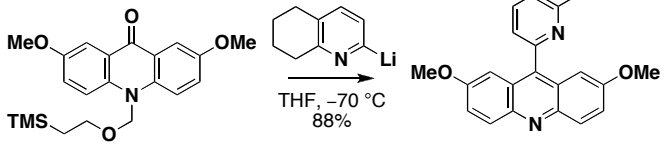


Dehydrogenation:

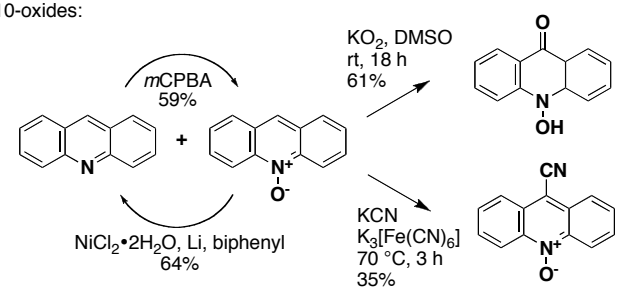


Substitution at 9-position:

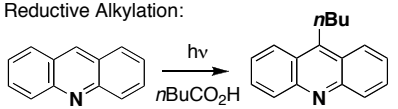




Acridine 10-oxides:

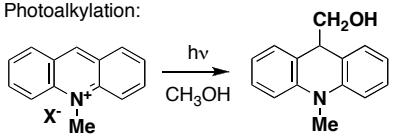


Reductive Alkylation:

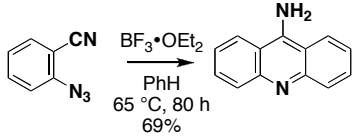


Tetrahedron **1969**, *25*, 1125

Photoalkylation:



Chem. Ber. **1964**, *97*, 2418



ARKIVOC **2006**, *(xii)*, 111

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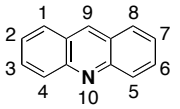
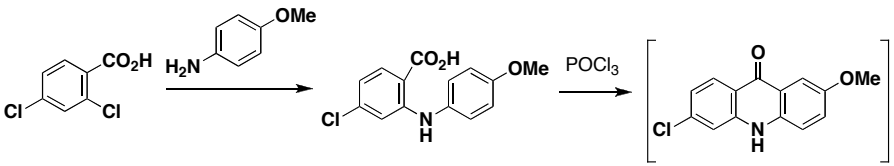


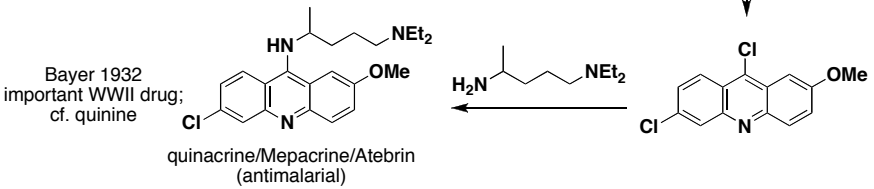
Acridine Alkaloids

Jonathan Lockner

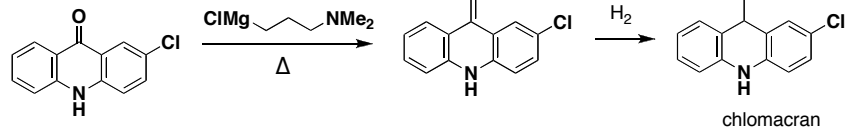
Drug Synthesis:



Mietzsch et al U.S. Patent **1938**, 2113357

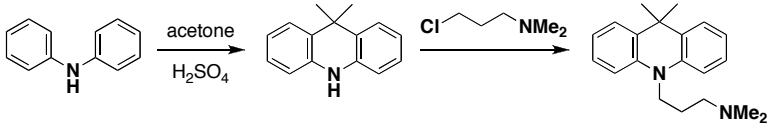


quinacrine/Mepacrine/Atebrin
(antimalarial)



Zirkle U.S. Patent **1964**, 3131190

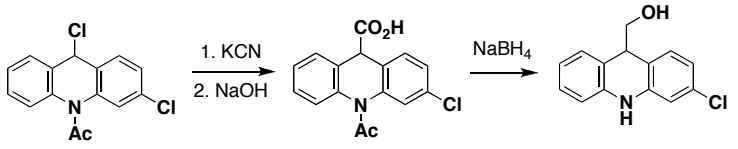
chlomacran
(antipsychotic)



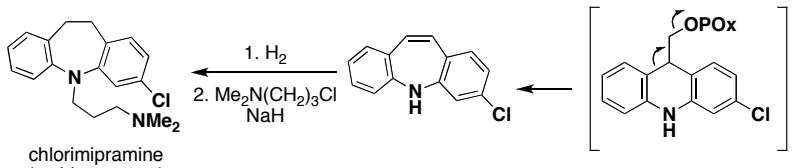
Holm Br. Patent **1963**, 933875

dimetacrine
(antidepressant)

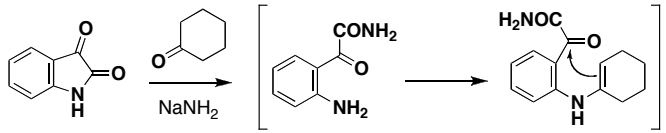
Lednicer, D. *Strategies for Organic Drug Synthesis and Design*,
John Wiley & Sons, New York, 1998, pp. 383-387



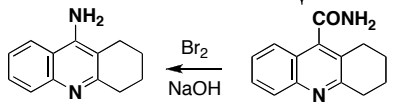
Zirkle et al *J. Org. Chem.* **1961**, *26*, 135



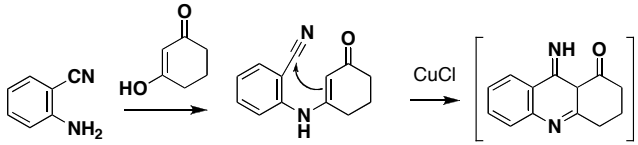
chlorimipramine
(antidepressant)



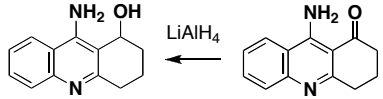
Bielavsky *Collect. Czech. Chem. Commun.* **1977**, *42*, 2802



tacrine/Cognex
(antidementia)

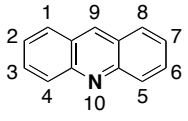


Shutske, G. M.; et al *J. Med. Chem.* **1988**, *31*, 1278



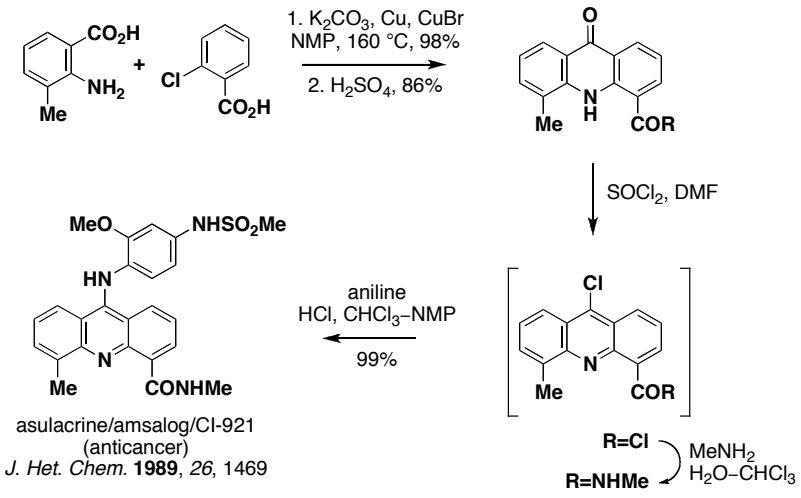
hydroxyl improves
oral absorption

velnacrine
(antidementia)

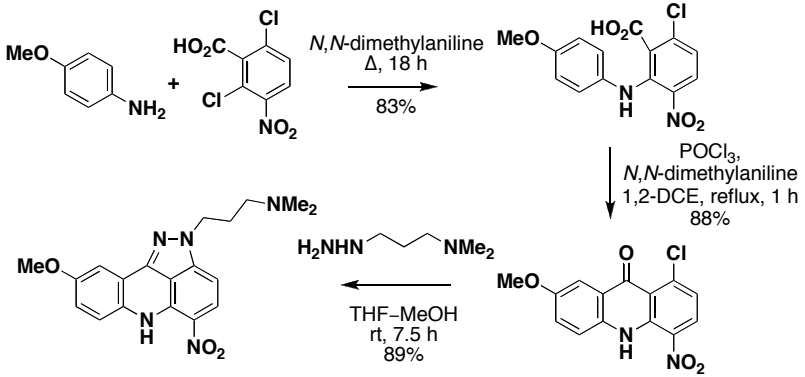


Acridine Alkaloids

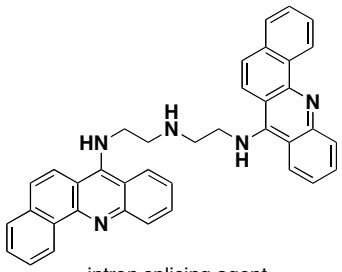
Jonathan Lockner



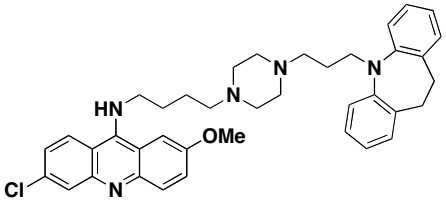
asulacrine/amsalog/CI-921
(anticancer)
J. Het. Chem. **1989**, *26*, 1469



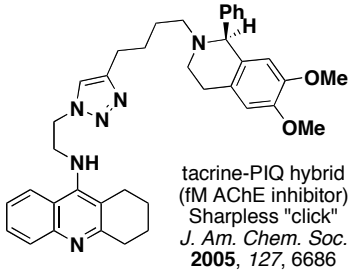
PZA/pyrazoloacridine
(antitumor)
J. Med. Chem. **1992**, *35*, 4770



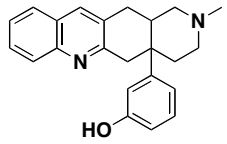
intron splicing agent
Bioorg. Med. Chem.
1997, *5*, 1185



quinpramine
(antiprion)
(for Creutzfeldt–Jakob disease)

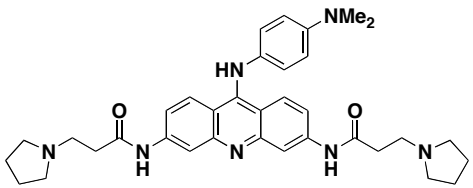


tacrine-PIQ hybrid
(fM AChE inhibitor)
Sharpless "click"
J. Am. Chem. Soc.
2005, *127*, 6686



(–)-TAN-67
(antinociceptive)
δ opioid receptor agonist

(+) isomer induced hyperalgesia
(opposite effect!)



BRACO-19
telomerase inhibitor
Neidle et al. *J. Med. Chem.* **2003**, *46*, 4463

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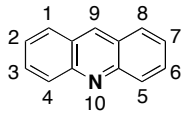
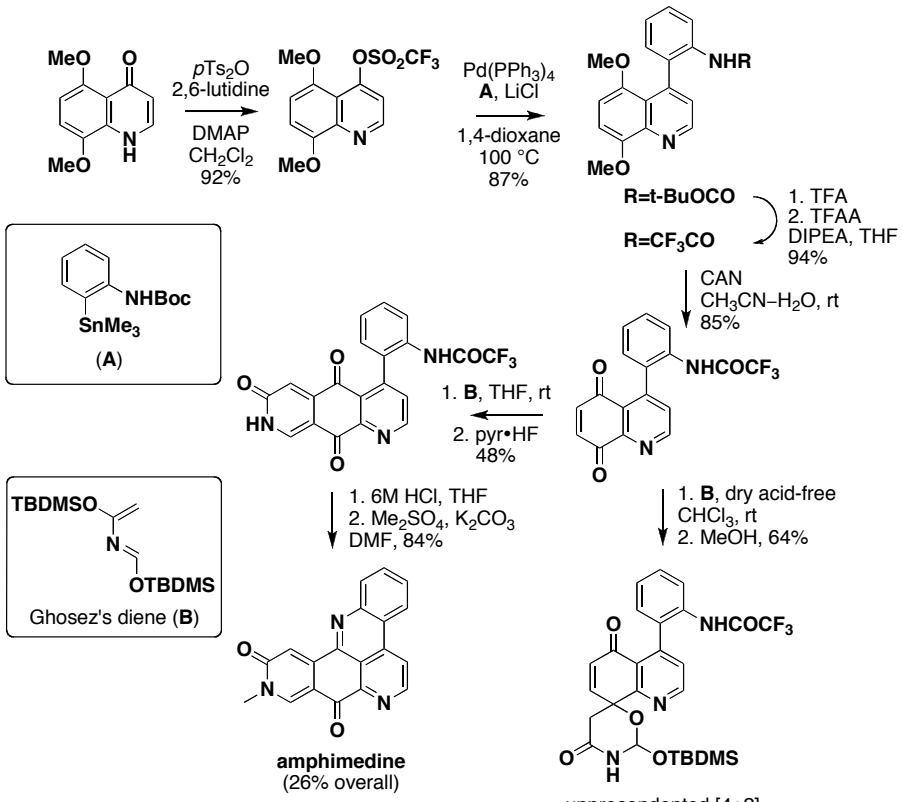


Acridine Alkaloids

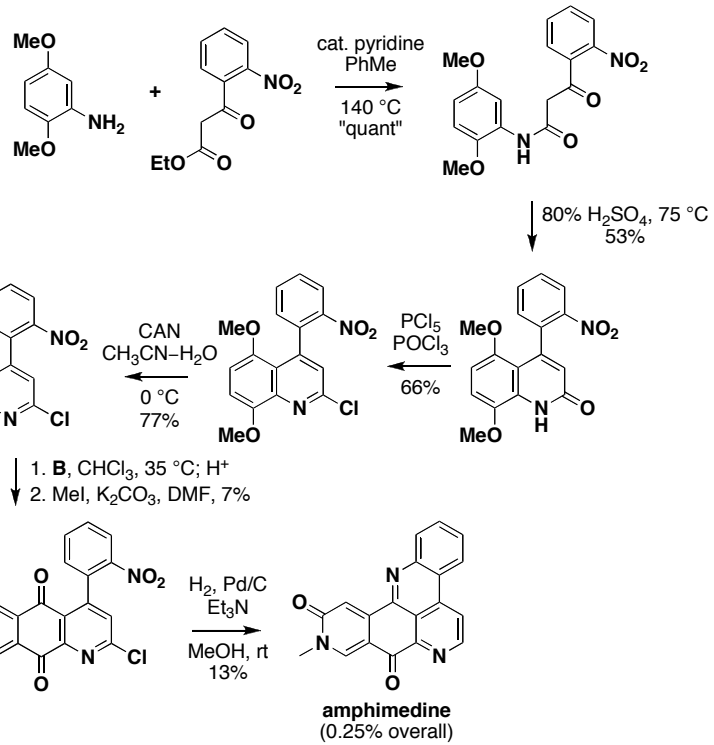
Jonathan Lockner

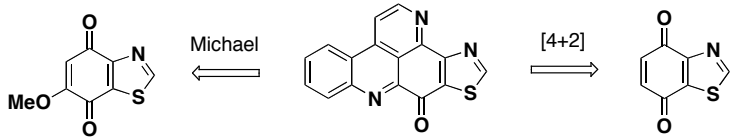
Natural Product Synthesis:

Amphimedine
Stille, *J. Am. Chem. Soc.* **1988**, *110*, 4051



Amphimedine
Nakahara, *Heterocycles* **1988**, *27*, 2095





kuanoniamine A
Nakahara, *Tetrahedron* **1997**, *53*, 17029
Hepburn, *Heterocycles* **2006**, *68*, 975

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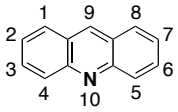


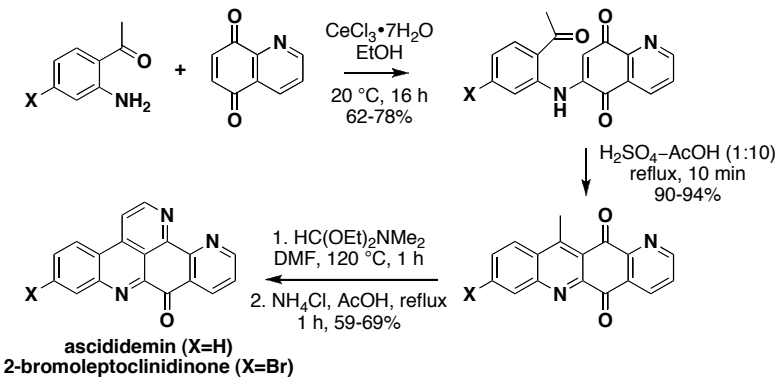
Acridine Alkaloids

For other pyridoacridines, see *Chem. Rev.* **1993**, *93*, 1825

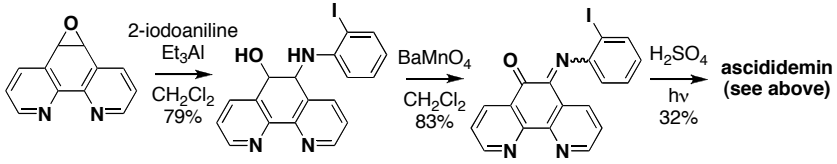
Jonathan Lockner

Natural Product Synthesis:

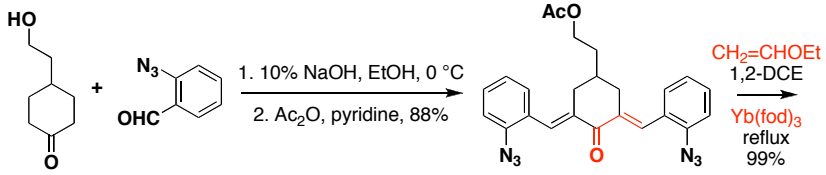
Ascididemin (X=H) and 2-Bromoleptoclinidinone (X=Br)
Bracher, F. *Heterocycles* **1989**, *29*, 2093
Bracher, F. *Liebigs Ann. Chem.* **1990**, 205

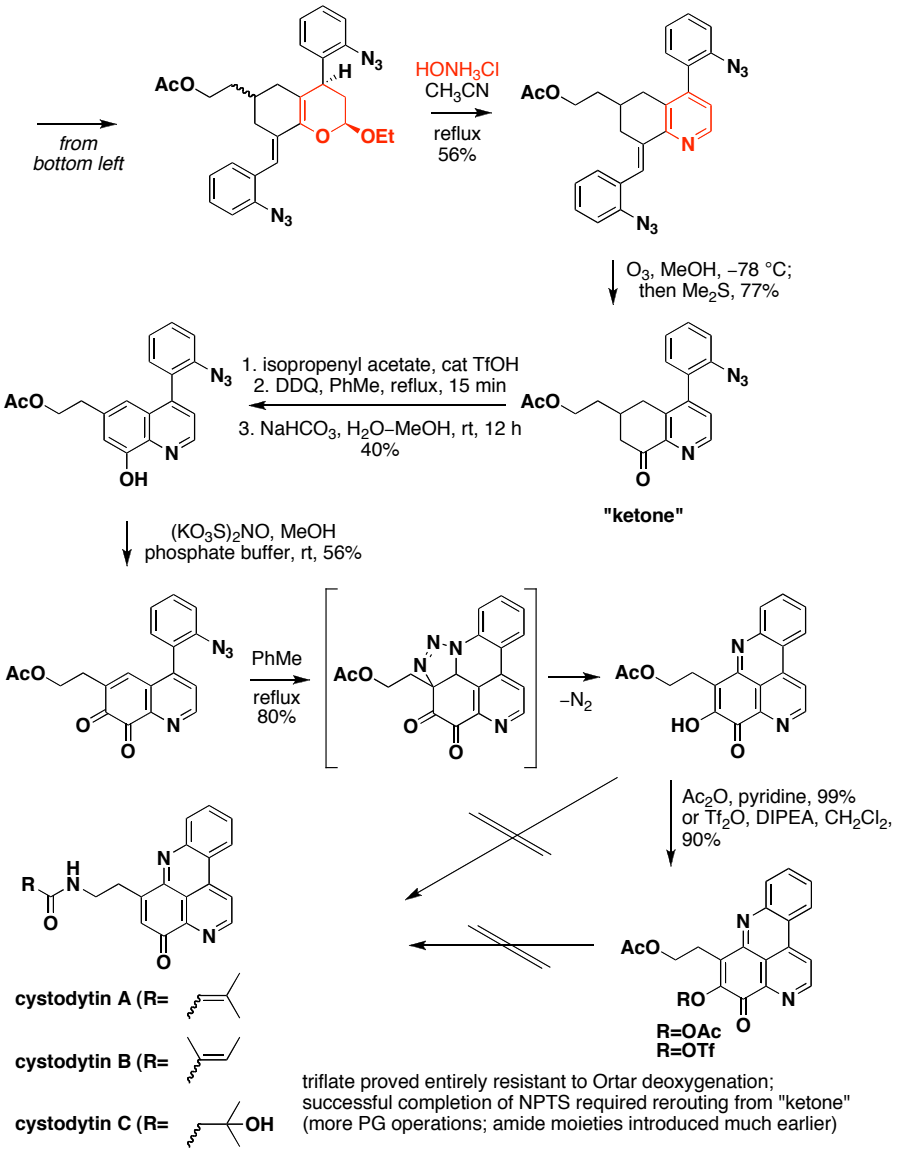


Ascididemin
Moody, C. J.; Rees, C. W.; Thomas, R. *Tetrahedron Lett.* **1990**, *31*, 4375



The Cystodytins
Ciufolini, M. A.; Byrne, N. E. *J. Am. Chem. Soc.* **1991**, *113*, 8016





triflate proved entirely resistant to Ortar deoxygenation;
successful completion of NPTS required rerouting from "ketone"
(more PG operations; amide moieties introduced much earlier)