SYNTHETIC STUDIES OF THE FORMATION OF PYRAZOLOISOQUINOLINES AND PYRIDOPHENOTHIAZINES

By

Christopher William Jenks
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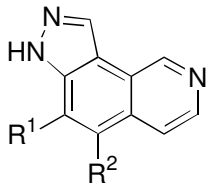
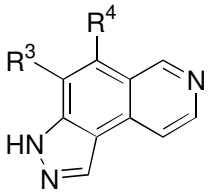
Abstract

Diazotization of 7-amino-5,8-dimethyl-6-(thiophenyl)isoquinoline in glacial acetic acid unexpectedly led to the formation of a new ring system, 3H-pyrazolo[3,4-*h*]isoquinoline **(A)** as its 5-methyl-6-thiophenyl derivative. In this work, the parent ring system was synthesized and characterized, along with its 5-methyl, 6-bromo-5-methyl, and 5-methyl-6-thiophenyl derivatives. The 3H-pyrazolo[4,3-*f*]isoquinoline isomer **(B)**, also previously unknown, was prepared in a similar manner and characterized along with its 5-methyl, 6-bromo-5-methyl, and 5-methyl-6-thiophenyl derivatives. Rates of formation for the 5-methyl and 5-methyl-6-thiophenyl derivatives were compared between ring systems in different strengths of acid. Diazotizations carried out in hydrochloric acid, followed by treatment with sodium azide, led to the expected aryl azides.

The new compounds 5,12-dimethyl-6H-pyrido[4,3-*b*]phenothiazine **(C)** and its 9-methoxy derivative were efficiently synthesized using a novel rearrangement to achieve the desired regiochemistry. Their anticipated conversion to ellipticines was thwarted by the lack of a suitable method for extruding sulfur.



(A)



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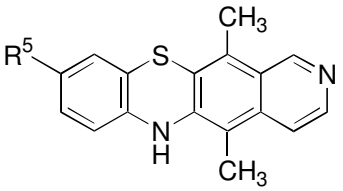


(C)

Acknowledgments

This work has been made possible by the friendship and teaching of Dr. Bryan Miller. He lets me call him Bryan, and I am honored. I have been lucky to work with him, not only because of his sharp scientific understanding, but because he cares how other people feel. When I interrupt Bryan in his office, he does not react with offense or impatience the way I sometimes do, but rather invites me inside and sacrifices a lot of time to listen to me and offer help. When I carelessly wreck his expensive equipment, he is slow to become angry and quick to forgive. Rather than be offended by my eccentric wise cracks, Bryan laughs and brings joy to the occasion. It has been good to be able to share my ideas, successes, and many failures with such a patient and compassionate man.

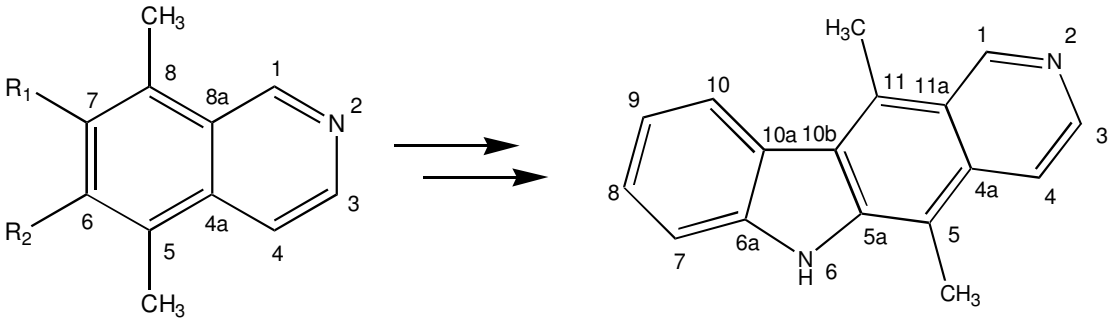
I am grateful to my parents, Robert and Sharon Jenks, for teaching me to be gentle, honest, loving, and faithful, and for teaching me the scientific path, and to my brother Andy for demonstrating independence and self-sufficiency. Their patience, acceptance, and support has eased my burden greatly over the years. Encouragement to complete this work has been provided by Dana Butler, whose love and friendship have brought me joy and whose love of Jesus has inspired me. My friends Dan Bender, Corvin Brown, Steve Farmer, Cary Friedman, Darin Kizer, Jim Kress, Dave Lane, Lee Lowry, Chris Lum, Shannon McQuaide, Michael Pearl, Bach Phan, Richard Scown, John Svoboda, and Mark and Susie Wilson have filled these years with happy memories.

Completing the graduate program has demanded more of my patience than anything else I have ever done. Watching as opportunities go foregone, inspirational plans are forgotten, and the cries of people who are suffering and dying go unanswered, has cost a substantial piece of my life. I am grateful for the tools and training I have been given, and look forward to integrating science with love so that my contribution to this world will bring joy and hope. I am eternally grateful to the one who gives me life and the opportunity to help unravel the mystery of humanity's self inflicted torment.

Table of Contents

Introduction

Ellipticine **(2)** and 9-methoxyellipticine **(7)** occur naturally in *Ochrosia elliptica* Labill[1] and other plants, and are moderately effective in the treatment of some forms of cancer[2]. They exert their action by lodging between strands of DNA and causing them to unravel[3]. A primary goal of the Miller group has been to develop syntheses of ellipticine **(2)** with selective substitutions on the 7, 8, 9, and 10-positions from an appropriately substituted benzene derivative and substituted isoquinolines **(1)** **(Fig. 1)**. Few methods currently exist for derivatizing these positions of ellipticine, and providing a practical means of doing so would facilitate testing of new ellipticine derivatives for cancer treatment.



6,7-Disubstituted-5,8-dimethylisoquinoline (1)

Ellipticine (2)

Figure 1

Early attempts to make ellipticine **(2)** and 9-methoxyellipticine **(7)** from available 6-bromo-5,8-dimethylisoquinoline **(133)** were very successful[4] **(Fig. 2)**. Commercially available 4-methoxy-2-nitroaniline **(3)** was heated with the isoquinoline **(133)**, copper-bronze, iodine, and potassium carbonate to give a moderate yield of the coupled nitrobiarylamine **(4)**. Reduction of the nitro group by hydrazine and Raney nickel in refluxing ethanol gave the amine **(5)** which was not fully purified. Treatment of the amine **(5)** with sodium nitrite in acetic acid gave the triazole **(6)** in an excellent 94% yield,

calculated from the nitro compound **(4)**. A solution of the triazole **(6)** was passed through a 500°C quartz tube, giving a good yield of 9-methoxyellipticine **(7)**.

This synthesis is practical for the preparation of ellipticine **(2)** and 9-methoxyellipticine **(7)** themselves, but poses problems as a general method. The fierce 500°C thermolysis may limit the procedure to durable ellipticine derivatives, and highly derivatized 2-nitroanilines may be difficult to obtain.

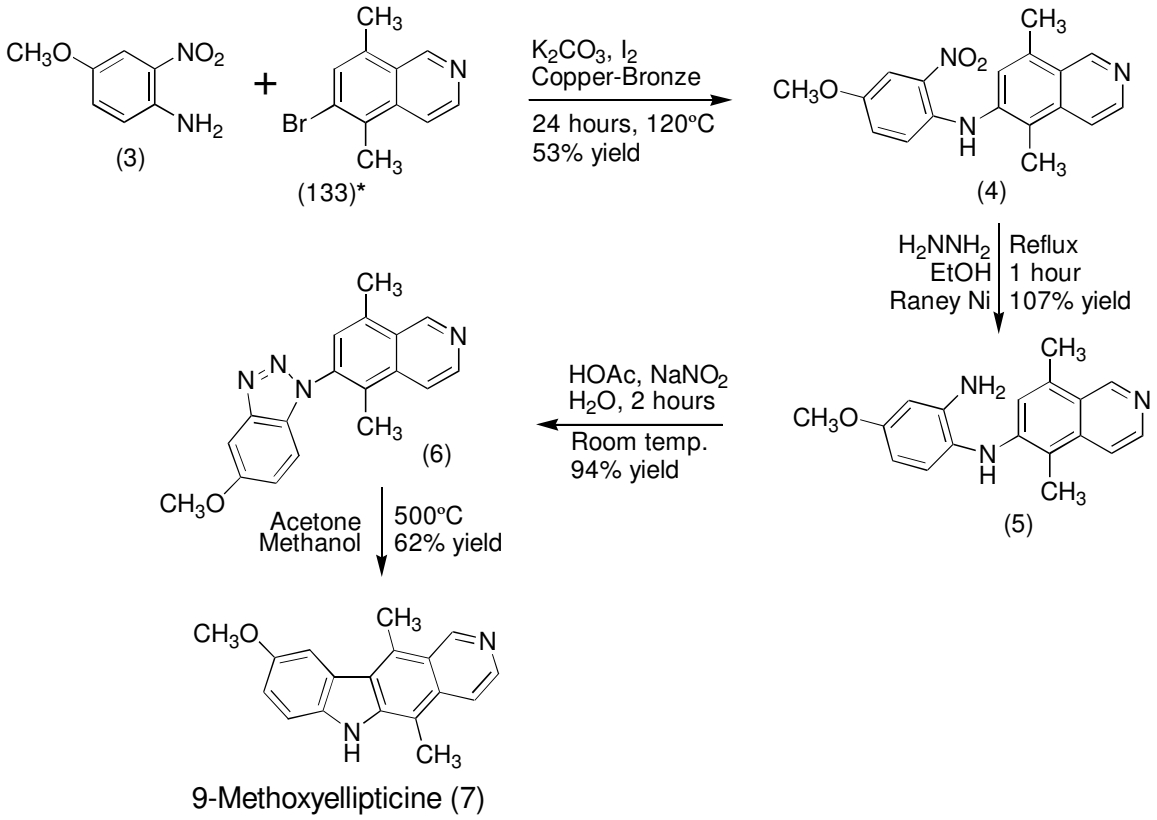


Figure 2

To reduce the severity of the final cyclization step, the triazole group was replaced with an azido group, which loses nitrogen to form a nitrene at only 200°C[5]. The ideal place for the azido group would have been the 6-position of the isoquinoline, but attempts to synthesize 6-amino-7-bromo-5,8-dimethylisoquinoline **(125) (Fig. 10)** failed when first attempted[6]. However, 6-bromo-7-nitro-5,8-dimethylisoquinoline **(165) (Fig. 7)** was available[7] and was successfully converted into isoellipticine through an azide[5], demonstrating the feasibility of this route to ellipticine **(2)**. Also, a mixture of isomers

was converted into an inseparable mixture of ellipticine **(2)** and isoellipticine using this route[5].

A less attractive approach[5] which used available materials was to place the azide group on the benzene ring, which would again limit the availability of starting materials for making ellipticine derivatives. The 7-bromo-5,8-dimethylisoquinoline **(8) (Fig. 3)** needed was efficiently synthesized from p-xylene[5]. Treatment of the isoquinoline **(8)** with n-butyllithium in THF, followed by treatment with trimethyl borate and hydrolysis with dilute acid, gave a boronic acid **(9)** which was extracted but not isolated. Further treatment with commercial 2-bromonitrobenzene in refluxing benzene and aqueous sodium carbonate with catalytic tetrakis(triphenylphosphine)palladium(0) gave a moderate yield of the coupled nitro compound **(10)**. Reduction by Raney nickel and hydrazine in refluxing ethanol gave the amine **(11)**, which was cleanly diazotized in hydrochloric acid and converted to the azide **(12)** by treating with sodium azide. Heating the azide **(12)** in dodecane gave a poor yield of ellipticine **(2)** and a good yield of an unexpected indolenine **(13)**.

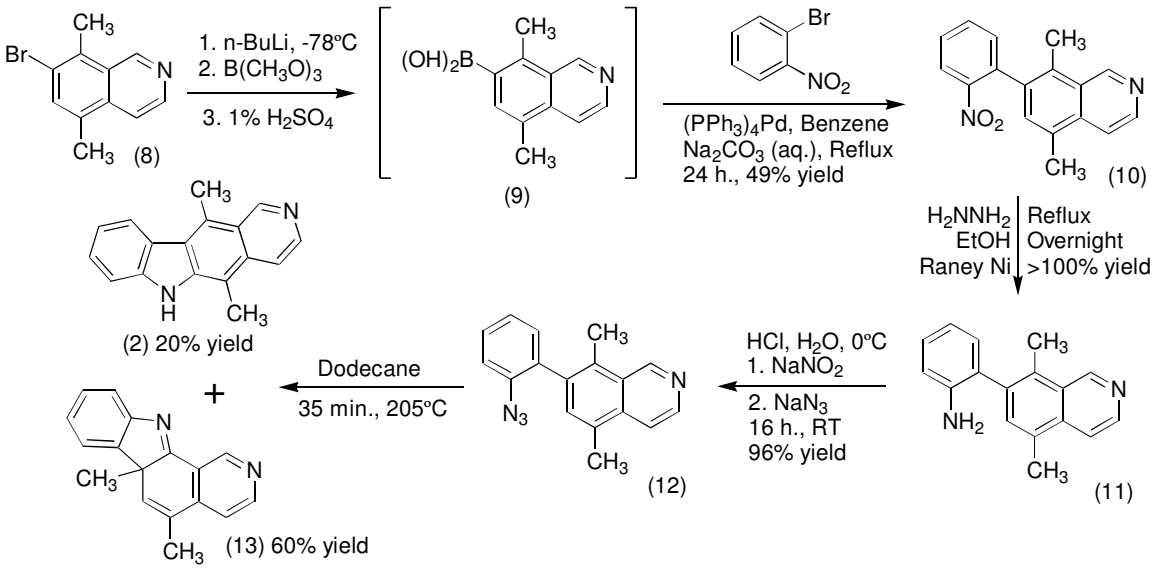


Figure 3

Inspection of the literature suggested[7] means of producing pure 9-methoxyellipticine **(7)** and other 9-substituted ellipticines in a novel manner. The first reaction[8] converted a biaryl azide **(14)** into 3-methylphenothiazine **(15)** with migration of sulfur **(Fig. 4)**. This migration is what would allow 9-methoxyellipticine **(7)** to be prepared without any contaminating isomer. A possible hurdle to overcome for this step is the disappointing yield.

In the second and last step, sulfur was handily removed from a variety of substrates. In the case of phenothiazine **(136)**, carbazole **(139)** was formed in acceptable yield, along with a minor amount of reduced diphenylamine **(16)** as a side product. No mention was made in the original publication[9] of any significant problems or limitations with this procedure.

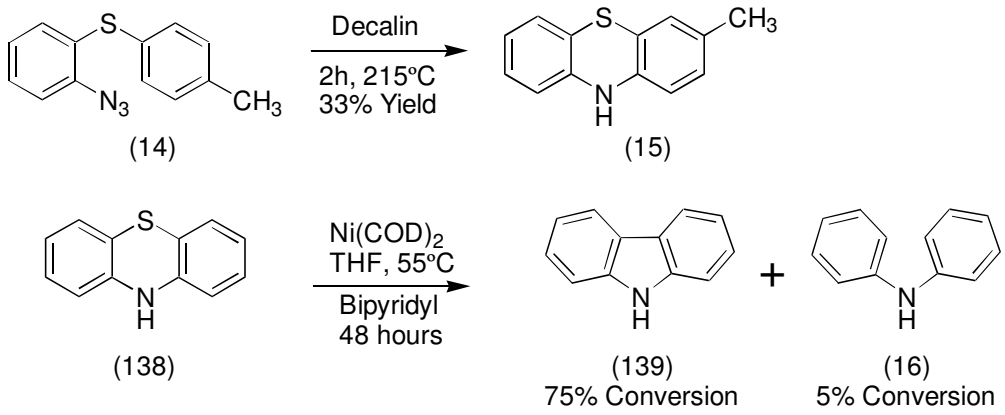


Figure 4

A strategy **(Fig. 5)** for synthesizing 9-methoxyellipticine **(7)** was cleverly assembled using these two novel and rarely employed reactions **(Fig. 4)**. The precursor 7-bromo-5,8-dimethyl-6-nitroisoquinoline **(123)**, if preparable, could be converted to 6-azido-5,8-dimethyl-7-(4'-methoxythiophenyl)isoquinoline **(136)** using well known methods. Thermolysis of the azide **(136)** should cause cyclization with migration of sulfur[8] to give 5,12-dimethyl-9-methoxy-6H-pyrido[4,3-*b*]phenothiazine **(137)**, which could then be converted to 9-methoxyellipticine **(7)** by extruding sulfur.

The anticipated mechanism[9] would involve a three membered transition state leading to the formation of nickel sulfide. Unfortunately the dipyridyl liberated in the process would complex with and deactivate any unreacted nickel reducing agent, requiring at least two equivalents of it to be used[10].

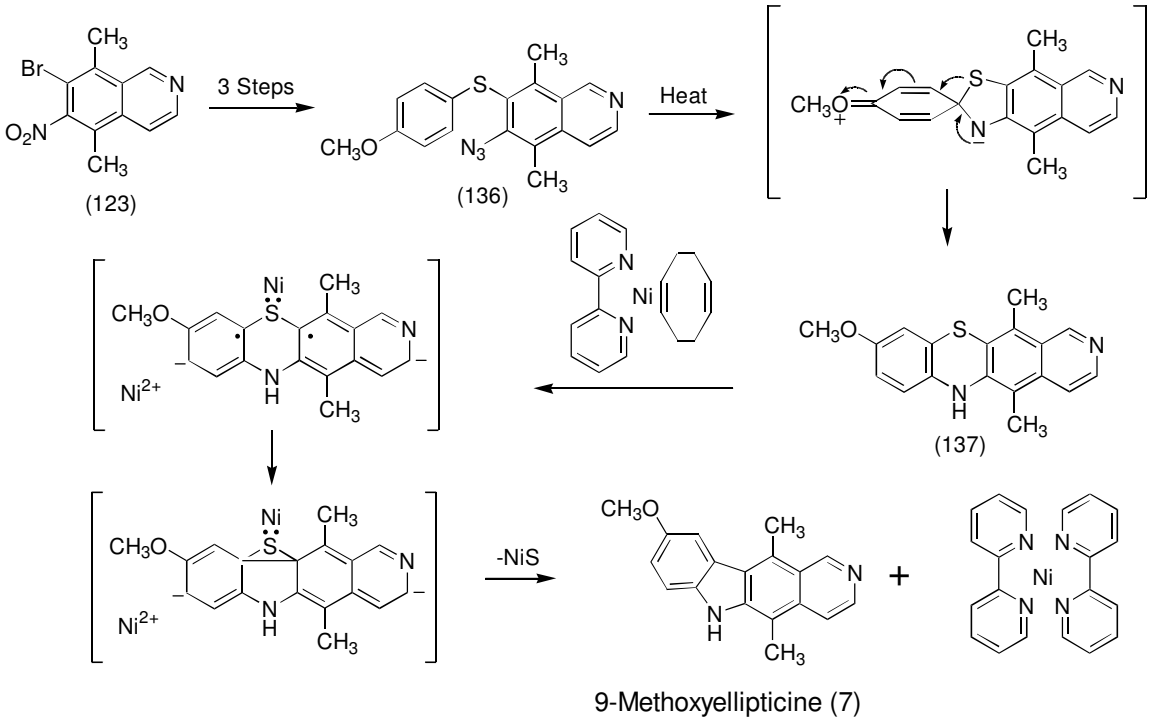


Figure 5

Although a synthesis of the optimum precursor **(123)** had not been developed at the time this strategy was conceived, there was still hope[5] to test the sulfur extrusion **(Fig. 6)**. Commercial 2-aminothiophenol **(17)** was coupled with 6-bromo-5,8-dimethylisoquinoline **(133)** using sodium hydride in hot DMF to give the sulfide **(18)** in good yield. Diazotization in hydrochloric acid followed by treatment with sodium azide gave the azide **(19)** in excellent yield. Thermolysis of the azide **(19)** in dodecane gave a surprisingly good yield of an unwanted rearranged byproduct **(20)** along with a poor yield of an equal mixture of phenothiazines **(21)** and **(132)**. The phenothiazine **(21)** contains a new ring system, but was unfortunately inseparable from its isomer **(132)**.

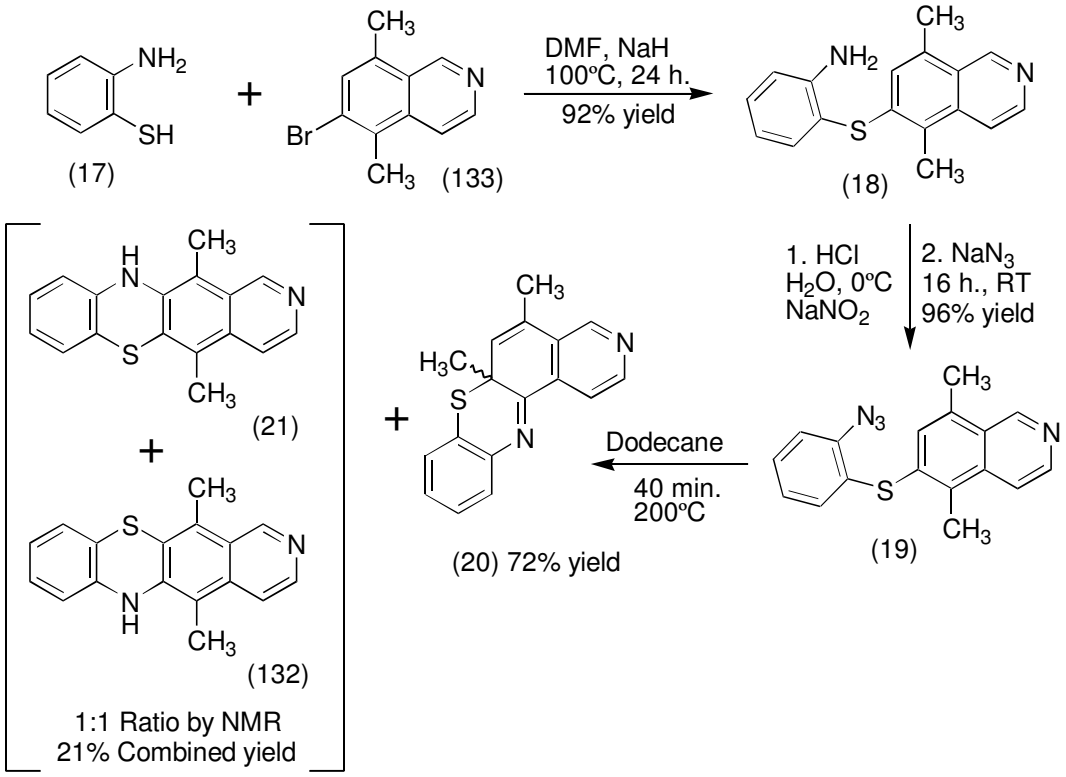


Figure 6

Another chance to test the sulfur extrusion method would require azide attached to isoquinoline, and the available precursor 6-bromo-5,8-dimethyl-7-nitroisoquinoline **(165)** was chosen to do so[7,11] **(Fig. 7)**. Reaction of **(165)** with thiophenylate in hot DMF gave a good yield of 5,8-dimethyl-7-nitro-6-thiophenylisoquinoline **(101)**, which then reduced cleanly with hydrazine and Raney nickel in refluxing ethanol to give a good yield of the amine **(103)**. Although hydrochloric acid has been the solvent of choice for the diazotizations illustrated so far, the amine **(103)** dissolved very poorly in it. Glacial acetic acid dissolved the amine very well, so the amine **(103)** was diazotized in cold glacial acetic acid, and then treated with sodium azide. Extensive analysis of the products showed little or none of the expected azide **(106)**, but instead a mixture of thiaellipticine **(105)** and a derivative of a new ring system, 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)**. Repetition of the diazotization without adding azide led to the same mixture of products.

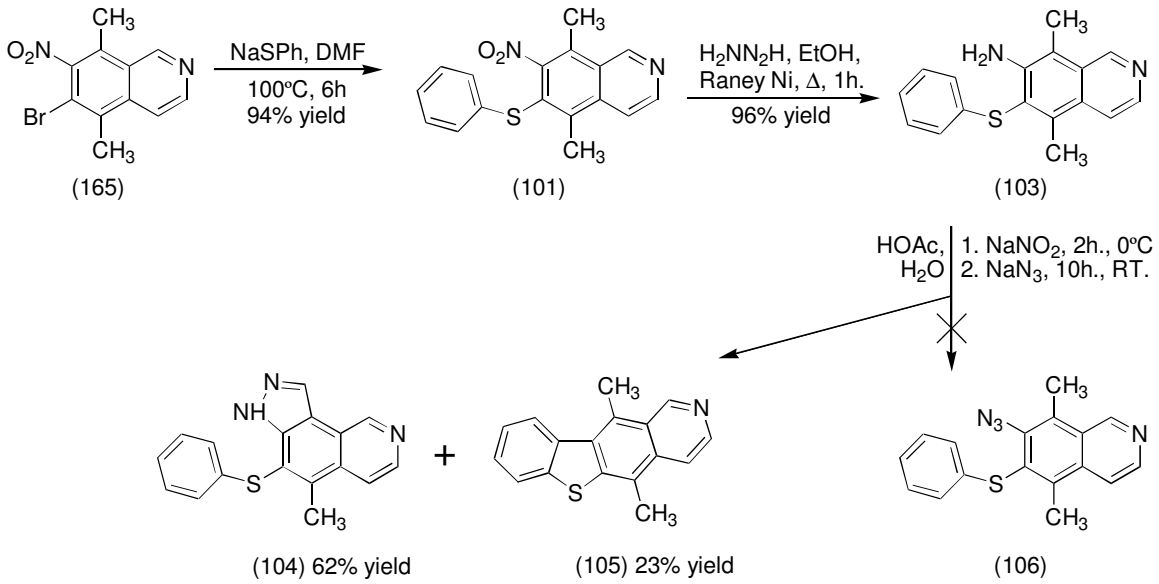


Figure 7

Stowell's preliminary synthesis[7] of the new ring system derivative 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104) (Fig. 7)** was not accompanied by complete analytical data. Repetition of the synthesis by Steve Farmer[11] provided a crystal for X-ray analysis[12] **(Fig. 8)**, **(Appendix A)**.

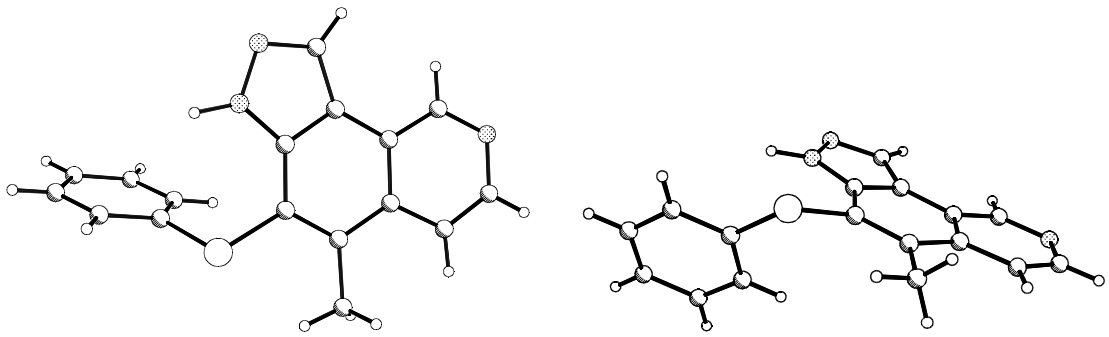


Figure 8

Replacement of a diazonium group by a nucleophile normally follows the S_N1 mechanism, but replacement by azide is different[13] **(Fig. 9)**. The main pathway involves formation of a diazoazide, some of which may cyclize to a pentazole, but most of which

loses nitrogen to give an azide. In the minor pathway, pentazole, which may form from either the diazonium salt and azide or from a diazoazide, undergoes a reverse cycloaddition or ring opening to lose nitrogen. In the major pathway the nitrogen atoms from the diazo group are retained, while in the minor pathway 50% of the terminal nitrogen atoms have been replaced by nitrogen from azide.

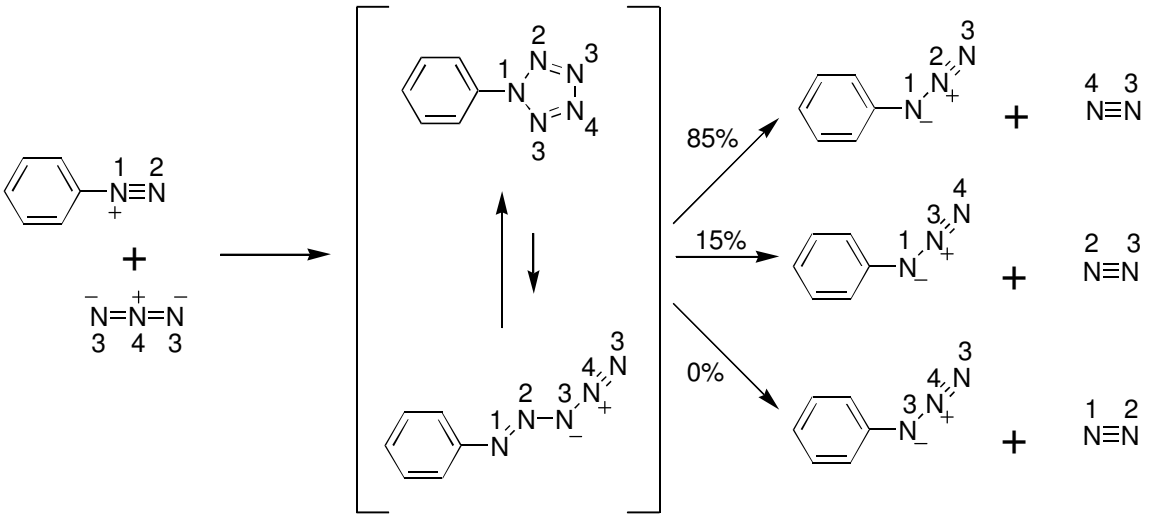


Figure 9

Upon the development of a 6-amino-7-bromo-5,8-dimethylisoquinoline **(125)** synthesis[6], it became possible to synthesize[14] 9-methoxyellipticine **(7)** using an azidoisoquinoline **(24)** (**Fig. 10**). Commercially available 3-methoxyphenylboronic acid **(22)** was coupled with the amine **(125)** in a refluxing mixture of benzene and aqueous sodium carbonate with catalytic $Pd(PPh_3)_4$ to give a biarylamine **(23)**. Diazotization in hydrochloric acid followed by treatment with azide gave a mediocre yield of the azide **(24)**. Thermolysis in decalin gave a mixture of 7-methoxyellipticine **(25)** and 9-methoxyellipticine **(7)**. Efforts to produce only one isomer have had limited success so far. This route is excellent for preparing ellipticine itself and 8- and 10-substituted ellipticines[14].

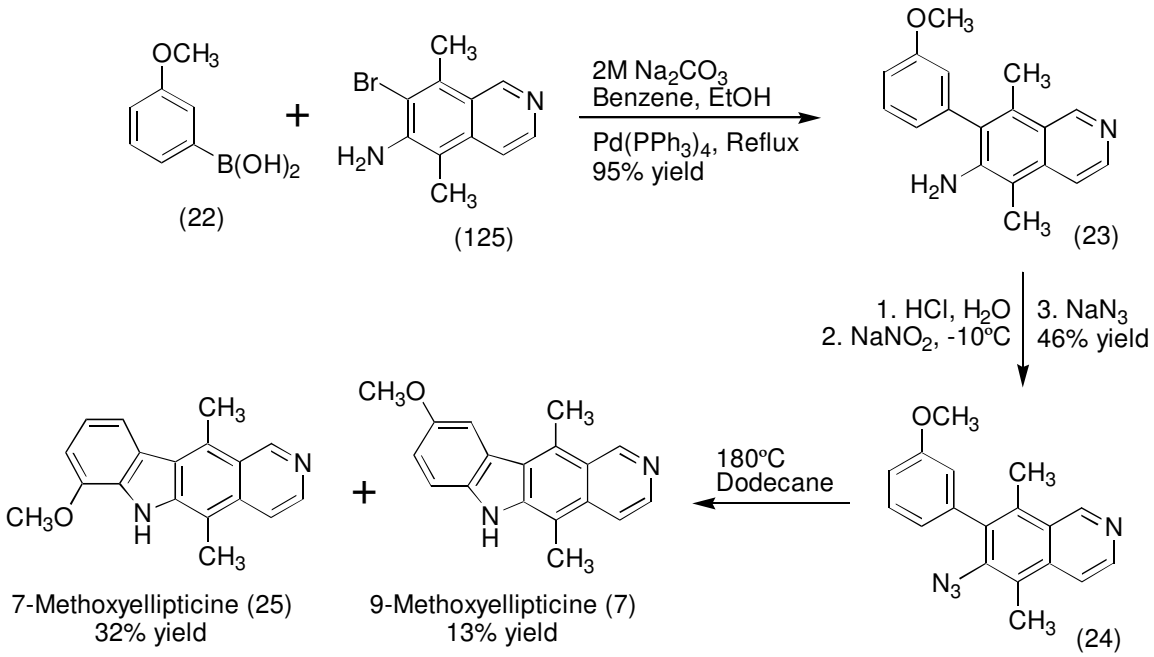


Figure 10

The unexpected formation of a derivative of a new ring system, 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104) (Fig. 7)**, raises the question of what features of isoquinolines allow them to become pyrazole derivatives. It has long been known[15,16] that a low yield of indazole **(27)** and a good yield of 5-nitroindazole **(29)** can be prepared by diazotizing the respective amines **(26)**, **(28)** in acetic acid **(Fig. 11)**. In fact, the only nitroindazole which forms in only moderate yield is 7-nitroindazole[17], which implies that cyclization is facilitated by withdrawing electron density from either the methyl or the diazo group.

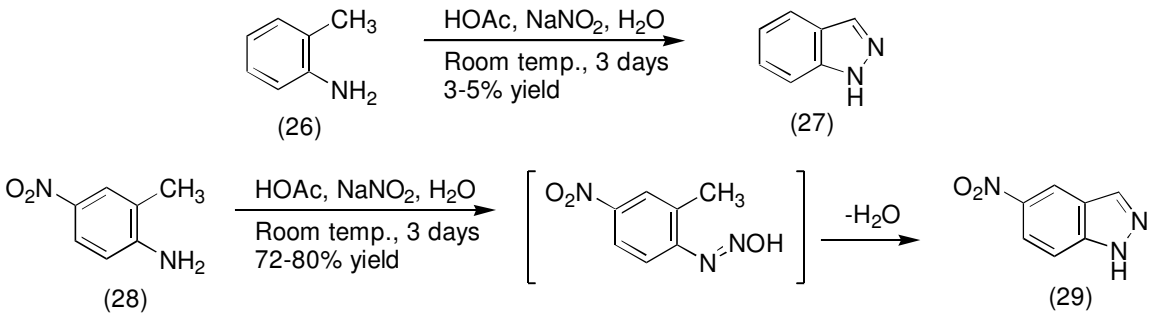


Figure 11

This method is practical only for making indazoles which bear electron withdrawing substituents[18]. To prepare a good yield of indazole itself, or indazoles bearing electron donating substituents, an amide **(30)** is used as a precursor instead of the corresponding amine[18] **(Fig. 12)**. The nitroso intermediate **(31)** can be isolated and dried, making the use of an aprotic solvent such as benzene possible in the subsequent cyclization. When heated, the nitroso compound **(31)** rearranges into an (E)-diazo ester **(32)**, followed by dissociation into a diazonium salt **(33)**, so the subsequent mechanism is the same as if an amine had been diazotized directly. With activation from the diazonium group, the methyl group relinquishes a proton to form a resonance stabilized carbanion **(34), (35)**, which quickly cyclizes to give 3H-indazole **(36)**, which then tautomerizes to the more stable, and fully aromatic, 1H-indazole **(37)**.

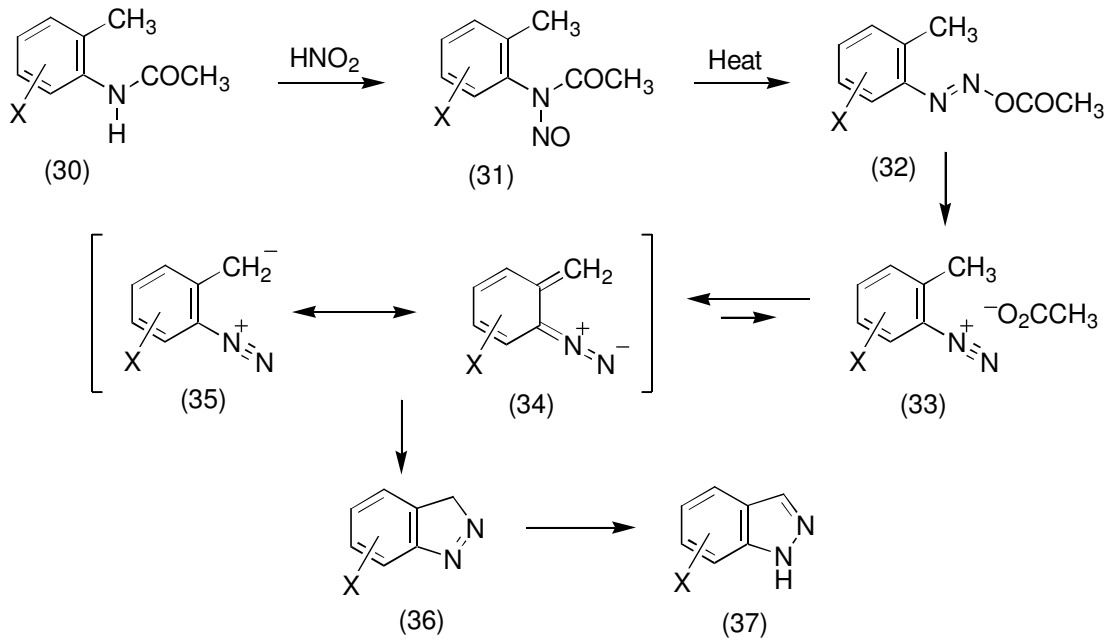


Figure 12

Several studies[18] support the proposed mechanism for indazole formation **(Fig. 12)**. Configuration of the (E) diazo ester **(32)** was demonstrated using cyclic precursors **(Fig. 13)**. In this case, to accommodate the trans double bond in a stable ring would require at least nine members, and thermolysis of the seven membered amide **(38)**

produced the expected indazole through the presumed nine membered intermediate. Thermolysis of **(39)** failed to produce an indazole, suggesting that the eight membered intermediate was too strained to form.

When N-(4-fluoro-2-tolyl)-N-nitrosobenzamide **(40)** is heated in benzene, the expected product, 5-fluoro-1H-indazole **(42)**, is contaminated by 5-benzoyloxy-1H-indazole **(41)**. For the fluoride to be displaced by benzoate this easily suggests that a powerful electron withdrawing group, such as diazonium, is involved.

Diazotization of a chiral amine **(43)** led to a racemic indazole **(44)**, providing compelling evidence for the methylene intermediate **(34)** **(Fig. 12)**. Diazotizations in D_2SO_4 gave little or no incorporation of deuterium into the resulting indazoles, suggesting that cyclization is rapid following deprotonation.

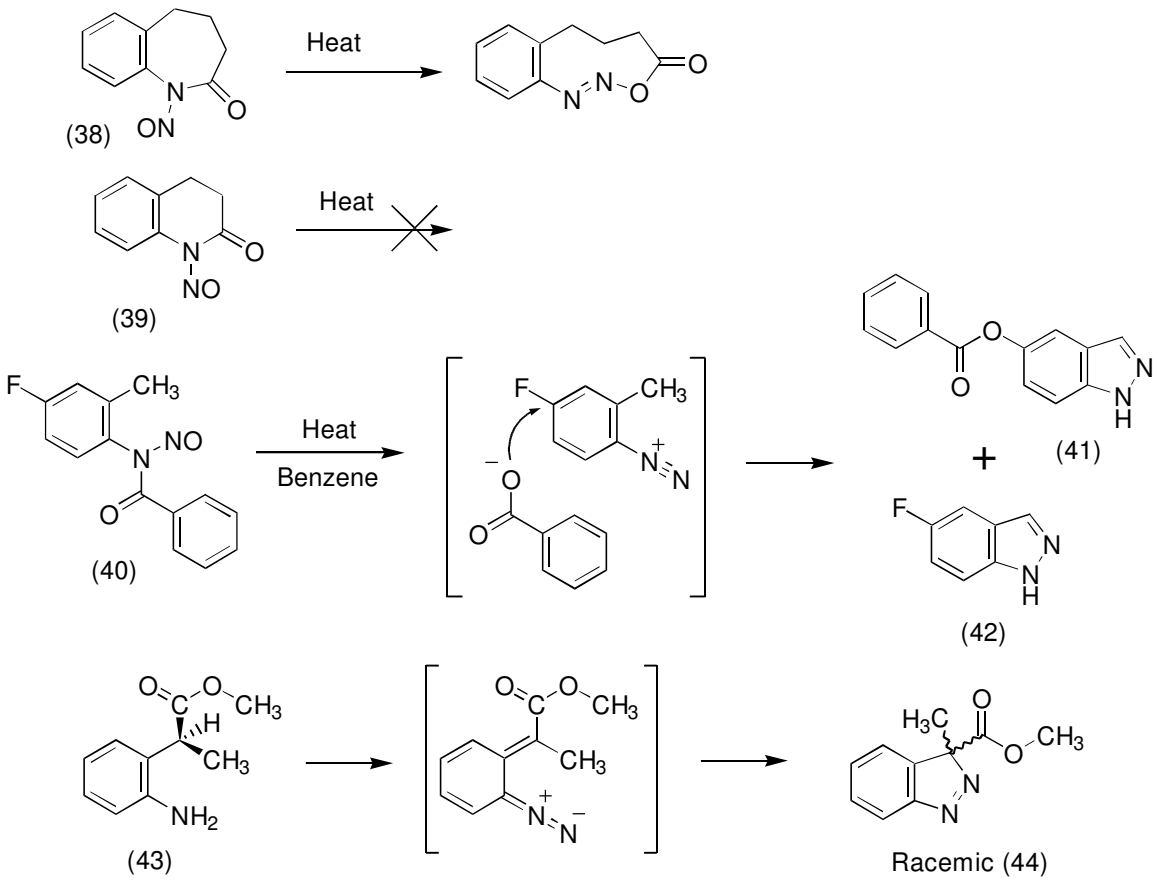


Figure 13

In an improved indazole synthesis[18] **(Fig. 14)**, 1,4-diamino-2,3,5,6-trtramethylbenzene **(45)** was treated with 2-pentyl nitrite, acetic anhydride, and anhydrous potassium acetate in refluxing benzene, and subsequently hydrolyzed in 7M HCl to give 4,5-dimethylbenzo[1.2-*d*:4.3-*d*']dipyrazole **(46)**, and none of the isomeric dipyrazole **(47)**.

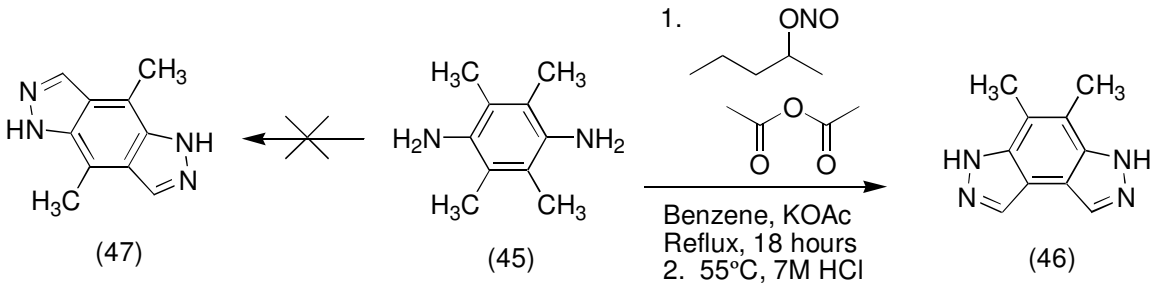


Figure 14

Diazotization can also be performed using nitrosyl chloride, as demonstrated by the syntheses of pyrazolo[4,3-*b*]pyridine[19] **(50)** and pyrazolo[3,4-*c*]pyridine[20] **(53)** derivatives **(Fig. 15)**. In the first step, an aminopyridine **(48)**, **(51)** and anhydrous potassium acetate in acetic anhydride and acetic acid were treated with nitrosyl chloride. The reaction was quenched with sodium carbonate, extracted with benzene, and the extract was refluxed to generate the acetylpyrazolopyridine **(49)**, **(52)**. Hydrolysis in dilute refluxing hydrochloric acid gave the pyrazolopyridine **(50)**, **(53)**.

The methoxy group of 1-acetyl-5-methoxy-1H-pyrazolo[4,3-*b*]pyridine **(49, R = OCH_3)** was cleaved during the subsequent hydrolysis to give 1H-pyrazolo[4,3-*b*]pyridin-5(4H)-one, and 2-acetyl-7-methoxy-2H-pyrazolo[3,4-*c*]pyridine **(52, R = H, R' = OCH_3)** met a similar fate when hydrolyzed. The desired methoxypyrazoloisoquinolines **(50)**, **(53)** were prepared by leaving acetic anhydride out of the cyclization reaction. The unsubstituted pyrazolo[3,4-*c*]pyridine **(53, R = H, R' = H)** was prepared using the first set of conditions below.

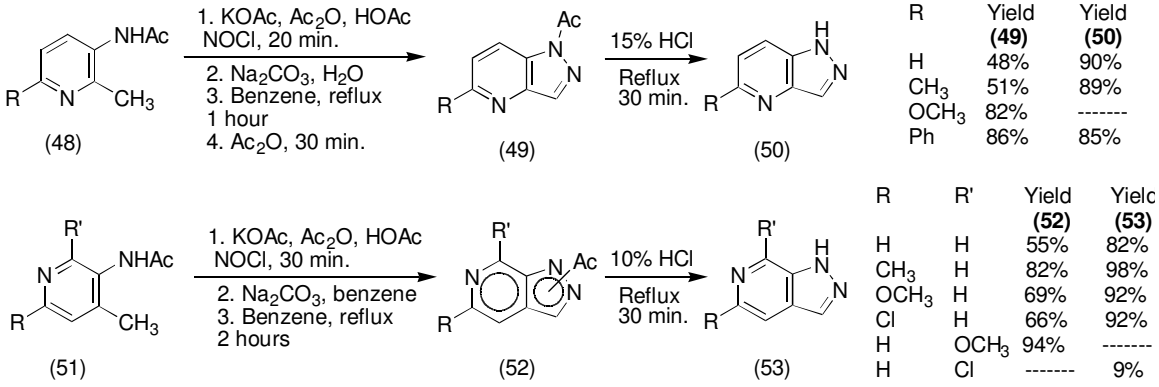


Figure 15

Bicyclic amines have also been converted to pyrazolo derivatives, such as in the synthesis of 3H-benz[*e*]indazole **(59) (Fig. 16)**. The synthesis begins with the formylation of b-naphthol **(54)** in boiling aqueous potassium hydroxide, followed by reduction with zinc in ammoniacal copper nitrate. The formylation and reduction are repeated a second time to give a mediocre yield of 1-methyl-2-naphthol[21] **(55)**. Treatment of the naphthol **(55)** with sodium bisulfite and aqueous ammonia in a hot sealed container gave 1-methyl-2-naphthylamine[22] **(56)**. The amine was converted to the acetamide[23] **(57)** in unspecified yield using acetic anhydride in acetic acid. The amide was treated with N_2O_3 in acetic acid and acetic anhydride to give N-(1-methyl-2-naphthyl)-N-nitrosoacetamide[23] **(58)**. Once dry, the nitroso derivative was heated in benzene to produce the indazole[24] **(59)**.

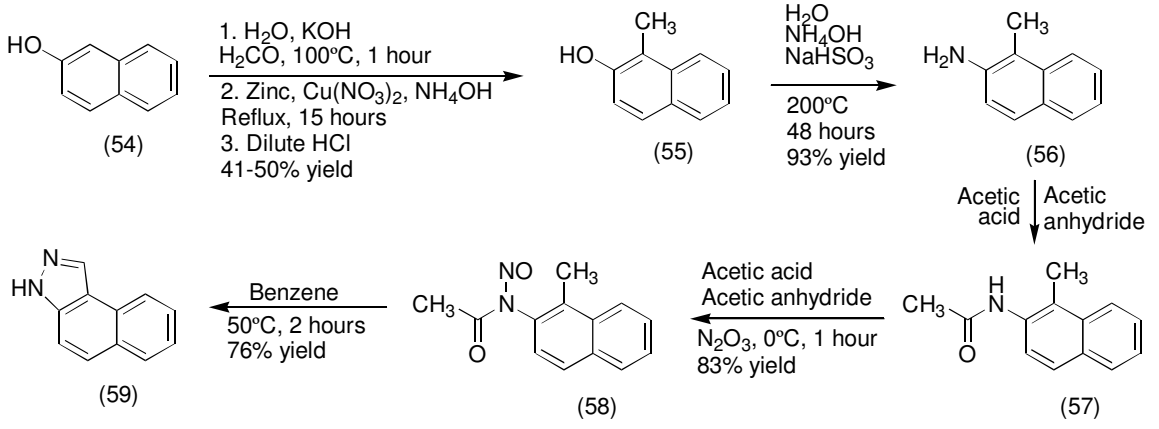


Figure 16

A study[25] has found that diazotization of 3-aminolepidine **(60)** in dilute sulfuric acid produces 3H-1,2,6-triaza-4,5-benzindene **(62)**, along with a small amount of tetrazaphenanthrene 3-oxide **(61)** **(Fig. 17)**. However, the benzindene **(62)** does not form in dilute hydrochloric acid, although the oxide **(61)** does. The 3-aminolepidine **(60)** also gave a low yield of the benzindene **(62)** after conversion to the acetamide with acetic anhydride, treatment with nitrosyl chloride, and refluxing in benzene. The structure shown for the benzindene **(62)** was tentative, and is more likely the fully aromatic tautomer.

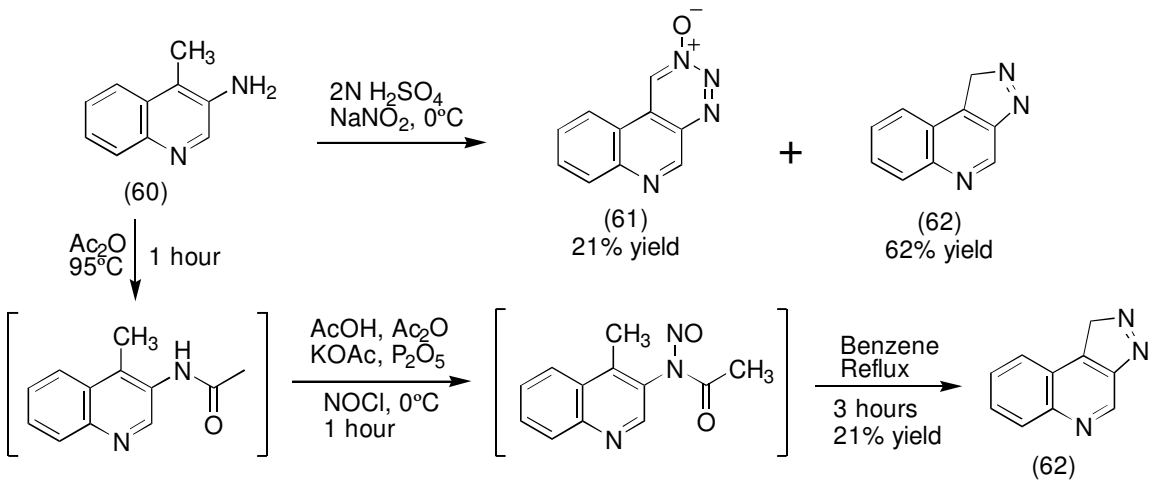
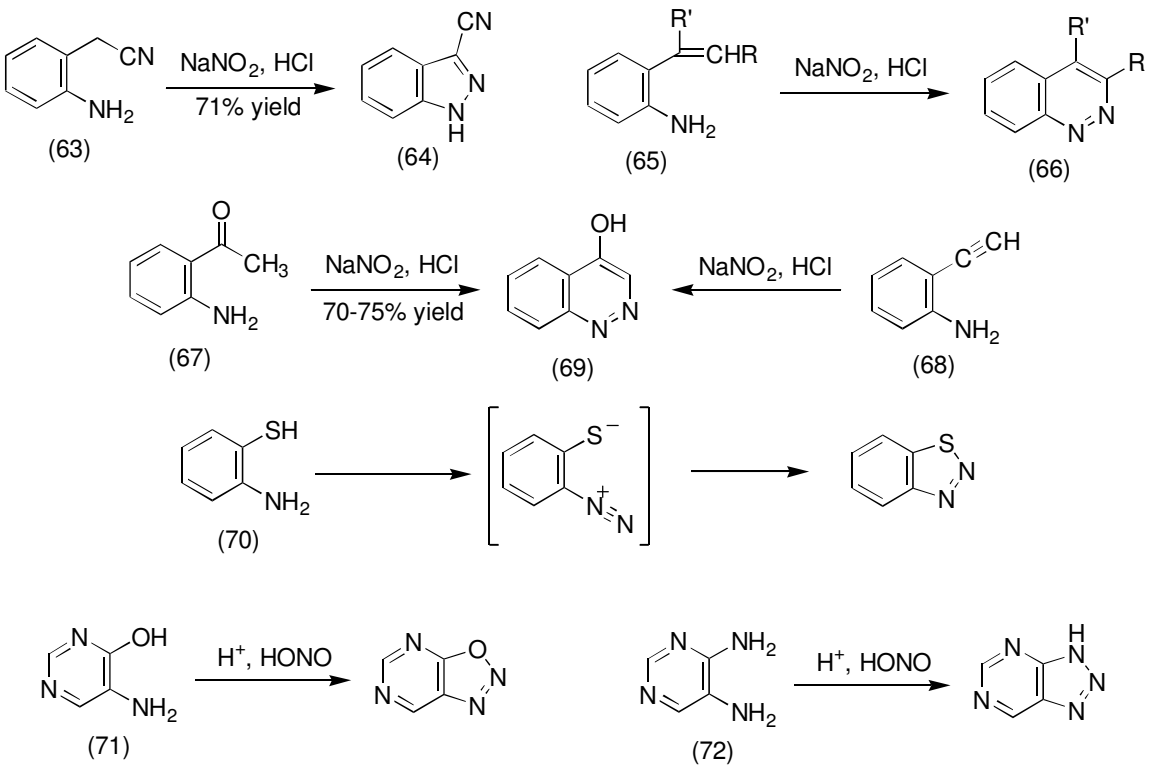


Figure 17

Cyclizations of diazonium salts come in many varieties[26]. Instead of reacting diazonium with methyl, a methylene group activated by an electron withdrawing substituent such as a nitrile may be used instead, for example in the conversion of nitrile **(63)** to 3-cyanoindazole **(64)** **(Fig. 18)**. In the Widman-Stoermer synthesis, an aminostyrene **(65)** will cyclize upon diazotization to form a cinnoline **(66)**. Either 2-aminoacetophenone **(67)** or 2-aminophenylacetylene **(68)** cyclize upon diazotization to form 4-hydroxycinnoline **(69)**. Atoms besides carbon, such as sulfur **(70)**, oxygen **(71)**, or nitrogen **(72)**, can also attack the diazonium group.


CN
NH2
(63)
NaNO2, HCl
71% yield
CN
N
N
H
(64)
R'
CHR
NH2
(65)
NaNO2, HCl
R'
R
N
N
(66)
O
CH3
NH2
(67)
NaNO2, HCl
70-75% yield
OH
N
N
(69)
NaNO2, HCl
C≡CH
NH2
(68)
SH
NH2
(70)
S−
N+
N
S
N
N
N
OH
NH2
(71)
H+, HONO
N
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N
N
N
NH2
NH2
(72)
H+, HONO
H
N
N
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Figure 18

Results and Discussion

To complete the set of experimental data for the pyrazoloisoquinoline **(104)** synthesis of Stowell[7] and Farmer[11] **(Fig. 7)**, samples of intermediates for elemental analysis needed to be prepared **(Fig. 19)**. Fortunately a convenient precursor[7], 6-chloro-5,8-dimethyl-7-nitroisoquinoline **(100)**, was available. It seemed very reluctant to react with thiophenylate in DMF, even though the corresponding bromo derivative **(165)** was known to react fine[7]. Forcing the reaction gave, after extensive analysis, the unexpected byproduct 5,8-dimethyl-6,7-bis(thiophenyl)isoquinoline **(102)**. Subsequent reading about nucleophilic aromatic substitution revealed[27] that the ease of displacement is in the order F > NO_2 > Cl, Br, I. The desired product 5,8-dimethyl-7-nitro-6-(thiophenyl)isoquinoline **(101)** was invisible during this conversion because only TLC was relied upon to detect it, and it is indistinguishable from starting material **(100)** by TLC. Fortunately, the product of the initial reaction, after removing the byproduct **(102)**, was the desired product **(101)**.

Reduction of nitroisoquinoline **(101)** by Raney nickel and hydrazine in refluxing ethanol produced 7-amino-5,8-dimethyl-6-(thiophenyl)isoquinoline **(103)** cleanly, without the feared removal of the thiophenyl group. Diazotization of the amine **(103)** in cold acetic acid with sodium nitrite gave a separable mixture of 5,11-dimethyl-[1]benzothieno[2,3-*g*]isoquinoline (6-thiaellipticine) **(105)** and the new ring system, 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)**.

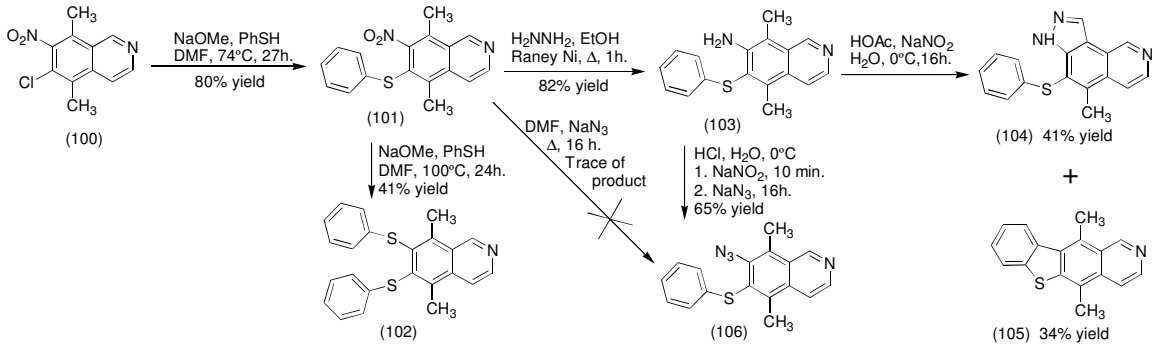


Figure 19

The vigor of nucleophilic displacement in DMF suggested that perhaps the previously sought[7] 7-azido-5,8-dimethyl-6-(thiophenyl)isoquinoline **(106)** could be prepared directly from the corresponding nitro compound **(101)**, and the reduction and subsequent perilous diazotization of **(103)** could be circumvented, but to no avail. The conditions needed to make the nitroisoquinoline **(101)** react with azide in DMF lead to a complex mixture, perhaps because thiophenyl itself can be displaced by azide.

The ratio of the products **(104)**, **(105)** is interesting **(Fig. 20)** because it provides an idea of how quickly the new ring system **(104)** forms. Switching the diazotization solvent to dilute hydrochloric acid allowed the azide **(106)** to be prepared cleanly, which was the original goal of the reaction[7]. A varying amount of starting material is left over, and it is not clear why. The sodium nitrite was dispensed accurately from a bulk solution using a quantitative syringe. In the case of aqueous hydrochloric acid the amine precipitated as its solution cooled. The solution was not dilute enough to allow all of the amine to redissolve during diazotization, causing some starting material to be recovered. In the case of acetic acid, it is the solvent which may precipitate if insufficient water is added to keep it from freezing.

When azide was added to the diazonium salt in acetic acid, the ratio of **(104)** to **(105)** reversed from about 2.7:1 to 0.9:1. While this is surprising, the ratios in hydrochloric acid (2.5:1 and 2:1) don't show this effect. Is this a fluke, or can the presence of azide influence the rates of the two cyclization reactions? Perhaps the ratio is temperature sensitive, because the diazotization had to be started before thermal equilibrium was achieved to prevent the acetic acid from freezing.

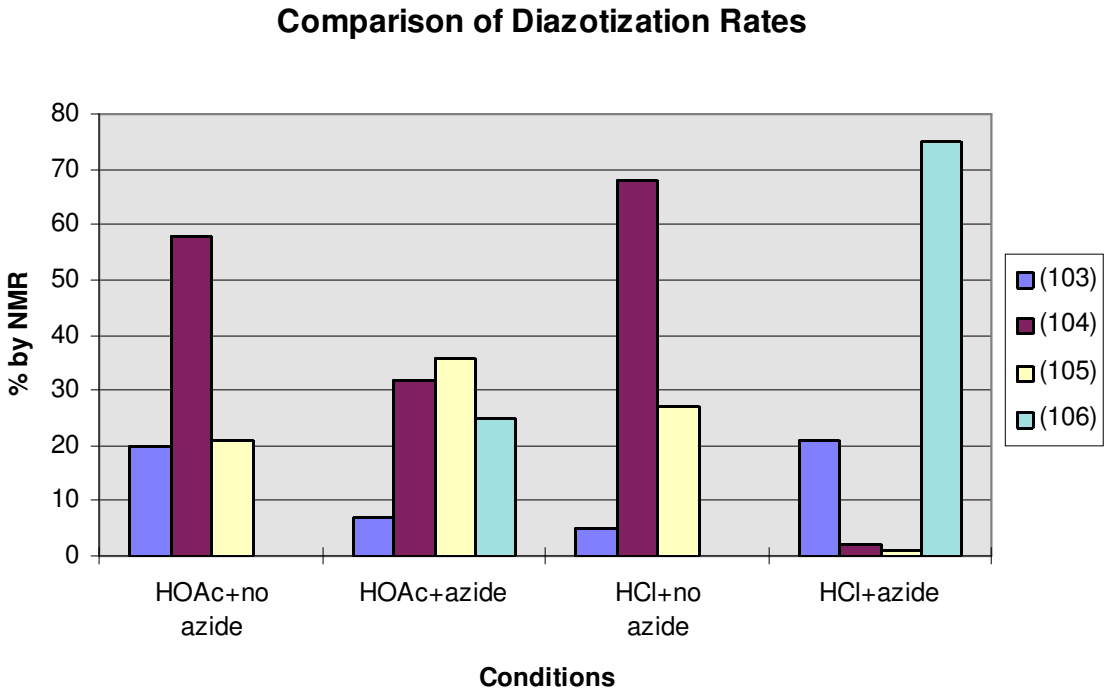


Figure 20

The expected mechanism **(Fig. 21)** for the formation of the new ring system may involve participation by the isoquinoline nitrogen, or by the substituent at the 6-position, in this case the thiophenyl group. According to the resonance forms shown, the thiophenyl group stabilizes both the diazonium group and the protonated ring nitrogen by helping to disperse their positive charges, and should facilitate cyclization. The ring nitrogen, once protonated, serves as a sink for the electron relinquished by the benzylic proton upon its departure, also causing faster cyclization. The effect these features have on the rate of cyclization can be measured by changing them one at a time in the amine and trying to cyclize it.

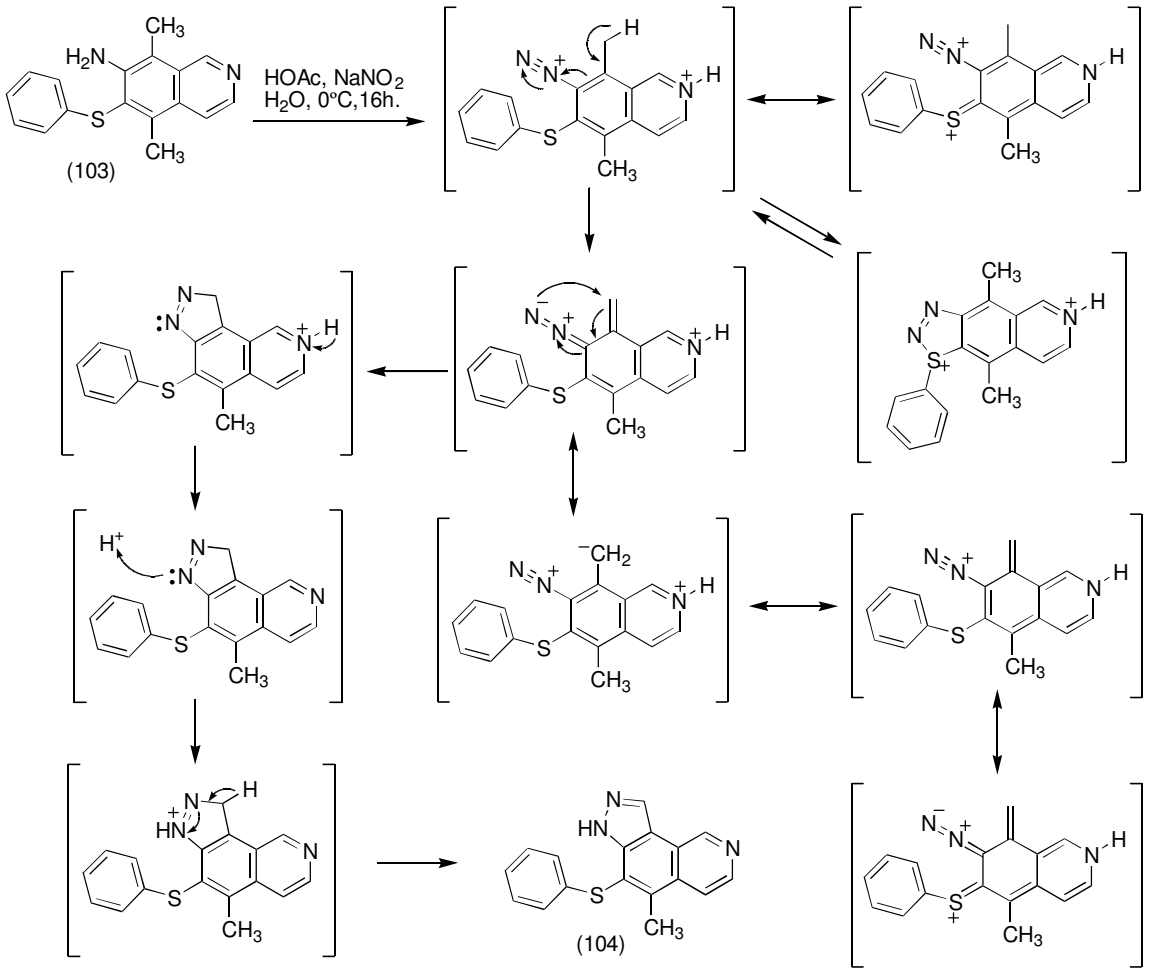
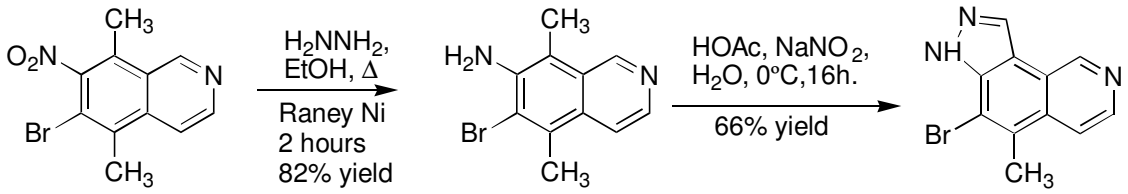


Figure 21

The easiest modification in the amine was to replace the thiophenyl group with a bromo group **(Fig. 22)** because some of the desired amine, 7-amino-6-bromo-5,8-dimethylisoquinoline[28] **(107)**, was already in hand. Bromine has lone pairs like sulfur, but is deactivating rather than activating due to induction[29]. Nevertheless, the reaction proceeded, showing that an activating substituent at the 6-position is unnecessary. More of the amine **(107)** had to be prepared for analysis from the corresponding nitroisoquinoline (**165)** by reduction with Raney nickel and hydrazine in refluxing ethanol.



(165) (107) (108)

Figure 22

To determine if a substituent at the 6-position is needed at all, 7-amino-5,8-dimethylisoquinoline **(114)** was prepared **(Fig. 23)** starting from a generous gift of 4,7-dimethylindanone[5] **(109)** already in hand. Treatment with cold fuming nitric acid quickly produced 4,7-dimethyl-6-nitroindanone **(113)**, which was reduced with great and satisfying ease by cold sodium borohydride in methanol to give the indanol **(111)**. Treatment with p-toluenesulfonic acid in refluxing benzene, while removing water, eliminated the alcohol to give the indene **(112)**. Treatment with ozone, followed by dimethyl sulfide and aqueous ammonia, gave 5,8-dimethyl-7-nitroisoquinoline **(113)** smoothly. The nitroisoquinoline **(113)** reduced surprisingly quickly with Raney nickel and hydrazine in refluxing ethanol to furnish the desired 7-amino-5,8-dimethylisoquinoline **(114)**. Diazotization in cold acetic acid indeed caused cyclization to the new compound 5-methyl-3H-pyrazolo[3,4-*h*]isoquinoline **(115)** in good yield.

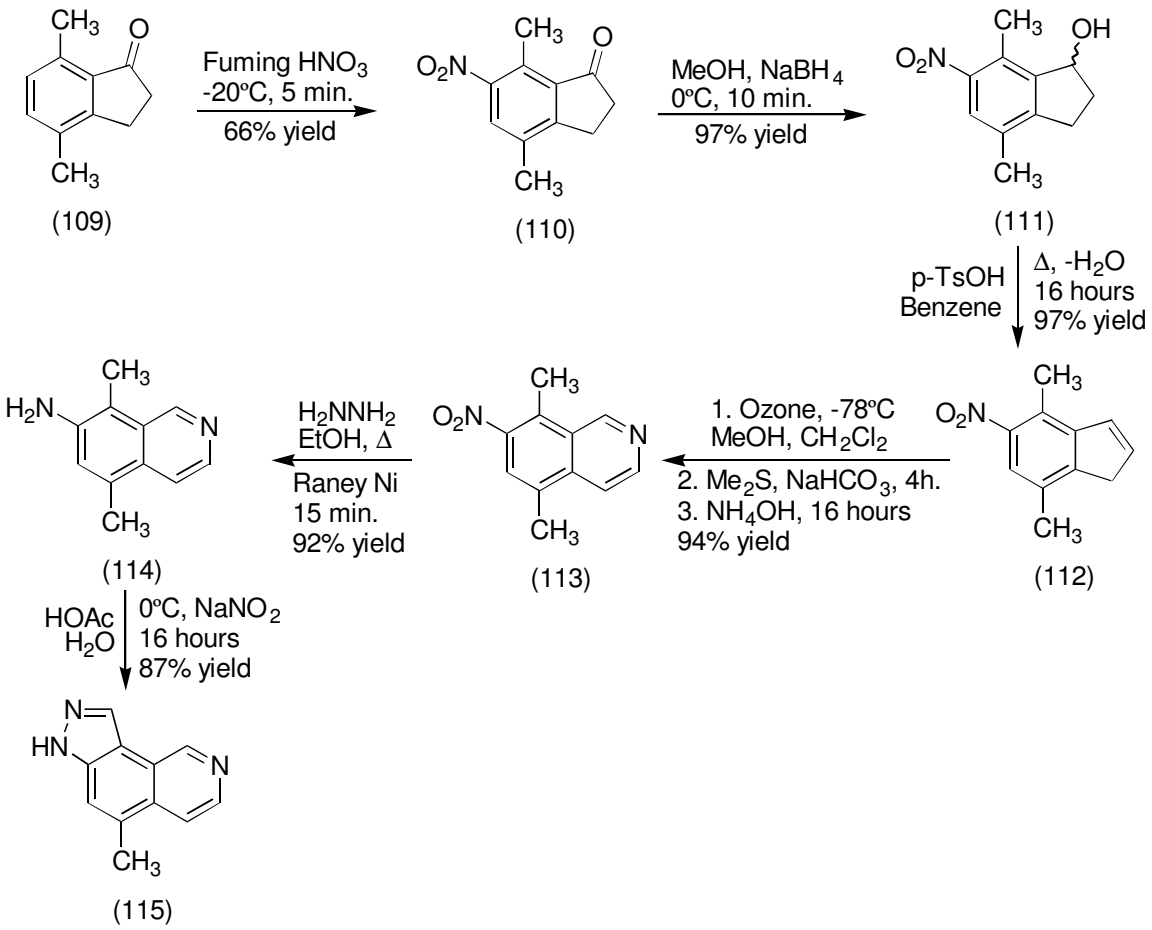


Figure 23

Now that all three 7-amino-5,8-dimethylsoquinolines had been cyclized successfully, the next question was whether the ring nitrogen was participating much in the rate of cyclization. To answer this question, derivatives of 6-amino-5,8-dimethylisoquinoline had to be prepared and their rates and yields of cyclization compared with those of their 7-amino counterparts.

One synthesis[6,14] which produces a suitable aminoisoquinoline was developed in the Miller group **(Fig. 24)**. Fortunately the intermediate 2,5-dimethylacetanilide **(116)** was on hand, which would otherwise have to be prepared from 2,5-dimethylaniline[30]. A two-phase Friedel-Crafts acylation in carbon disulfide gave a substituted propiophenone **(117)** which was then intramolecularly alkylated and hydrolyzed by heating in concentrated sulfuric acid to give 5-amino-4,7-dimethylindanone **(118)**.

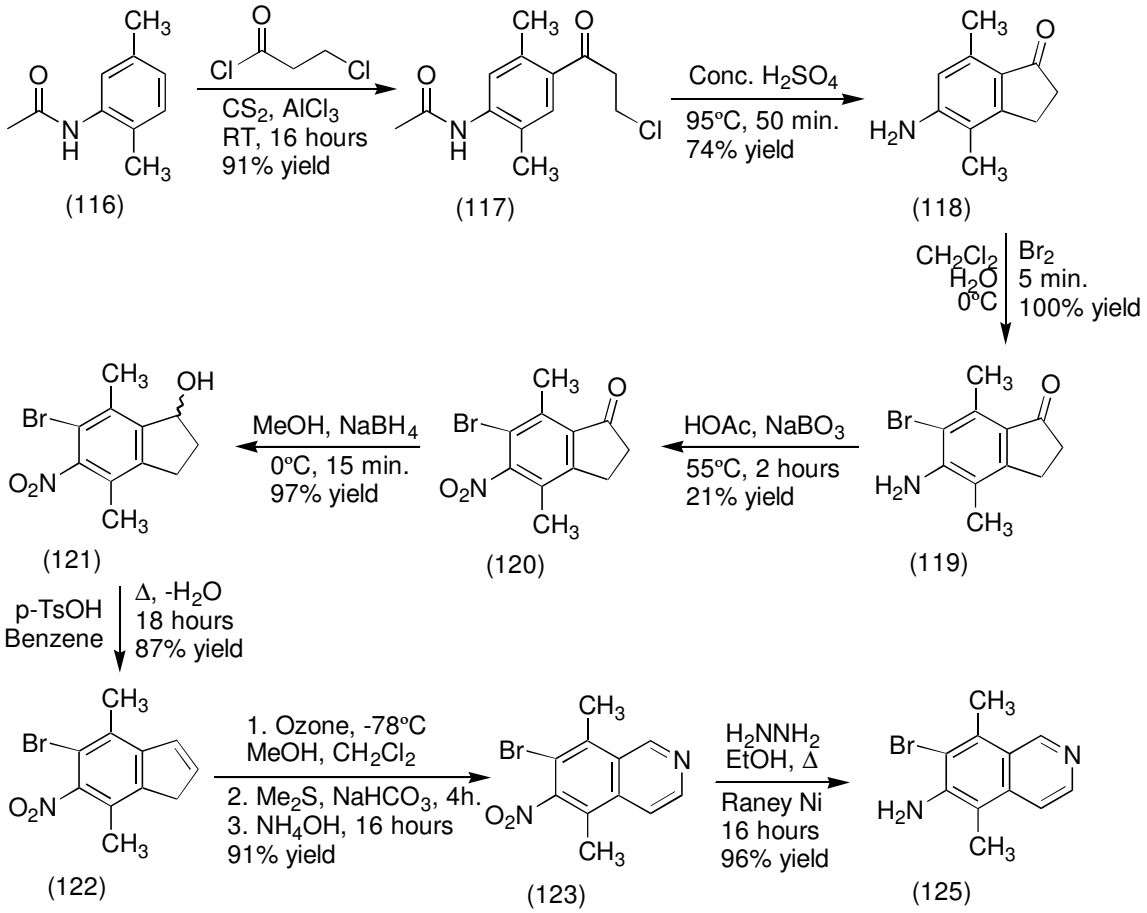


Figure 24

The cyclization of halide **(117)** to indanone **(118)** in sulfuric acid gave poor yields when first attempted on a large scale, and presented a bottleneck in the synthesis. Since the synthesis is used for ellipticine research and has been repeated several times[6,14], some time was invested optimizing the conditions. Using sets of identical reactions, and analyzing the amount of product by NMR, revealed **(Fig. 25)** that the key to a good yield was to make the reaction sufficiently dilute, while time and temperature had less effect.

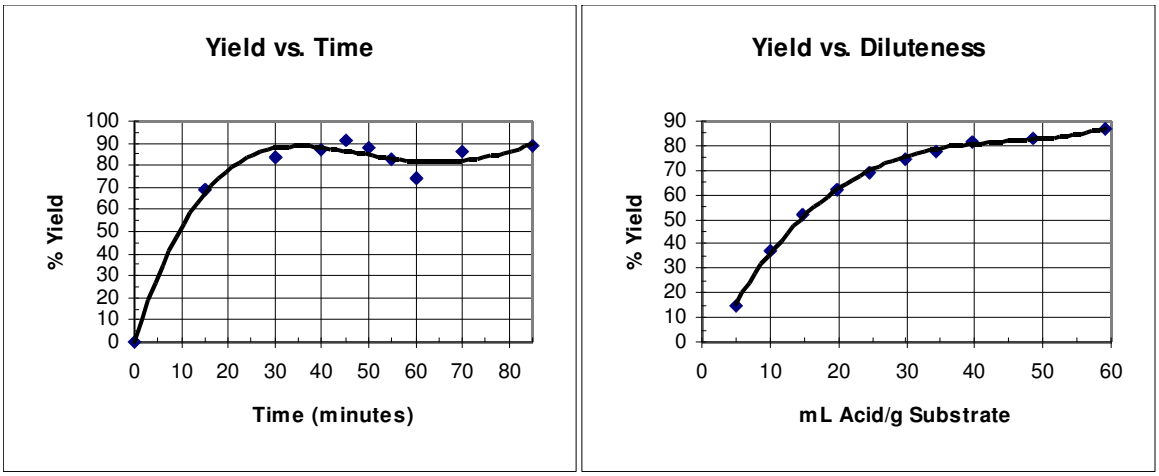


Figure 25

Brominating the 5-amino-4,7-dimethylindanone **(118)** was not expected to be a problem. Other reports[6,14] suggested that this bromination would take place in methylene chloride over hours to give a quantitative yield of pure product. Disappointingly, a precipitate of hydrobromides formed as soon as the bromine was added. The portion of starting material which formed an insoluble hydrobromide could no longer react, while the product remaining in solution over brominated. In a desperate attempt to solve this undocumented problem, water was added before the bromine to dissolve the hydrobromides which would form, and keep them in aqueous solution, allowing them continued contact with and opportunity to react with the bromine. This was a rare success, with bromination being complete in just minutes without the formation of side products.

Oxidation of the amino group of 5-amino-6-bromo-4,7-dimethylindanone **(119)** with sodium perborate gave very impure product and a low yield of pure 6-bromo-4,7-dimethyl-5-nitroindanone **(120)**. The yield of 21% is for recrystallized product. This step is now the new bottleneck in the scheme.

Reduction of the indanone **(120)** to the indanol **(121)** by sodium borohydride in cold methanol was fast and clean. Elimination of the indanol **(121)** by p-toluenesulfonic acid in refluxing benzene while removing water also proceeded smoothly to provide 5-bromo-4,7-dimethyl-6-nitroindene **(122)**. Ozonolysis followed by treatment with dimethyl

sulfide and aqueous ammonia provided the expected 7-bromo-5,8-dimethyl-6-nitroisoquinoline **(123)**. During reduction of the nitroisoquinoline **(123)** to the amine **(125)** by Raney nickel and hydrazine in refluxing ethanol, a varying amount of product was debrominated. Fortunately, in this case that side product **(126)** is useful!

Eager to prepare ellipticine **(2)** by a novel new route, intermediate **(123)** was treated, as planned, with thiophenylate in DMF **(Fig. 26)**. The product seemed to be as expected by NMR spectroscopy, and much material was wasted in repeating the reaction on a cavalier scale. For some reason reduction of the product to an amine failed. The correct identity of the product **(124)** was deduced while laying in a sunny meadow, as treatment for severe frustration, and later confirmed by several chemical tests.

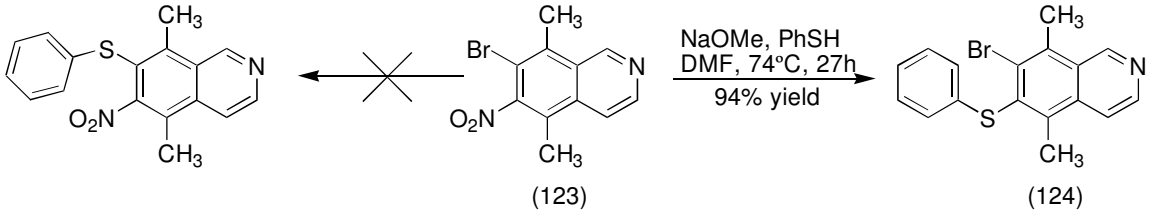


Figure 26

Comparing this reaction with the formation of 5,8-dimethyl-7-nitro-6-(thiophenyl)isoquinoline **(101)** **(Fig. 7)** shows (**Fig. 27**) that the 6-position of isoquinoline is more easily attacked by nucleophiles than the 7-position. The reactant 6-bromo-5,8-dimethyl-7-nitroisoquinoline **(165)**, which is known to produce **(101)** as shown[7], was used for this illustration so that the only remaining variable would be the position of the isoquinoline ring nitrogen. Observe how the ring nitrogen can help share the negative charge, stabilizing the transition state, if thiophenylate attacks the 6-position but not the 7-position. This stabilization appears more important than that provided by the electron withdrawing nitro group.

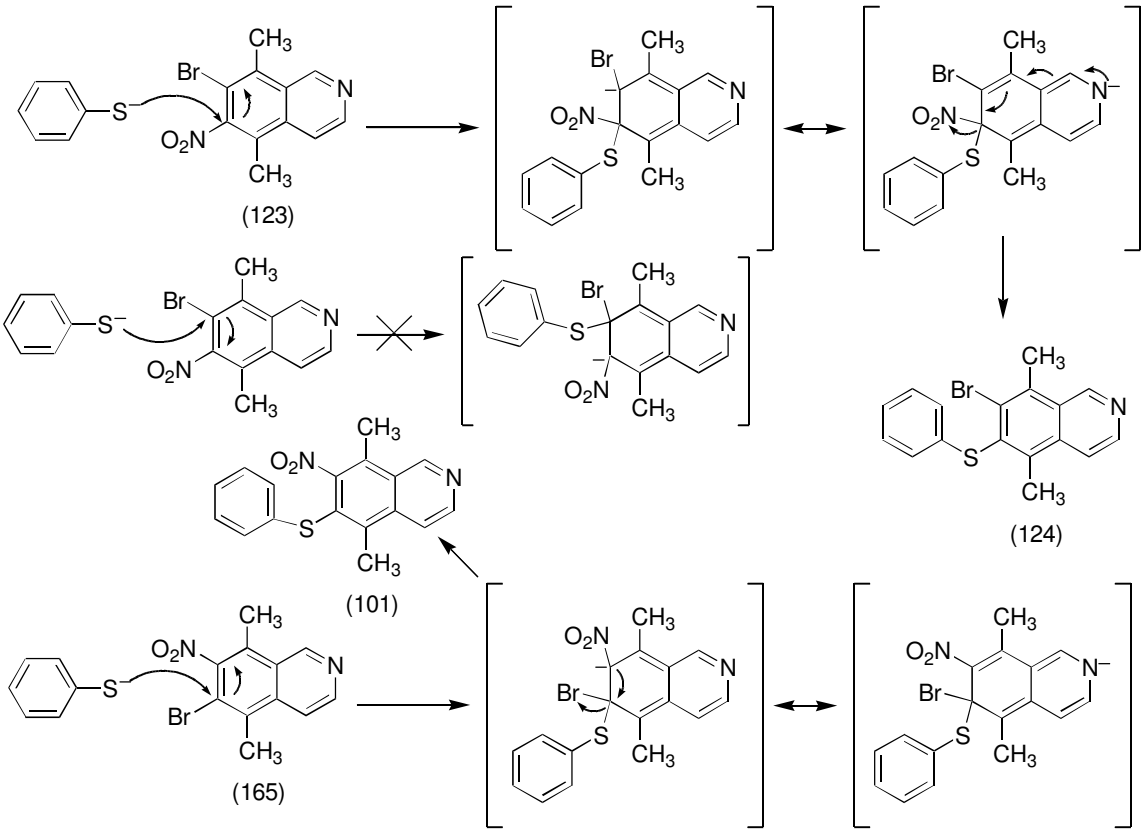


Figure 27

Thiophenylate in DMF is able to displace nitrite from even an unactivated isoquinoline at the 7-position when forced, as demonstrated by the formation of 5,8-dimethyl-6,7-bis(thiophenyl)isoquinoline **(102) (Fig. 19)**. This implied that thiophenylate might displace the bromo group from 6-amino-7-bromo-5,8-dimethylisoquinoline **(125) (Fig. 29)**. Unfortunately, thiophenylate was unable to displace the bromo group from o-bromoaniline in a test reaction **(Fig. 28)** even after days of refluxing in DMF. The test reaction involved breaking the aromaticity of a benzene ring, which admittedly takes much more energy than disrupting the aromaticity in one ring of isoquinoline[31].

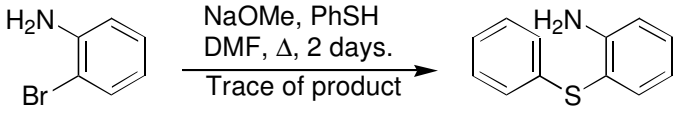


Figure 28

Fortunately a new thiolation reaction[32] presented itself **(Fig. 29)**. Poor results were obtained with 7-bromo-5,8-dimethyl-6-nitroisoquinoline **(123)**, but the corresponding amine **(125)** worked fine, producing 6-amino-5,8-dimethyl-7-(thiophenyl)isoquinoline **(128)** when refluxed in butanol with sodium thiophenylate in the presence of tetrakis(triphenylphosphine)palladium(0). The yield was much higher when the palladium catalyst was reasonably fresh. Similar treatment of amine **(125)** with sodium 4-methoxythiophenylate gave the corresponding 6-amino-5,8-dimethyl-7-(4'-methoxythiophenyl)isoquinoline **(135)**. Diazotization of either amine **(128)**, **(135)** in very dilute hydrochloric acid gave clean conversion to the corresponding azide **(131 or 136)**, and given the purity of the crude products the yields are surprisingly low. Cyclization of the either azide **(131)**, **(136)** at 215°C in decalin gave 5,12-dimethyl-6H-pyrido[4,3-*b*]phenothiazine **(132)** or 5,12-dimethyl-9-methoxy-6H-pyrido[4,3-*b*]phenothiazine **(137)** respectively in yields much higher than expected[8].

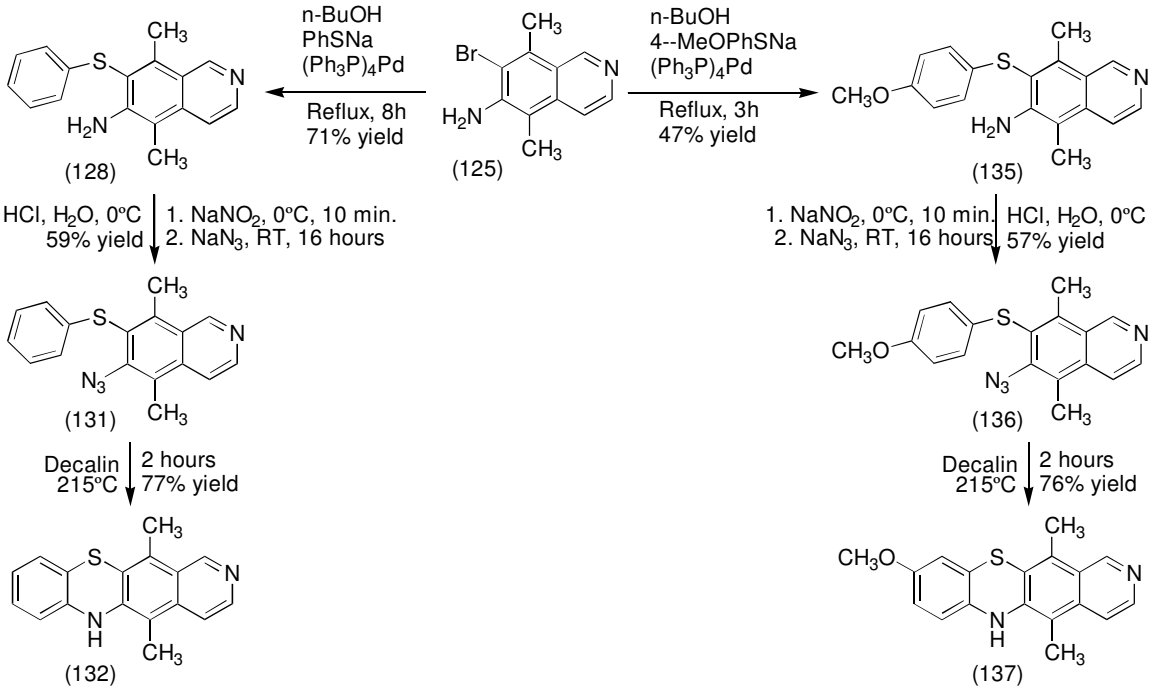


Figure 29

The position of the methoxy group on 5,12-dimethyl-9-methoxy-6H-pyrido[4,3-*b*]phenothiazine **(137)** was verified by X-ray analysis[12] **(Fig. 30), (Appendix B)**. This analysis showed that the rearrangement of the thiophenyl moiety of the cyclizing azide **(136)** took place as expected and that the methoxy group of the phenothiazine **(137)** should occupy the desired 9-position of ellipticine **(2)** upon sulfur extrusion.

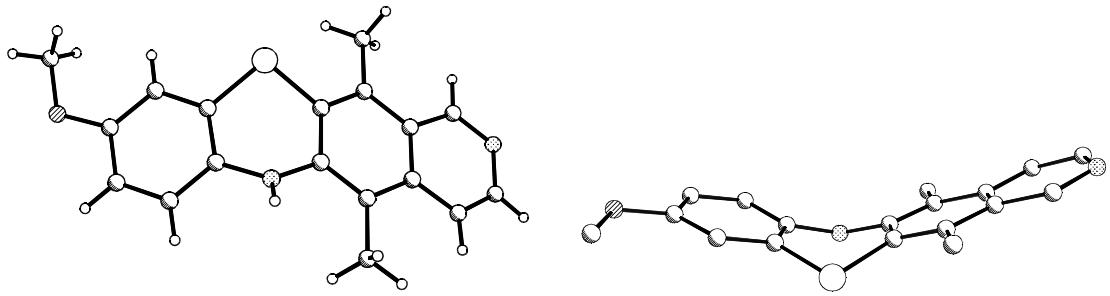


Figure 30

A general reaction[33] to insert sulfur between aromatic rings intramolecularly **(Fig. 31)** promised a quick route to more 5,12-dimethyl-6H-pyrido[4,3-*b*]phenothiazine **(132)**, and eventually its methoxy derivative **(137)**, starting with plentiful[34] 6-bromo-5,8-dimethylisoquinoline **(133)**. Heating **(133)** with aniline in the presence of copper-bronze powder, potassium carbonate, and catalytic iodine gave poor conversion to the 6-anilino-5,8-dimethylisoquinoline **(134)**, which was difficult to separate from unreacted starting material, even by acid extraction. Once purified, the amine **(134)** was refluxed with sulfur and iodine in o-dichlorobenzene. Comparing the complex mixture obtained with genuine pyridophenothiazine **(132)** made it clear that none of the desired product was present.

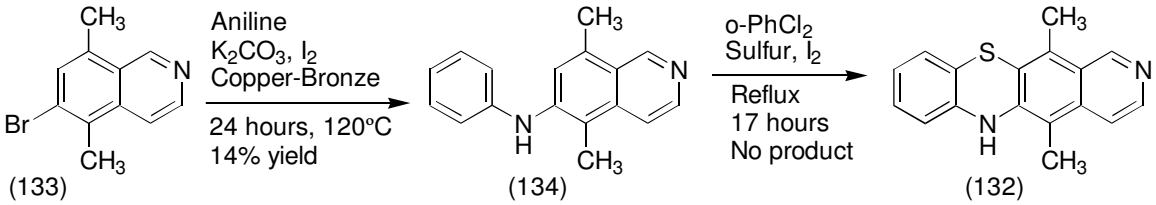


Figure 31

With ellipticine **(2)** just one step away from the pyridophenothiazine **(132)** now in hand, the essential sulfur extruding reaction was studied carefully. The first unwelcome discovery was that the indispensable reducing agent, bis(cycloocadienyl)nickel(0) **(73)**, was twice as costly as gold[35], and two equivalents of it had to be used. Ugly surprise number two was unveiled as the fresh, yellow **(73)** turned black after being sealed in ampules under argon so as to protect it and make it last!

A second bottle, purchased with great reluctance, was monomaniacally rushed to the freezer of a helium filled glove box. Five test reactions using phenothiazine **(138)** were performed with great care, with more precautions taken with each failure. All gave roughly the same result according to NMR: 22 to 33% conversion to inseparable carbazole **(139)** **(Fig. 32)**. The ellipticine precursors **(132)** and **(137)** were saved in case a better sulfur extrusion method should someday become available.

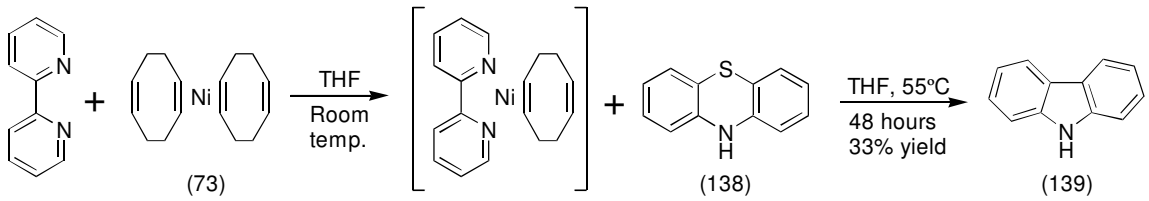
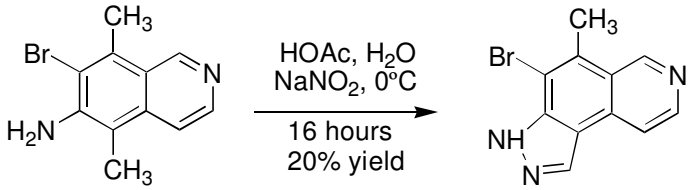


Figure 32

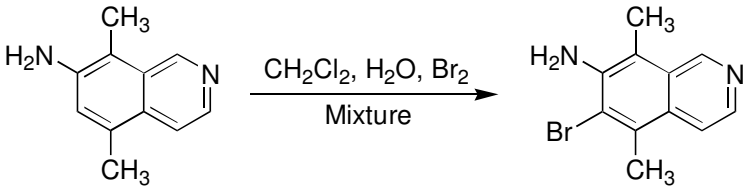
With the approach to ellipticine through pyridophenothiazines exhausted, attention was returned to the formation of pyrazoloisoquinolines. The 6-amino-7-bromo-5,8-dimethylisoquinoline **(125)** cyclized when diazotized in cold acetic acid **(Fig. 33)** to give 6-bromo-5-methyl-3H-pyrazolo[4,3-*f*]isoquinoline **(127)**, a derivative of a new ring system, in surprisingly poor yield (20%). The product **(127)** is the only derivative of either pyrazoloisoquinoline **(Fig. 44)** which precipitates from the reaction mixture. The only solvent found which will produce concentrated enough solutions of the pyrazoloisoquinolines for ^{13}C NMR is acetic acid-d_4, but with **(127)** even this solvent is barely adequate. Nitrous acid is known to evaporate over time[36], and perhaps this evaporation is competitive with the diazotization of amine **(125)**.



(125) (127)

Figure 33

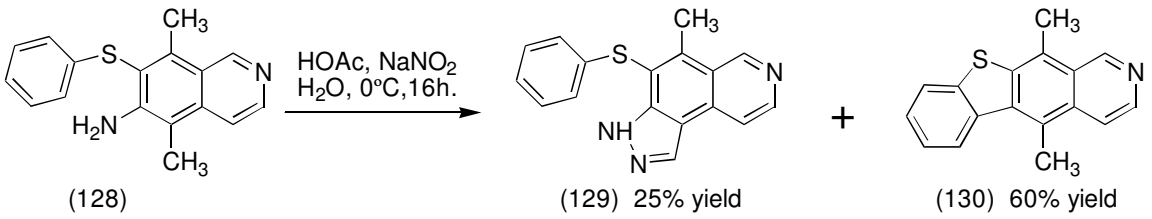
In response to chagrin that so much 7-bromo-5,8-dimethyl-6-nitroisoquinoline **(123)** was squandered, a quick route to the corresponding amine **(125)** was tested **(Fig. 34)**. A solution of 7-amino-5,8-dimethylisoquinoline **(114)** in methylene chloride was brominated in the presence of water, using the conditions which worked so well for the bromination of 5-amino-4,7-dimethylindanone **(118)**. Unfortunately only a complex mixture was obtained in this case, perhaps because the 6-position of isoquinoline is known to be less nucleophilic than the 7-position[37].



(114) (107)

Figure 34

Another opportunity for a reaction rate comparison has presented itself. How fast is the formation of pyrazoloisoquinoline **(129) (Fig. 35)** compared with its isomer **(104) (Fig. 19)**? The Pschorr cyclizations which gave rise to isothiaellipticine **(130)** and thiaellipticine **(105)** should have similar rates because they don't require participation from the isoquinoline ring, which is what changed.



(128) (129) 25% yield (130) 60% yield

Figure 35

From inspection it is clear that **(104)** forms more readily than **(129)**. More precisely, given that **(105)** and **(130)** form at a similar rate, then:

$$\textbf{(104)}\ \text{forms}\ \frac{\left(41\%\ \text{of}\ (104) \big/ 34\%\ \text{of}\ (105)\right)}{\left(25\%\ \text{of}\ (129) \big/ 60\%\ \text{of}\ (130)\right)} = 2.9\ \text{times faster than}\ \textbf{(129)}.$$

It feels good to use a common precursor for different syntheses, and producing the next pyrazoloisoquinoline **(144)** for the table (**Fig. 44**) presented such an opportunity **(Fig. 36)**. 5-Amino-4,7-dimethylindanone **(118)** was oxidized to the nitroindanone **(140)** using sodium perborate in acetic acid, but the yield given is for crude material which was quite impure. Once purified, the indanone **(140)** was reduced by sodium borohydride in cold methanol to give indanol **(141)** in excellent yield. Elimination by p-toluenesulfonic acid in refluxing benzene with removal of water gave 4,7-dimethyl-6-nitroindene **(142)** in very good yield. Sequential treatment of the indene with ozone, dimethyl sulfide, and aqueous ammonia produced 6-nitro-5,8-dimethylisoquinoline **(143)** in good yield. Reduction by Raney nickel and hydrazine in refluxing ethanol gave a record yield of the amine[38] **(126)**. Diazotization of **(126)** in cold acetic acid gave **(144)** in a higher yield than the previous two 6-aminoisoquinolies would have predicted.

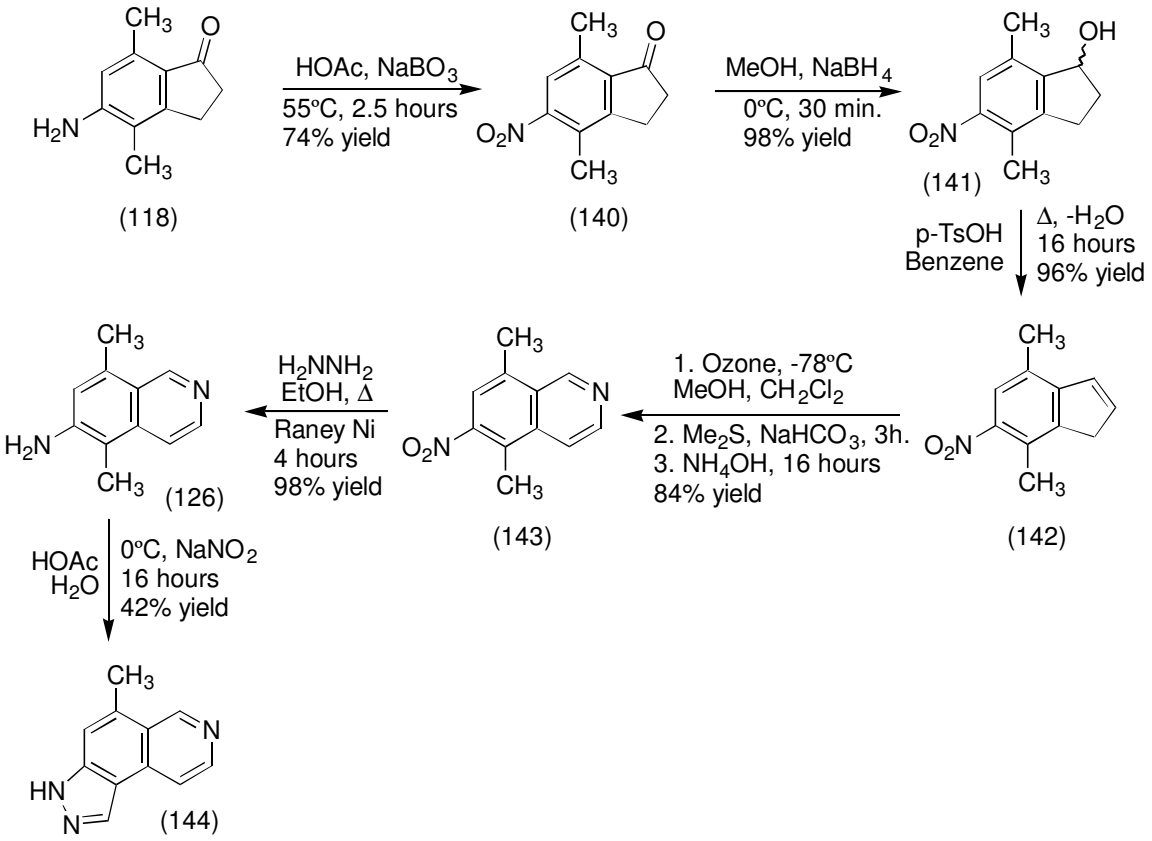


Figure 36

Assuming that the diazonium salts of 7-amino-5,8-dimethylisoquinoline **(114)** and its isomer **(126)** (**Fig. 37**) react more quickly with azide than they cyclize, it should be possible to measure their rates of cyclization by treating them with azide at varying times during the reaction. By varying the acidity independently, the rates of cyclization in different strengths of acid can be measured, unless the rates are not too great or small. Batches of nine reactions were run, each batch using the same amine and solvent, varying only the time before quenching with azide.

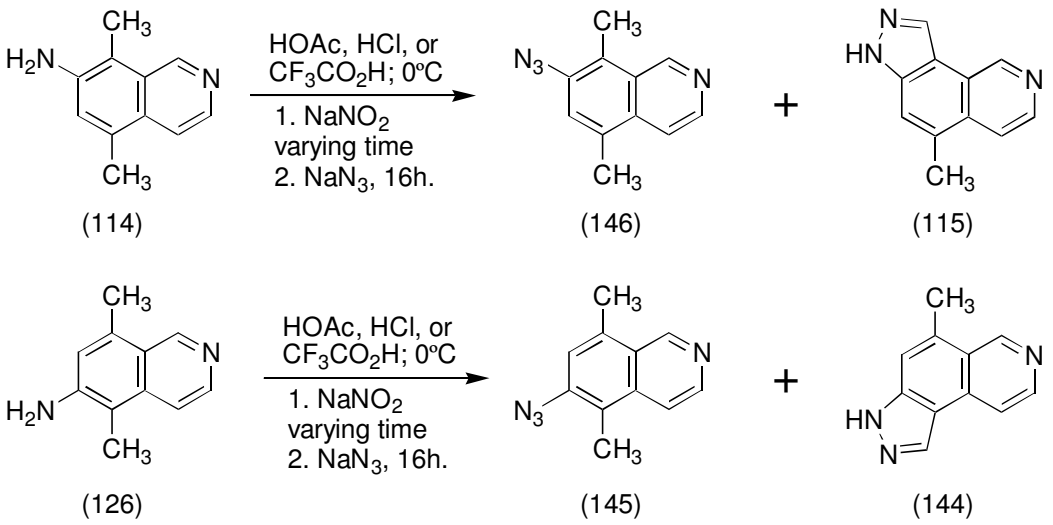


Figure 37

The reactions in acetic acid **(Fig. 38)** show 7-amino-5,8-dimethylisoquinoline **(114)** diazotizing faster than 6-amino-5,8-dimethylisoquinoline **(126)**, and cyclizing faster also, as predicted by the thiophenyl derivatives **(103) (Fig. 19)** and **(128) (Fig. 35)**. After 4096 seconds (68 minutes), the yield of 5-methyl-3H-pyrazolo[4,3-*f*]isoquinoline **(144)** is 18%, while after the same time, 5-methyl-3H-pyrazolo[3,4-*h*]isoquinoline **(115)** has formed in 33% yield, so **(115)** forms about 1.8 times faster than **(144)**. Likewise after one second, 6-azido-5,8-dimethylisoquinoline **(145)** has formed in 23% yield, while the yield of 7-azido-5,8-dimethylisoquinoline **(146)** is 56%, so **(114)** diazotizes about 2.5 times faster than **(126)**. Even though azide may not react with the diazonium salts on this short a time scale, the nitrous acid is destroyed by azide[39] very quickly, so that continued diazotization is halted. The slow diazotization in acetic acid is surprising, especially in contrast to the instant diazotization in HCl and TFA.

The stability of the diazonium salts in HCl and TFA was surprising in light of the 68% yield of 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)** shown in **(Fig. 20)**. Having a thiophenyl group in the 6-position is the only difference which made cyclization in strong acid possible.

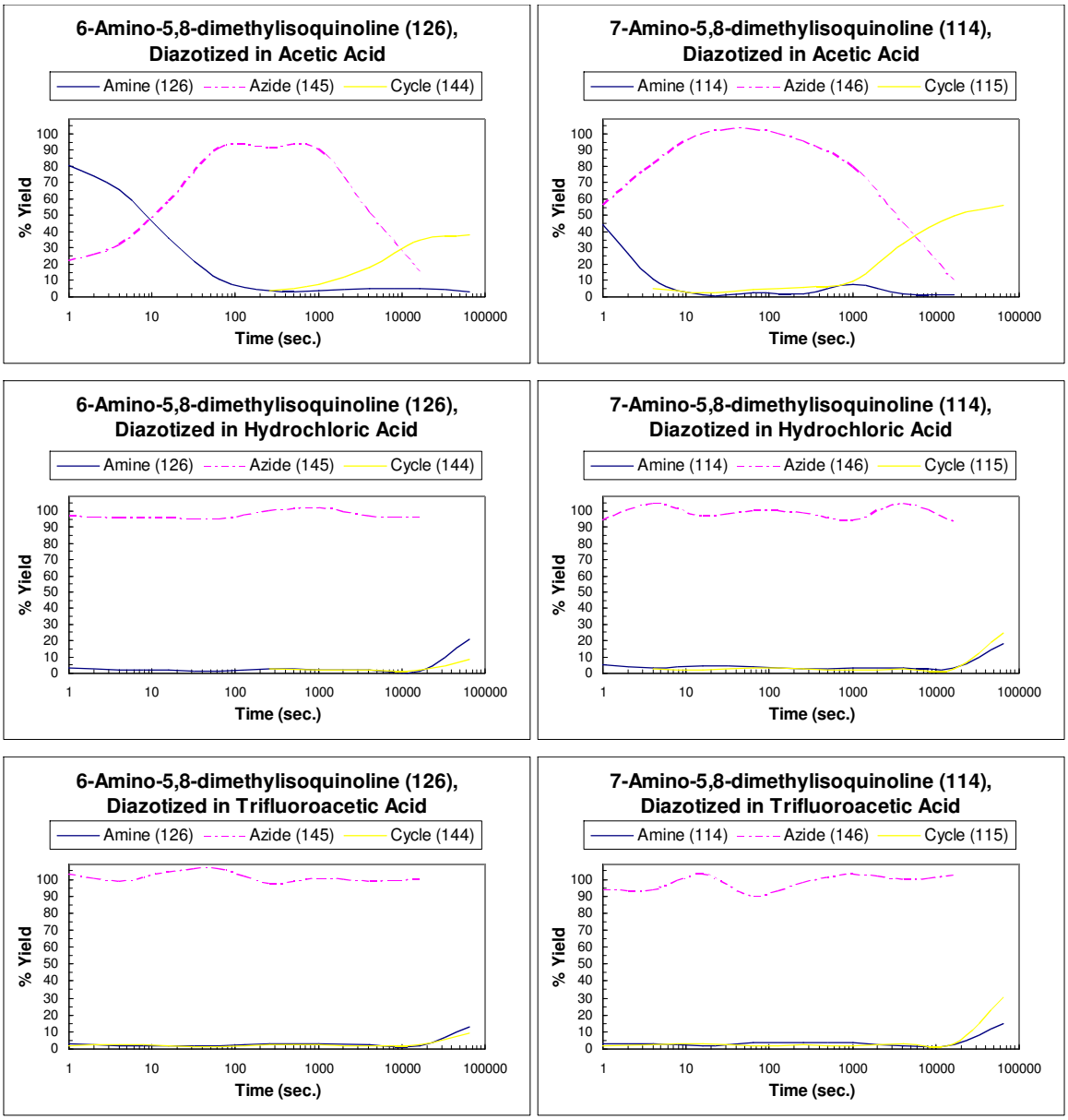


Figure 38 (Rates of Cyclization Compared)

The fluctuations in the measured yield of azide were disappointing. Likely causes were either low accuracy in the GC syringe used for measurement, or in the integration of the NMR spectrum. Weaker acid, and therefore stronger base, seems vital to the formation of prazoloisoquinolines, as demonstrated by their formation in only acetic acid when quenched with azide. The formation of pyrazoloisoquinolines in the HCl and TFA reactions that were quenched with ammonia instead of azide apparently formed in the few

minutes between quenching and extraction. The amine recovered from these mixtures probably resynthesized by displacement of diazonium by ammonia - a known reaction[40].

Finally it is necessary to make the prototypes of these new pyrazoloisoquinolines. An enticing starting point would be nitration[41] of 8-methylisoquinoline **(147)**, a sample of which was available[42], if only some of the nitration would occur at the 7-position. Alas, cold sulfuric acid containing potassium nitrate converted **(147)** to the undesired 8-methyl-5-nitroisoquinoline **(148) (Fig. 39)** which is the more likely product given the greater nucleophilicity of isoquinoline at the 5-position rather than the 7-position[37]. The identity of the product was determined using a Nuclear Overhauser Effect (NOE) experiment. Irradiating the methyl peak caused a 13% increase in integration for the most upfield doublet, showing it to correspond to the ortho hydrogen at the 7-position of **(148)**.

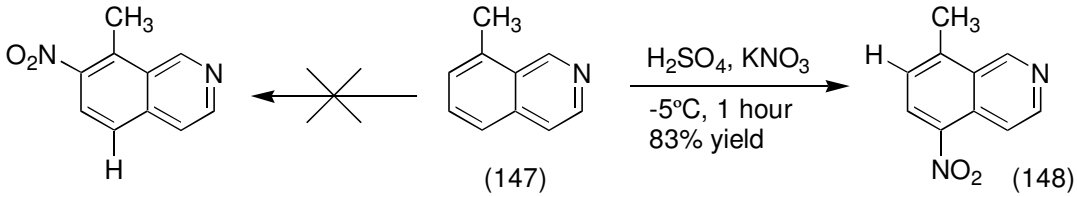


Figure 39

Fortunately a very suitable precursor, 3-amino-2-methylbenzyl alcohol **(149)**, for a more selective route **(Fig. 40)**, was commercially available. Acetylation of **(149)** by acetic anhydride in ethanol gave the amide[43] **(150)** quickly, cleanly, and simply. The risk of esterifying the benzyl alcohol was eliminated by choosing ethanol as the solvent, and by never heating the reaction. The 3-acetamido-2-methylbenzyl alcohol **(150)** was oxidized to the aldehyde **(151)** by pyridinium chlorochromate in acetone, quenching with isopropyl alcohol when complete. Condensation[44] of the aldehyde **(151)** with refluxing aminoacetaldehyde diethyl acetal gave good conversion to the imine **(152)**. Cyclization of **(152)** in hot sulfuric acid containing phosphorous pentoxide gave very poor yield of very impure 7-amino-8-methylisoquinoline **(153)**, as expected[45]. Fortunately, diazotization of **(153)** in cold acetic acid gave the final product, 3H-pyrazolo[3,4-*h*]isoquinoline **(154)**, in unexpectedly good yield.

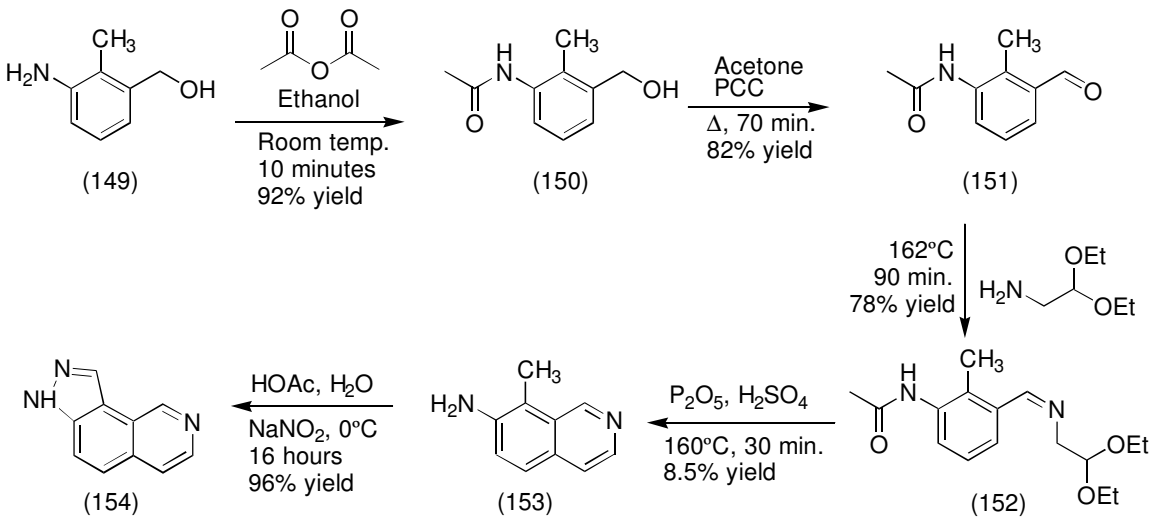


Figure 40

Not all of the 3-amino-2-methylbenzyl alcohol **(149)** was used up, so a route was sought which would turn it into the last needed 6-amino-5-methylisoquinoline **(163)**. An elegant possibility (**Fig. 41**), if the intermediate 3-amino-2-methylphenethylamine **(74)** could be prepared, would be the time-tested Bischler Napieralski reaction[46] followed by dehydrogenation to give the desired amine **(163)**.

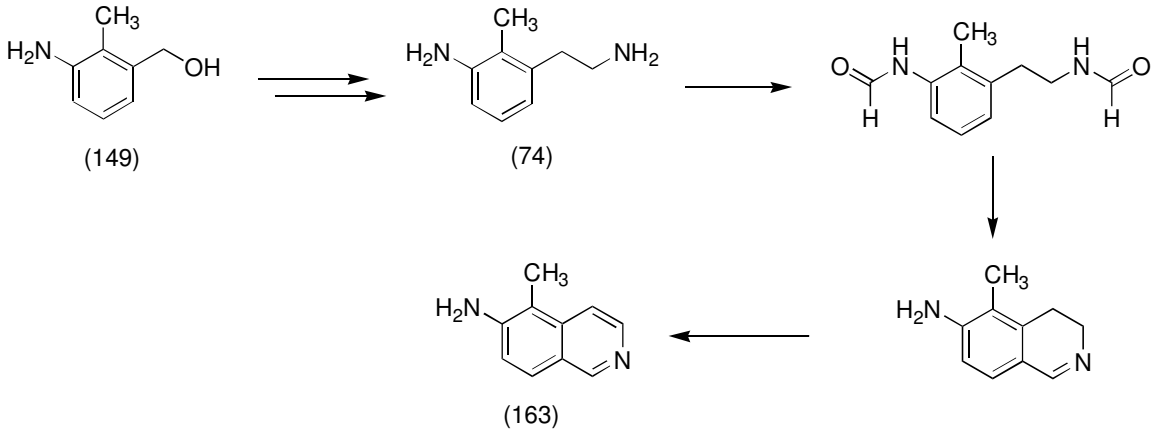


Figure 41

Many grams of precious 3-acetamido-2-methylbenzyl alcohol **(150)** were sacrificed in vain trying to prepare intermediates to the desired phenethylamine **(74)**, but to no avail **(Fig. 42)**. New nitrile syntheses were attempted[47,48], with and without protecting the amine. In one case, mistakenly thinking the alcohol **(150)** had been changed, reduction of the expected nitrile by hydrogen and palladium in ethanolic hydrochloric acid was attempted only to produce 2,3-dimethylacetanilide **(156)**.

A second promising reaction[48] converted the alcohol **(150)** into the benzyl chloride before converting it into 3-acetamido-2-methylphenylacetonitrile **(155)**. In this case the starting material **(150)** would not dissolve in CCl_4 for the first part of the reaction, but adding DMSO prematurely would oxidize the PPh_3 and prevent formation of the halide. The product would sometimes disappear from the reaction mixture, and even when it remained, it was inseparable from Ph_3PO.

Condensation of benzaldehyde derivatives with nitromethane (the Henry reaction)[49] is usually very reliable[50], but it gave no major product from 3-acetamido-2-methylbenzaldehyde **(151)** despite trying either acetic acid or nitromethane as solvent. Had the nitrostyrene **(157)** formed it might have been hydrolyzed and reduced to provide 3-amino-2-methylphenethylamine **(74)**.

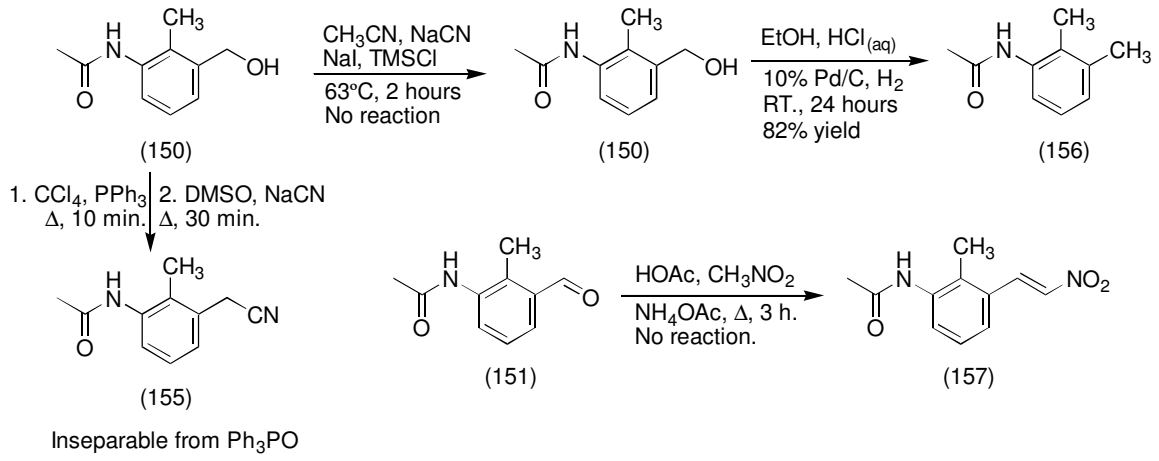


Figure 42

Turning to the literature, a procedure[51] was discovered which would get about halfway to the desired 6-amino-5-methylisoquinoline **(163)** **(Fig. 43)** using the 3-

acetamido-2-methylbenzaldehyde **(151)** already in hand! Condensation of the aldehyde with malonic acid in refluxing pyridine, with piperidine as a catalyst, gave the corresponding cinnamic acid **(158)**. The acid was treated with ethyl chloroformate and triethylamine in acetone, followed by sodium azide to give 3-acetamido-2-methylcinnamoyl azide **(159)**. Starting material is recovered from these first two steps, and the excellent yields based on recovered starting material are shown. The azide **(159)** was heated in diphenyl ether at 240°C to quickly produce 6-acetamido-5-methylisoquinolin-1(2H)-one **(160)**, which is the last compound from this synthesis that appears in the literature.

Conversion of **(160)** to the chloroisoquinoline **(161)** in refluxing phosphorous oxychloride is traditionally done over hours[52], but using such reaction times in this case led to substantial insoluble side product. Progressively halving the reaction time eventually gave reasonable yield and purity, and demonstrated that the long reaction times can be unnecessary.

Fortunately, the 1-position of isoquinoline is the easiest[53] to reduce a chlorine atom off of using hydrogen and palladium, and 6-acetamido-5-methylisoquinoline **(162)** was obtained without difficulty. Triethylamine was used instead of the usual potassium hydroxide[54] to insure that the chloro group would not be displaced by hydroxide. The amide **(162)** was hydrolyzed efficiently[51] in refluxing ethanolic hydrochloric acid to give 6-amino-5-methylisoquinoline **(163)**. The coveted amine **(163)** was diazotized in cold acetic acid to give 3H-pyrazolo[4,3-*f*]isoquinoline **(164)** in lower yield than its isomeric amine **(153)**, just as predicted by the three derivatives of each **(Fig. 44)**.

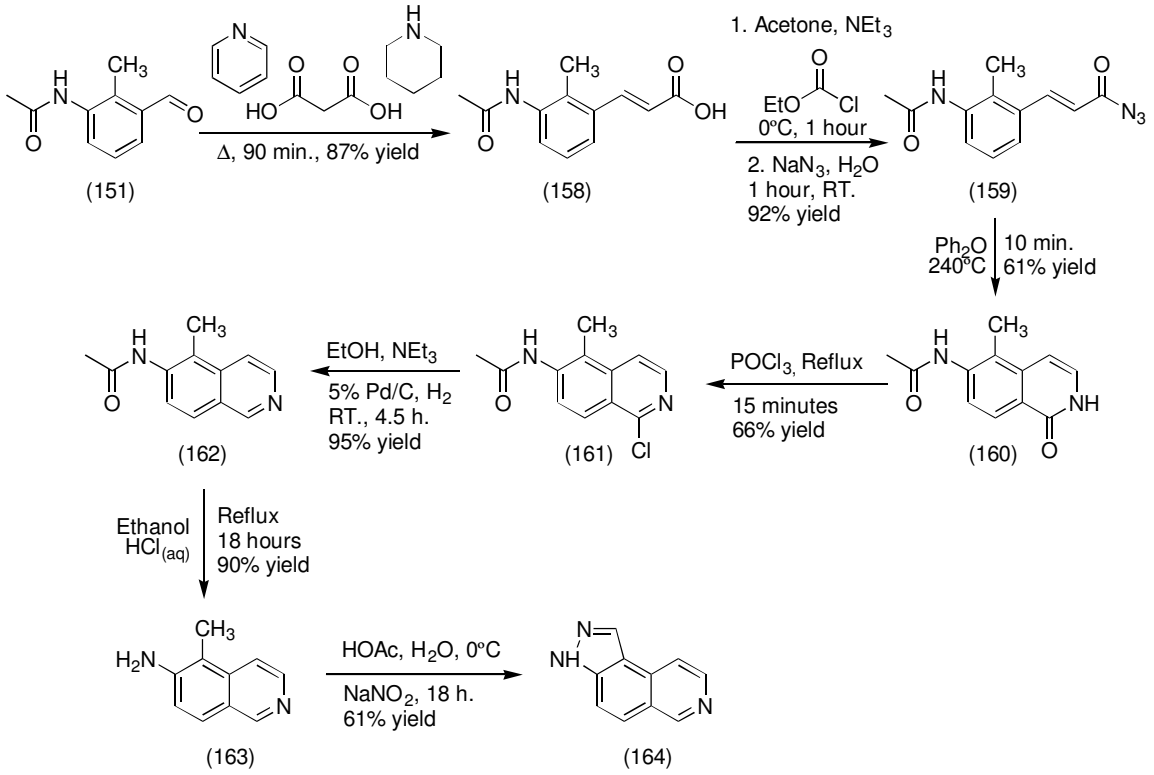


Figure 43

In all aminoisoquinolines cyclized, the 7-amino series cyclized in better yield, and probably faster, than the 6-amino **(Fig. 44)**.

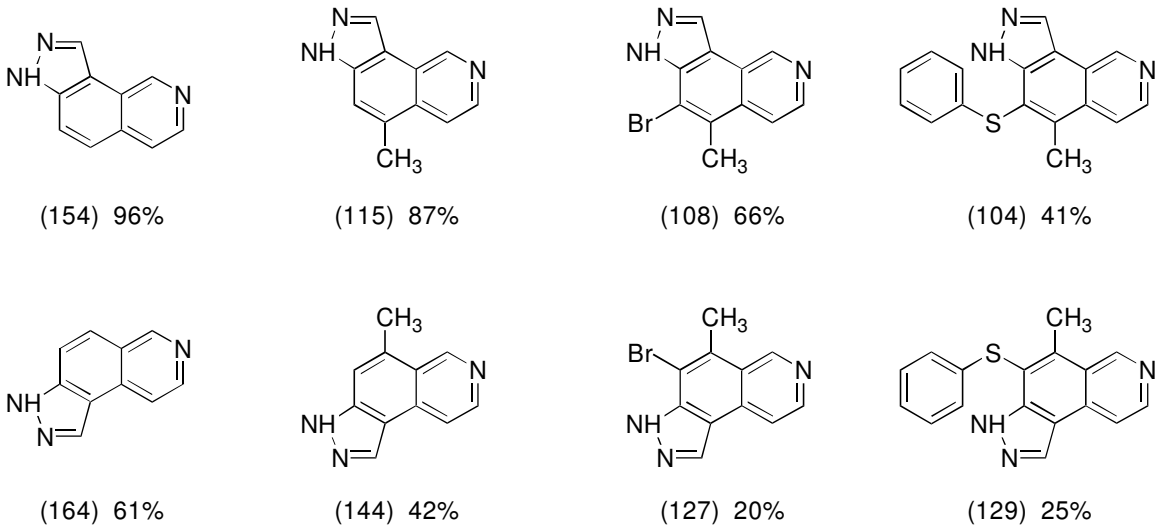


Figure 44

Why does the position of the isoquinoline nitrogen affect the rate of cyclization? For cyclization to occur, the methyl group to be reacted must first lose a hydrogen **(Fig. 45)**. Only when the methyl is in the 8-position, rather than the 5-position, can the isoquinoline nitrogen participate in its deprotonation.

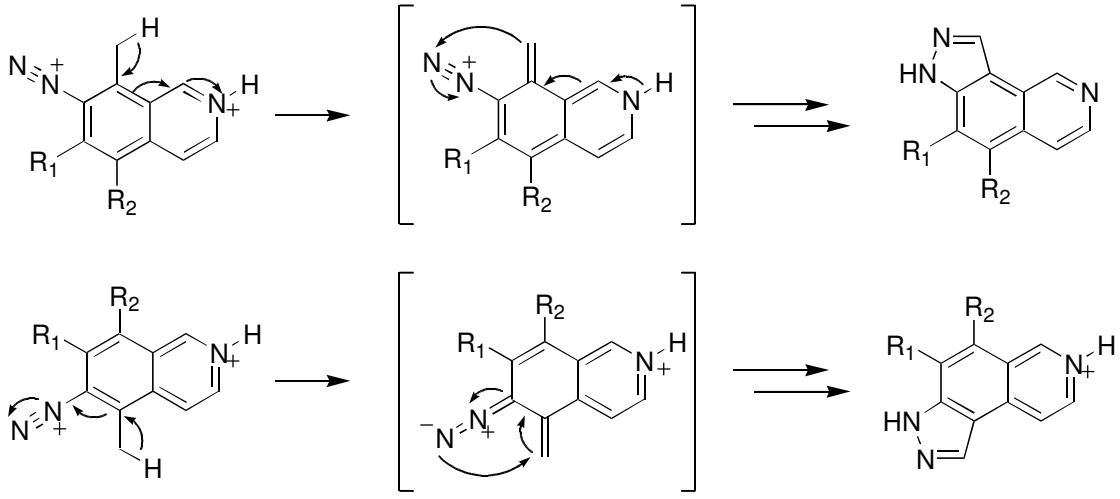


Figure 45

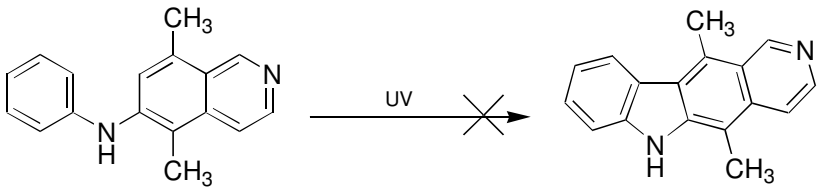
Why then do 6-amino-5-methylisoquinolines cyclize at all? Even o-toluidine is known to cyclize in low yield under these conditions **(Fig. 11)**, but having an electron withdrawing group para to the diazonium group increases the yield greatly[26], possibly by increasing the reactivity of the diazonium group. When 6-amino-5-methylisoquinoline **(163)** is diazotized in acid, the protonated ring nitrogen would serve to withdraw electron density from the diazonium group, facilitating cyclization. To verify that the isoquinoline ring nitrogen is facilitating cyclization, 1-methyl-2-naphthylamine[22] **(56)**.**(Fig. 16)** should be synthesized and its cyclization attempted in acetic acid.

The low yields from the brominated amines is another mystery. Electron withdrawing groups should accelerate the cyclization, and bromine is mildly withdrawing[29]. Perhaps the rate is limited by the diazotization step, which was shown to be slow even without the sterically hindering bromine atom.

Future Recommendations

The most disappointing failure in this work has been the inability to extrude sulfur from phenothiazine **(138)** to give carbazole **(139)** **(Fig. 32)** in an effective and practical manner. One solution[10] for this problem is to synthesize $Ni(COD)_2$ **(73)** which is purer than what is commercially available and try the extrusion again. Unfortunately the synthesis[55] of $Ni(COD)_2$ **(73)** is difficult and dangerous, and attempts to make the sulfur extrusion catalytic in $Ni(COD)_2$ have been unsuccessful[55]. A second solution is to try a different sulfur extrusion method. A review[56] of possible alternatives has been published recently.

A revolutionary approach **(Fig. 46)** to ellipticine **(2)** from a plentiful, easily prepared precursor, 6-anilino-5,8-dimethylisoquinoline **(134)**, would have provided grams of 9-substituted ellipticine derivatives had it succeeded[34]. Diphenylamines are easily cyclized to give carbazoles in excellent yields using ultraviolet radiation[57], but **(134)** failed to cyclize at all under a variety of conditions. Only the extra delocalization resulting from the bicyclic nature of the isoquinoline ring system seems responsible for the failed coupling in this case. To make matters worse, ultraviolet radiation causes ellipticine **(2)** to decompose[34].



(134) (2)

Figure 46

Another method for the cyclization of diphenylamines uses palladium acetate[58], which can be used catalytically in some cases when regenerated by cupric chloride[59]. The optimized cyclization of **(134)** using one equivalent of palladium acetate gave 16%

conversion to ellipticine[34] **(2)**, along with 65% recovered starting material, for a 46% yield based on recovered starting material. Unfortunately, attempts to use less than one equivalent of palladium acetate gave inferior results. Since palladium acetate is more cost effective[60] for making ellipticine than $Ni(COD)_2$ **(73)**, this route is certainly competitive with the potential sulfur extrusion route using $Ni(COD)_2$.

A less elegant, but more financially practical, alternative **(Fig. 47)** would allow cyclization using ultraviolet radiation by reducing the isoquinoline to a tetrahydro derivative **(75)**. All reactions involved are well known[57,61,62] and there is every reason to expect them to succeed, providing a selective, practical route to 9-substituted ellipticines **(76)**.

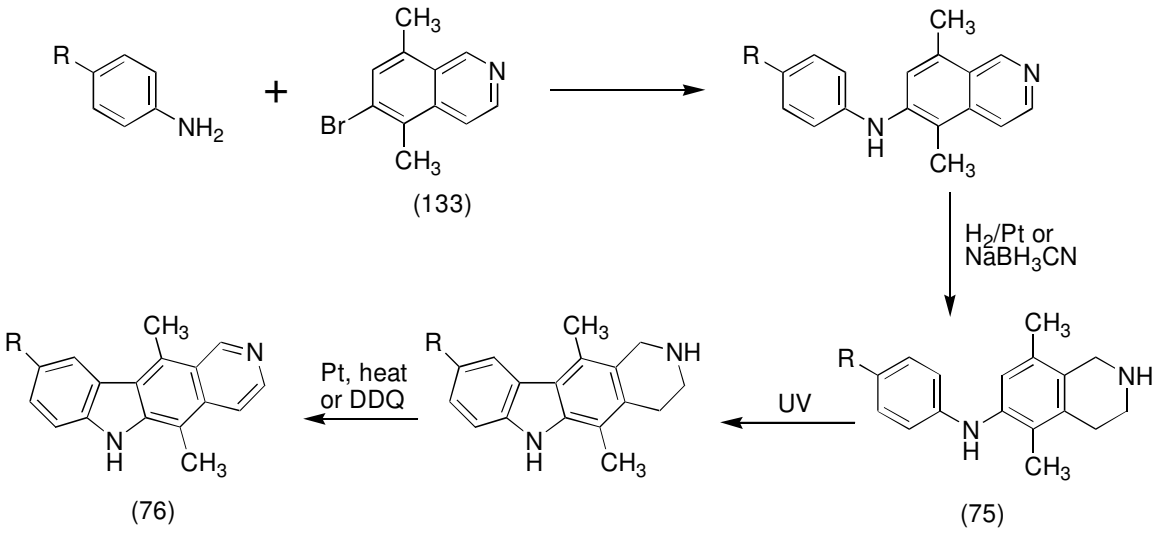


Figure 47

A less attractive approach **(Fig. 48)** would take advantage of the Pschorr cyclization[63] to produce 9-substituted ellipticines **(76)** under mild conditions. Although initial attempts to couple anilines with 6-bromo-5,8-dimethyl-7-nitroisoquinoline **(165)** have so far failed[64], there are many promising methods which have not been tried[65]. A potential problem[66] would be the competitive formation of the pyrazoloisoquinoline **(77)**, analogous to that of 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)** **(Fig. 7)**.

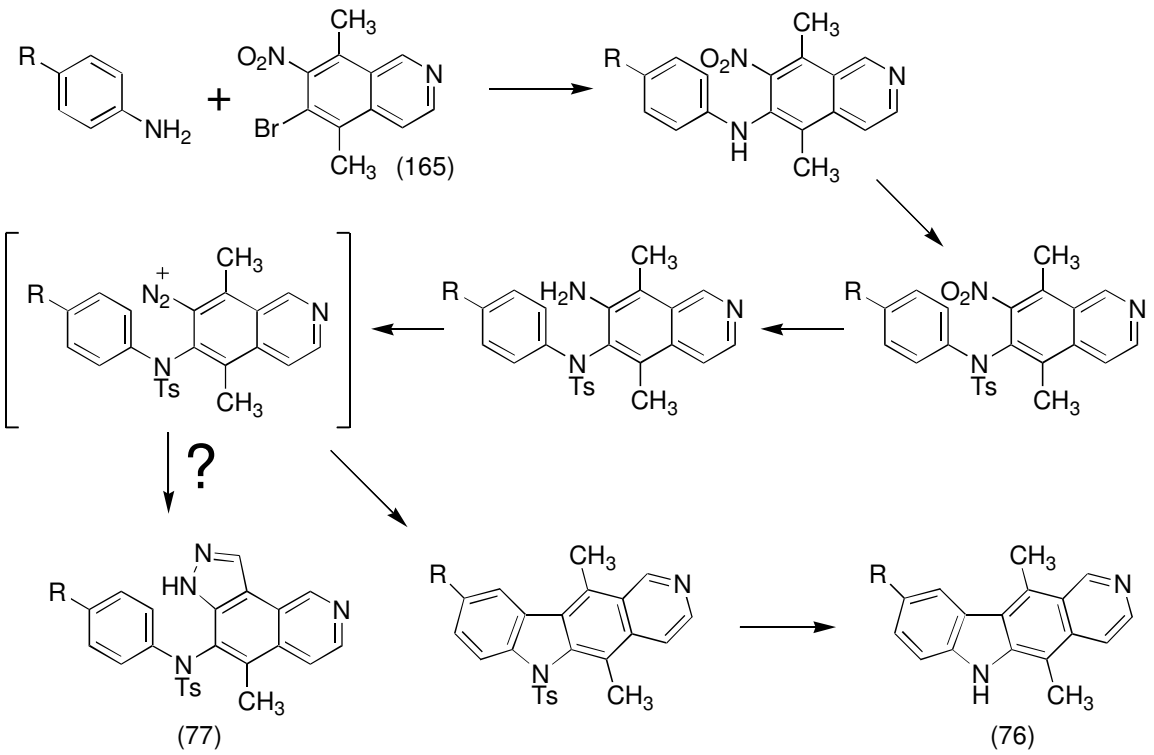


Figure 48

The ultimate 9-methoxyellipticine **(7)** synthesis, first proposed by T. E. Moock[67], would use the ancient Bucherer reaction[68] **(Fig. 49)**. The glaring disadvantage of this approach, if it works, would be its dependence on costly commercial 4-methoxyphenylhydrazine and other scarce phenylhydrazine derivatives, although this has not stopped others[69]. On the other hand, what a simple reaction!

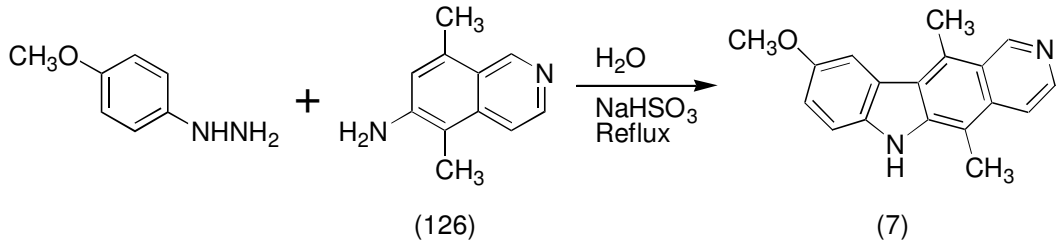
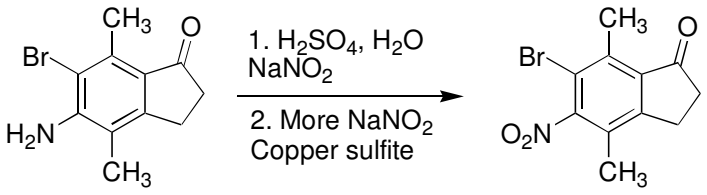


Figure 49

The bottleneck in the synthesis **(Fig. 24)** of 6-amino-7-bromo-5,8-dimethylisoquinoline **(125)** is the replacement of the amino group of 5-amino-6-bromo-

4,7-dimethylindanone **(119)** with a nitro group. A possible improvement **(Fig. 50)** would employ a diazo reaction, with the help of a copper catalyst[70]. Initial efforts[71] suggest that an organic solvent, such as acetone, is needed to dissolve the diazonium salt and allow it to react with nitrite. Although diazo reactions have succeeded in acetone[63], acetone can react with diazonium salts[72]. Also, an electron withdrawing group para to the diazonium group increases the rate of indazole formation[18].



(119) (120)

Figure 50

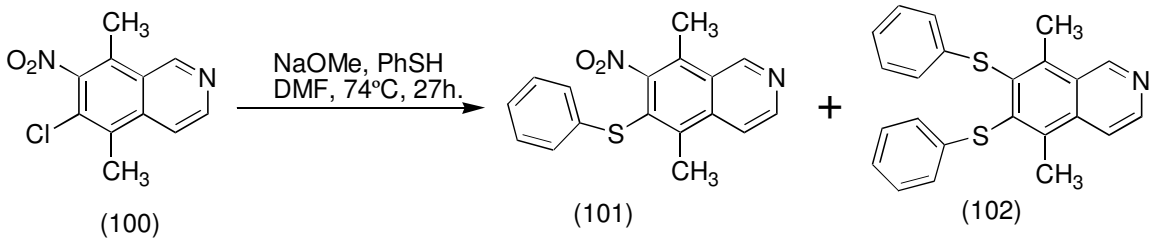
Experimental Section

General

All of the following applies to the Experimental Section except where noted otherwise. Infrared spectra, recorded on a Mattson Galaxy Series FTIR 3000 Infrared Spectrometer, are reported in cm^{-1}, and were obtained by evaporating a solution of the analyte in chloroform on a disk of sodium chloride. Values with an "s" next to them are among the strongest absorptions in the IR spectrum, while values with a "b" next to them are especially broad. ^{1}H NMR were obtained on a General Electric QE-300 at 300 MHz in $CDCl_3$ using TMS as the reference. Other reference peaks are 2.03 ppm for CD_3CO_2D, 2.49 ppm for Me_2SO-d_6 and 3.30 ppm for CD_3OD. ^{13}C NMR were typically obtained at 75 MHz in $CDCl_3$ using $CHCl_3$ at 77.0 ppm as the reference. Other reference peaks are 178.4 ppm for CD_3CO_2D, 39.7 ppm for Me_2SO-d_6 and 49.0 ppm for CD_3OD.

All melting points not from the literature are corrected and were measured using a Thomas Hoover Capillary Melting Point Apparatus. Solvents were evaporated using a Büchi R110 Rotovapor, organic solutions were dried using anhydrous sodium sulfate, and reactions were generally run unprotected from the air. Chromatography was accomplished using 70 to 230 mesh silica gel in columns whose dimensions are given as width by height. Thin Layer Chromatography (TLC) was performed using plastic backed Silicagel 60 F_{254} plates from EM Separations Technology. When multiple portions of solvent were used in an extraction, the number of portions used is followed by an "x" and the volume of each portion.

Ozonolysis was performed using a Welsbach T-23 ozonator at 110V at a flow of 0.08 CFM and pressure of 5.5 lb/in^2. Elemental analysis was performed by Midwest Microlab, LTD., 7212 N. Shadeland Ave., Indianapolis, IN 46250. High Resolution Mass Spectroscopy (HRMS) was performed on a VG 7070 Mass Spectrometer by UCR Mass Spec. Facility, Department of Chemistry, University of California, Riverside, CA 92521.



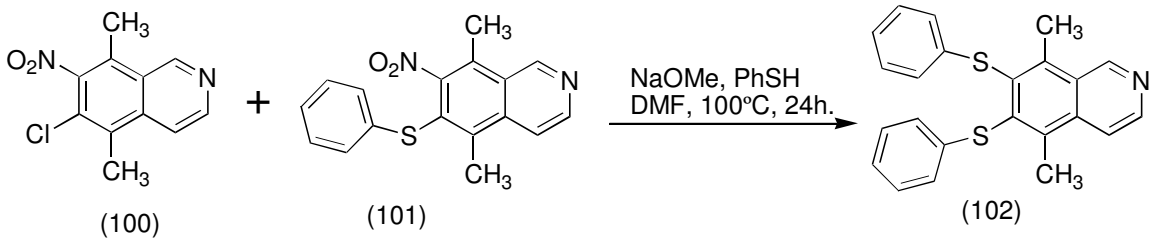
(100) (101) (102)

5,8-Dimethyl-7-nitro-6-(thiophenyl)isoquinoline **(101)**

Into a 15 mL Erlenmeyer flask were placed thiophenol (0.293 g, 2.66 mmol, 3 eq.), DMF (6.2 mL), and a magnetic stir bar. Once the solution was stirring, sodium methoxide (0.072 g, 1.33 mmol, 1.5 eq.) was added, followed by 6-chloro-5,8-dimethyl-7-nitroisoquinoline **(100)** (0.210 g, 0.886 mmol, 1 eq.), mp. 182.5-183.5°C (lit. mp. 180-181°C)[7]; IR: 3035, 2904, 1604, 1530s, 1388s, 1364s, 1303, 1224, 1076, 1001, 917, 838s, 817s, 747, 628s; ^{1}H NMR d: 2.63 (s, 3H), 2.70 (s, 3H), 7.76 (d, 1H, J = 6.0), 8.70 (d, 1H, J = 6.0), 9.42 (s, 1H); ^{13}C NMR d: 12.92, 15.11, 116.95, 124.76, 124.94, 125.98, 132.08, 135.40, 145.59, 148.23, 150.10.

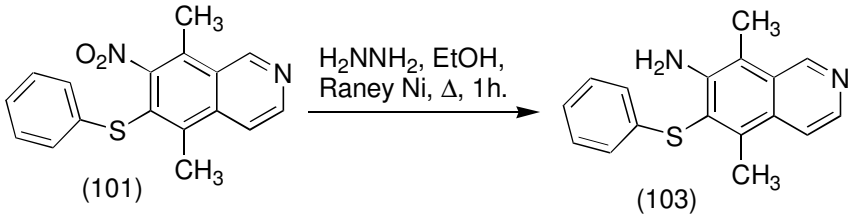
The stoppered reaction mixture was stirred at about 74°C for 27 hours. The solution was allowed to cool and diluted with ethyl acetate (50 mL) and washed with water (50 mL) , sat. sodium bicarbonate (25 mL), water (25 mL), and brine (15 mL) and then it was dried. The solvent was evaporated and the residue eluted from a 2 by 19 cm column using 2:1 petroleum ether/ethyl acetate. The minor component (0.0346 g, 12% yield) was 5,8-dimethyl-6,7-bis(thiophenyl)isoquinoline **(102)** - see then next procedure or analytical data. The major component (0.221 g, 80% yield) was 5,8-dimethyl-7-nitro-6-(thiophenyl)isoquinoline **(101)** but was initially mistaken for the starting material due to their identical R_fs on TLC, and had to be recovered from the next reaction for analysis. Recrystallizing from isopropanol gave light yellow needles, mp. 155.5-156.5°C (lit. mp. 155.5-157°C)[7]; IR: 3074b, 3004, 2968, 2918, 1605, 1580, 1533s, 1478, 1440s, 1384, 1361s, 1300, 1279, 1216, 1087, 997, 837s, 739s, 684s, 628; ^{1}H NMR d: 2.69 (s, 3H), 2.76 (s, 3H), 7.1-7.3 (m, 5H), 7.83 (d, 1H, J = 6.6), 8.72 (d, 1H, J = 5.7), 9.53 (s, 1H); ^{13}C NMR d: 13.11, 16.70, 117.59, 124.59, 125.00, 126.52, 126.70, 127.95, 129.11, 135.15,

135.50, 140.88, 145.26, 150.21, 153.64; Elemental analysis: C: 65.69, H: 4.49, N: 8.97; $C_{17}H_{14}N_2O_2S$ requires C: 65.79, H: 4.55, N: 9.03%.



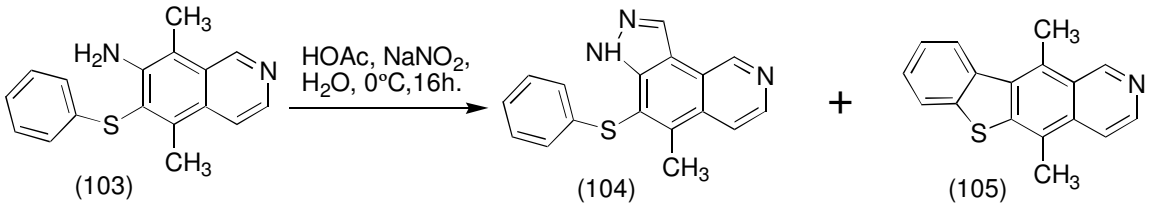
5,8-Dimethyl-6,7-bis(thiophenyl)isoquinoline **(102)**

The product of the previous reaction **(101)** was combined with fresh starting material (0.191g, 1.52 mmol total, 1 eq.) and reacted again with thiophenol (0.384 g, 3.48 mmol, 2.3 eq.) and sodium methoxide (0.141 g, 2.61 mmol, 1.7 eq.) in DMF (12.2 mL) at 100°C for 24 hours, followed by the previous workup and purification procedure. Substantial 5,8-dimethyl-6,7-bis(thiophenyl)isoquinoline **(102)** (0.244 g, 41% yield) was obtained which was recrystallized from isopropanol to form light yellow crystals, mp. 117-118°C; IR: 3066b, 3015, 1595s, 1581s, 1535, 1477s, 1439s, 1377, 1210, 1082, 1024, 981, 875, 820, 736s, 688s; ^{1}H NMR: d: 2.81 (s, 3H), 2.97 (s, 3H), 6.9-7.2 (m, 10H), 7.79 (d, 1H, J = 6.0), 8.64 (d, 1H, J = 6.0), 9.54 (s, 1H); ^{13}C NMR d: 17.80, 18.19, 117.58, 125.05, 125.18, 126.51, 126.83, 127.77, 128.77 (extra large - probably two carbons), 135.95, 136.26, 137.96, 138.15, 138.79, 140.20, 140.64, 144.32, 150.39. Also generated/recovered was 5,8-dimethyl-7-nitro-6-(thiophenyl)isoquinoline **(101)** (0.275 g, 55% yield).



7-Amino-5,8-dimethyl-6-(thiophenyl)isoquinoline **(103)**

Into a 15 mL round-bottomed flask were placed 5,8-dimethyl-7-nitro-6-(thiophenyl)isoquinoline **(101)** (0.1621 g, 0.522 mmol, 1 eq.) , absolute ethanol (4.2 mL), hydrazine monohydrate (0.157 g, 3.13 mmol, 6 eq.), a 50% slurry of Raney nickel in water (0.135 g, 1.15 mmol, 2.2 eq.) and a magnetic stir bar. The mixture was refluxed with stirring for one hour, and then most of the solvent was boiled off. Ethyl acetate (50 mL) was added and the product extracted into dilute hydrochloric acid (250 mL). The aqueous layer were basified with potassium hydroxide solution and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine, dried, and evaporated leaving bright yellow solid (0.1208 g, 82% yield). Recrystallizing from isopropanol gave dark yellow needles, mp. 141-141.5°C; IR: 3448, 3312bs, 3180b, 3069, 2922b, 2863, 1631s, 1563s, 1477s, 1439, 1375s, 1279, 1238, 1151, 1079, 1008, 805, 738s, 688; ^{1}H NMR d: 2.51 (s, 3H), 2.83 (s, 3H), 4.78 (bs, 2H), 7.00 (d, 2H, J = 8.1), 7.11 (t, 1H, J = 7.2), 7.20 (t, 2H, J = 7.2), 7.69 (d, 1H, J = 6.0), 8.36 (d, 1H, J = 6.0), 9.37 (s, 1H); ^{13}C NMR d: 11.83, 17.09, 111.03, 117.84, 122.97, 125.61, 126.17, 128.83, 129.17, 129.33, 135.64, 139.10, 139.59, 144.19, 148.22; Elemental analysis: C: 72.85, H: 5.93, N: 9.96; $C_{17}H_{16}N_2S$ requires C: 72.82, H: 5.75, N: 9.99%.



(103) (104) (105)

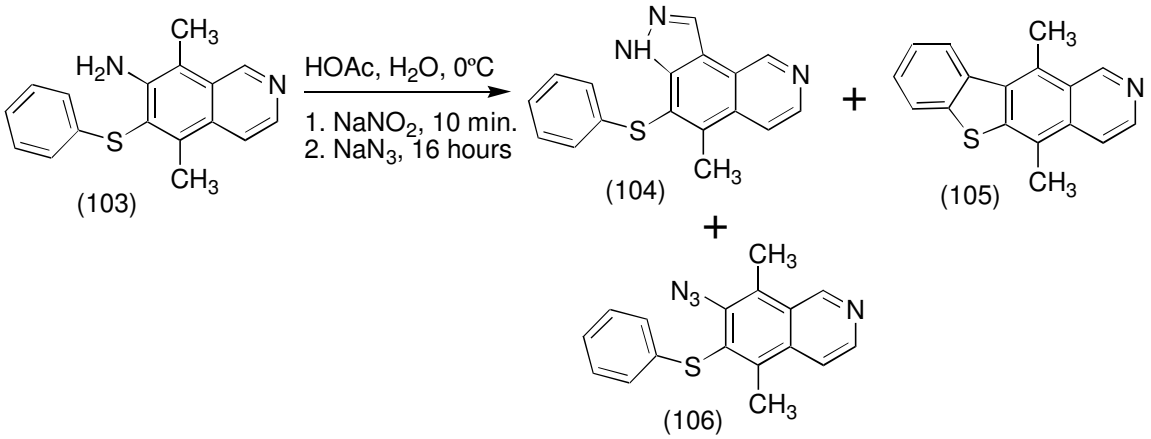
5-Methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)** and 5,11-Dimethyl-[1]benzothieno[2,3-*g*]isoquinoline (6-Thiaellipticine) **(105)**

Into a 5 mL round-bottomed flask were placed a solution of 7-amino-5,8-dimethyl-6-(thiophenyl)isoquinoline **(105)** (0.0821 g, 0.293 mmol, 1 eq.) in glacial acetic acid (2.3 mL), and a magnetic stir bar. The flask was cooled with stirring in an ice bath, and before the solution had a chance to freeze a solution of sodium nitrite (0.022 g, 0.322 mmol, 1.1 eq.) in water (0.29 mL) was added dropwise over 30 seconds. The ice bath was allowed to warm to room temperature overnight.

The reaction mixture was poured into 20% aqueous ammonia (30 mL) and confirmed to be basic before extracting with methylene chloride (2 x 30 mL). The combined organic layers were washed with water (25 mL) and brine (25 mL), dried and evaporated. The residue was purified on a 2 by 15 cm column of 80-200 mesh Brockman activity I basic alumina using methylene chloride. The 6-thiaellipticine **(105)** (0.0264g, 34% yield) obtained was boiled with decolorizing carbon in ethyl acetate. The mixture was filtered, evaporated, recrystallized from methanol, and again from heptane to produce light orange-yellow flakes, mp. 153.5-154°C (lit. mp. 152.5-153.5°C)[73]; IR: 3059, 3006b, 2952, 2894b, 2871b, 1597s, 1442s, 1377s, 1324, 1297, 1265, 1214, 1169, 1091, 1075, 1021, 982, 809s, 783, 763s, 732s, 687; ^{1}H NMR d: 2.80 (s, 3H), 3.27 (s, 3H), 7.45-7.55 (m, 2H), 7.81 (d, 1H, J = 6.3), 7.88 (t, 1H, J = 4.5), 8.47 (t, 1H, J = 4.6), 8.57 (d, 1H, J = 6.0), 9.78 (s, 1H); ^{13}C NMR d: 15.62, 16.78, 115.71, 122.80, 123.52, 124.68, 125.72, 126.38, 127.14, 130.26, 132.39, 133.27, 136.81, 139.85, 141.93, 142.31, 150.36.

Eluting the column further with ether, ethyl acetate, and finally methanol gave the product **(104)** (0.0350 g, 41% yield). Recrystallization from chloroform produced light yellow prisms, mp. 219.5-220.5°C (lit. mp. 195-200°C)[7]; IR: 3052b, 2955, 2920, 2863, 2769b, 1610, 1582s, 1511, 1477s, 1439s, 1375, 1321, 1302, 1253, 1209, 1152, 1082,

1022, 931s, 861b, 817s, 783, 736s, 687, 627; ^{1}H NMR d: 2.90 (s, 3H), 7.05-7.25 (m, 5H), 7.88 (d, 1H, J = 6.0), 8.52 (s, 1H), 8.70 (d, 1H, J = 5.7), 9.62 (s, 1H), 11.35 (bs, 1H); ^{13}C NMR d: 16.29, 102.86, 116.10, 118.83, 122.30, 126.51, 127.39, 129.49, 133.35, 133.60, 134.66, 138.65, 140.38, 143.71, 147.60. The structure was verified by single crystal X-ray analysis - see Appendix A.



Measurement of Azide Formation for 7-Amino-5,8-dimethyl-6-(thiophenyl)isoquinoline in Acetic Acid

In a 5 mL round-bottomed flask containing a magnetic stir bar 7-amino-5,8-dimethyl-6-(thiophenyl)isoquinoline **(103)** (11.0 mg, 0.039 mmol, 1 eq.) was dissolved in acetic acid (0.31 mL) and water (one drop). The solution (reaction A) was cooled in an ice bath and then an aqueous solution (44 mL) of sodium nitrite (2.98 mg, 0.043 mmol, 1.1 eq.) was injected in one portion. In an otherwise identical reaction, reaction B, an aqueous solution (56 mL) of sodium azide (5.61 mg, 0.086 mmol, 2.2 eq.) was injected ten minutes after the injection of sodium nitrite. At the same time water (56 mL) was injected into reaction A as a control. Both flasks were wrapped in aluminum foil to protect them from light and the ice baths were allowed to warm to room temperature overnight.

Each reaction mixture was separately poured into dilute ammonia and confirmed to be basic before being extracted three times with chloroform. The combined organic layers were washed with brine, dried and evaporated to give a dark yellow oil.

The composition of each product mixture was measured using the integrations of the most cleanly integrated peaks on the NMR spectrum, as shown on the following tables. Although a 2.0 mL sample of methylene chloride was placed in each NMR tube as a reference, the resulting calculations were off by as much as 15%. Fortunately the NMR spectra were clean, with no substantial peaks other than those of known compounds, so the sum of the moles of these known compounds are assumed to equal the moles of

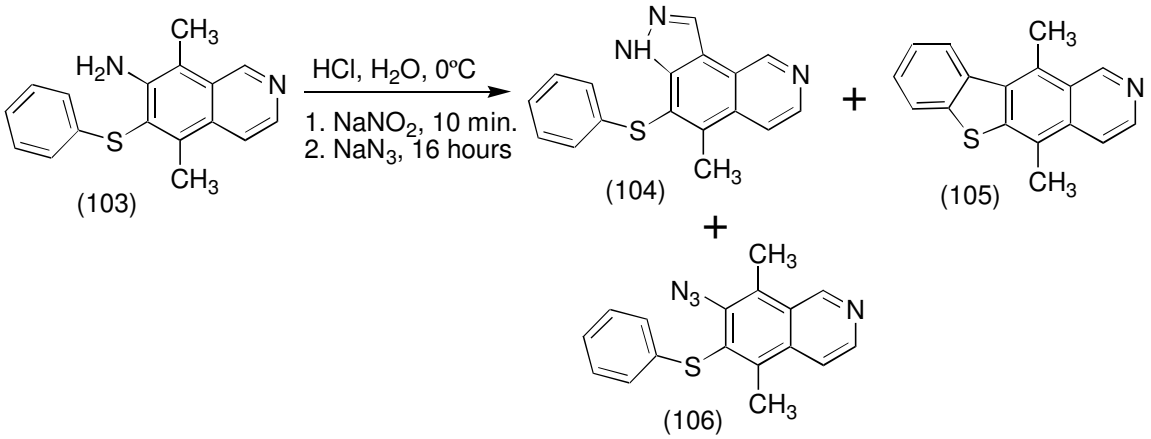
starting material for these calculations. Reaction A (without azide) gave according to NMR: 20% starting material **(103)**, 58% 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)**, and 21% 6-thiaellipticine **(105)**. Reaction B gave: 7% starting material **(103)**, 32% 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)**, 36% 6-thiaellipticine **(105)**, and 25% 7-azido-5,8-dimethyl-6-(thiophenyl)isoquinoline **(106)**.

Reaction A

(103)	9.37 (s, 1H)		2.51 (s, 3H)			66.37/328.33
	16.63	+	49.74	=	66.37	* 100% = **20%**
(104)	9.62 (s, 1H)		2.90 (s, 3H)			191.63/328.33
	44.07	+	147.56	=	191.63	* 100% = **58%**
(105)	9.78 (s, 1H)		3.27 (s, 3H)			70.33/328.33
	19.31	+	51.02	=	70.33	* 100% = **21%**
Total Integration					328.33	

Reaction B

(103)	9.37 (s, 1H)		2.51 (s, 3H)			15.74/233.99
	5.64	+	10.10	=	15.74	* 100% = **7%**
(104)	9.62 (s, 1H)		2.90 (s, 3H)			75.97/233.99
	16.90	+	59.07	=	75.97	* 100% = **32%**
(105)	9.78 (s, 1H)		3.27 (s, 3H)			83.65/233.99
	21.01	+	62.64	=	83.65	* 100% = **25%**
(106)	9.48 (s, 1H)		2.78 (s, 3H) &			58.63/233.99
			2.87 (s, 3H)			*100%
	13.48	+	(46.65+43.66)/2	=	58.63	= **25%**
Total Integration					233.99	



Measurement of Azide Formation for 7-Amino-5,8-dimethyl-6-(thiophenyl)isoquinoline in Hydrochloric Acid

In a 5 mL round-bottomed flask containing a magnetic stir bar 7-amino-5,8-dimethyl-6-(thiophenyl)isoquinoline **(103)** (12.9 mg, 0.046 mmol, 1 eq.) was dissolved in water (1 mL) and concentrated hydrochloric acid (0.3 mL). The mixture was heated to boiling to dissolve the solid. The solution was cooled in an ice bath and an aqueous solution (94 mL) of sodium nitrite (3.49 mg, 0.051 mmol, 1.1 eq.) was injected in one portion. In an otherwise identical reaction, reaction B, an aqueous solution (100 mL) of sodium azide (6.58 mg, 0.101 mmol, 2.2 eq.) was injected ten minutes after the injection of sodium nitrite. At the same time water (100 mL) was injected into reaction A. Both flasks were wrapped in aluminum foil to protect them from light and the ice bath was allowed to warm to room temperature overnight.

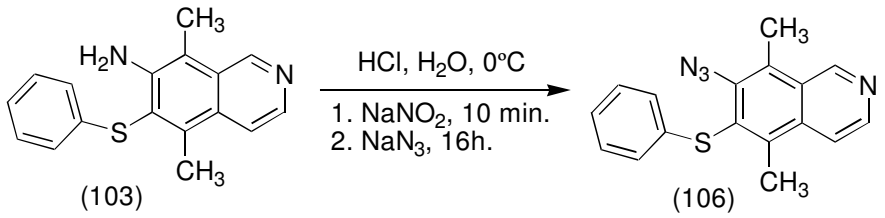
Each reaction mixture was separately poured into dilute ammonia and confirmed to be basic before being extracted four times with methylene chloride. The combined organic layers were washed with brine, dried and evaporated to obtain a dark yellow oil. Reaction A (without azide) gave according to NMR: 5% starting material **(103)**, 68% 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)**, and 27% 6-thiaellipticine **(105)**. Reaction B gave: 21% starting material **(103)**, 3% 5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)**, 1% 6-thiaellipticine **(105)**, and 75% 7-azido-5,8-dimethyl-6-(thiophenyl)isoquinoline **(106)**.

Reaction A

(103)	9.37 (s, 1H)		2.51 (s, 3H)			13.59/298.49
	3.82	+	9.77	=	13.59	* 100% = **5%**
(104)	9.62 (s, 1H)		2.90 (s, 3H)			203.10/298.49
	45.39	+	157.71	=	203.10	* 100% = **68%**
(105)	9.78 (s, 1H)		3.27 (s, 3H)			81.80/298.49
	19.91	+	61.89	=	81.80	* 100% = **27%**
Total Integration					298.49	

Reaction B

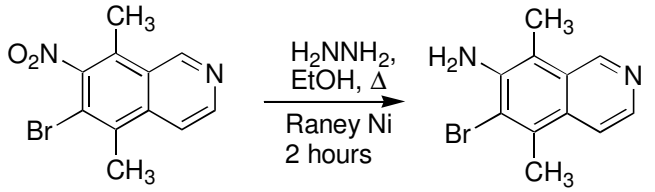
(103)	9.37 (s, 1H)		2.51 (s, 3H)			50.01/235.47
	11.91	+	38.10	=	50.01	* 100% = **21%**
(104)	9.62 (s, 1H)		2.90 (s, 3H)			5.29/235.47
	1.71	+	3.58	=	5.29	* 100% = **2%**
(105)	9.78 (s, 1H)		3.27 (s, 3H)			2.08/235.47
	0.77	+	1.31	=	2.08	* 100% = **1%**
(106)	9.48 (s, 1H)		2.78 (s, 3H) & 2.87 (s, 3H)			178.09/235.47 *100%
	41.73	+	(135.27+137.46)/2	=	178.09	= **75%**
Total Integration					235.47	



7-Azido-5,8-dimethyl-6-(thiophenyl)isoquinoline **(106)**

Into a 250 mL Florence flask were placed 7-amino-5,8-dimethyl-6-(thiophenyl)isoquinoline **(103)** (20.0 mg, 0.071 mmol, 1 eq.), water (36 mL) and concentrated hydrochloric acid (0.46 mL), and the solid was crushed while being heated to dissolve it. A magnetic stir bar was added and the flask cooled to 4°C with stirring, during which time the bright yellow solution sometimes precipitated. Sodium nitrite (7.4 mg, 0.107 mmol, 1.5 eq.) was added and the mixture stirred in the ice bath for ten minutes, during which time any solid redissolved. Sodium azide (93 mg, 1.43 mmol, 20 eq.) was added and the flask was wrapped in aluminum foil to protect it from light. The ice bath was allowed to warm to room temperature overnight.

Ethyl acetate (40 mL) was added to the clear yellow solution and the aqueous layer basified by adding aqueous sodium carbonate. The aqueous layer was extracted with ethyl acetate (2 x 30 mL), and the combined extracts were washed with brine, dried, filtered and evaporated. The residue was eluted from a 2 by 9 cm column using 1:1 petroleum ether/ethyl acetate (175 mL). The product slowly formed orange crystals which were recrystallized from ethyl acetate to produce long yellow needles (14.3 mg, 65% yield), mp. 114-114.5°C; IR: 3054b, 2954, 2926b, 2251, 2176b, 2112s, 1600, 1581, 1574, 1551, 1537, 1478s, 1439s, 1379, 1363s, 1334s, 1285, 1261, 1211, 1072, 1042, 1023, 992, 913b, 822, 741s, 691, 679, 649; ^{1}H NMR d: 2.78 (s, 3H), 2.87 (s, 3H), 7.05 (d, 2H, J = 7.0), 7.15 (t, 1H, J = 7.3), 7.22 (t, 2H, J = 7.4), 7.80 (dd, 1H, J = 5.9, 0.6), 8.62 (d, 1H, J = 5.9), 9.48 (s, 1H); ^{13}C NMR d: 13.43, 17.06, 117.73, 125.97, 126.90, 126.96, 127.95, 129.16, 131.31, 133.83, 136.45, 138.70, 139.65, 143.39, 149.78.



(165) (107)

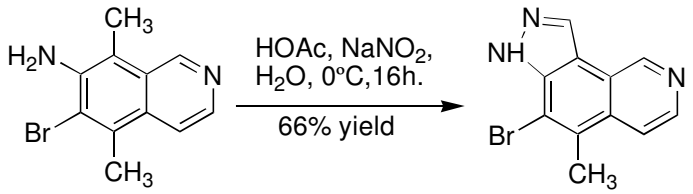
7-Amino-6-bromo-5,8-dimethylisoquinoline **(107)**

Into a 25 mL pear shaped flask were placed absolute ethanol (6.6 mL), 80% Raney nickel in water (24.9 mg, 0.34 mmol, 0.28 eq.), hydrazine monohydrate (0.36 g, 7.2 mmol, 6 eq.), and 6-bromo-5,8-dimethyl-7-nitroisoquinoline **(165)** (0.3374 g, 1.20 mmol, 1 eq.), mp. 194-197°C (lit. mp. 194-195°C)[7]; IR: 3063b, 2926b, 2893b, 1604s, 1577, 1532s, 1487, 1456b, 1405, 1387s, 1362, 1357, 1298, 1279, 1221, 1178, 1096, 1074, 1043, 994, 905, 835s, 821, 798, 779, 743, 707b, 617; ^{1}H NMR d: 2.65 (s, 3H), 2.76 (s, 3H), 7.78 (d, 1H, J = 5.9), 8.70 (d, 1H, J = 6.0), 9.42 (s, 1H); ^{13}C NMR d: 13.18, 18.59, 115.77, 117.17, 125.44, 125.77, 134.52, 135.29, 145.60, 150.20, 157.43; Elemental analysis: C: 46.84, H: 3.09, N: 9.72; $C_{11}H_9BrN_2O_2$ requires C: 47.17, H: 2.88, N: 10.00%.

The mixture was refluxed for 90 minutes but little change is visible by TLC, probably because the nickel dried partially on storage. A bit of wet Raney nickel from a different bottle was added to the flask, causing immediate frothing. More hydrazine monohydrate (0.36 g, 7.2 mmol, 6 eq.) was added and reflux resumed for two more hours, by which time the reaction is complete by TLC. Silica gel (1.175 g) was added to the cooled mixture and the solvent evaporated. Chloroform was added to the resulting yellow powder and the solvent evaporated again to strip ethanol away.

The product was eluted from a 2 by 10 cm column using 2% methanol/chloroform (200 mL) producing sulfur yellow solid (0.248 g, 82% yield) contaminated by a trace of 7-amino-5,8-dimethylisoquinoline **(114)**. Further chromatography using ethyl acetate was little help, so repeated recrystallizations from 1:1 ethyl acetate/heptane or acetonitrile were resorted to, giving fluffy white clumps, mp. 163-164°C (lit. mp. 155-157)[28]; IR: 3456b, 3328bs, 3217b, 1627s, 1574, 1554, 1490, 1452, 1420, 1381s, 1277, 1235s, 1150, 1082, 1005s, 913, 805s, 757, 693, 671; ^{1}H NMR d: 2.49 (s, 3H), 2.70 (s, 3H), 4.48 (bs,

2H), 7.60 (dd, 1H, J = 5.9, 0.6), 8.33 (d, 1H, J = 5.9), 9.28 (d, 1H, J = 0.6); ^{13}C NMR d: 11.95, 18.89, 111.87, 117.14, 120.60, 127.19, 129.45, 131.67, 139.93, 140.11, 148.03; Elemental analysis: C: 52.96, H: 4.28, N: 11.42; $C_{11}H_{11}BrN_2$ requires C: 52.61, H: 4.41, N: 11.16%.



(107) (108)

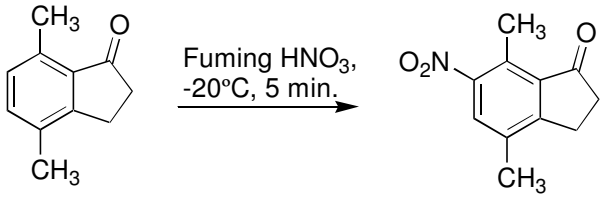
6-Bromo-5-methyl-3H-pyrazolo[3,4-*h*]isoquinoline **(108)**

Into a 25 mL round-bottomed flask were placed a magnetic stir bar and glacial acetic acid (4.3 mL) containing 7-amino-6-bromo-5,8-dimethylisoquinoline **(107)** (0.1363 g, 0.543 mmol, 1 eq.). The solution was cooled with stirring in an ice bath, and before it had a chance to freeze a solution of sodium nitrite (0.0412g, 0.597 mmol, 1.1 eq.) in water (0.54 mL) was added dropwise over 30 seconds. The ice bath was allowed to warm to room temperature overnight

The reaction mixture was poured into 20% aqueous ammonia (50 mL) and confirmed to be basic before being extracted with methylene chloride (2 x 30 mL). The combined organic layers were extracted with dilute hydrochloric acid (3 x 40 mL), and the combined aqueous layers carefully basified with sodium bicarbonate. The aqueous mixture was extracted with methylene chloride (4 x 20 mL) and the combined organic layers were washed with brine, dried and evaporated to give a yellow-orange solid (0.1306 g, 92% yield).

The solid was deposited onto triethylamine-treated silica gel and loaded onto a 4 by 9 cm column which was packed using 1% triethylamine in chloroform. The column was eluted with chloroform (100 mL), 3% methanol/chloroform (200 mL) and 7% methanol/chloroform (200 mL) to furnish a yellow solid (0.0933 g, 66% yield). Recrystallization from chloroform gave yellow needles, mp. >300°C; IR: 2913, 2848, 2760b, 1596s, 1446s, 1380, 1324, 1208s, 1156, 1095, 1002, 936s, 850b, 821s, 744, 716s; ^{1}H NMR (Me_2SO-d_6) d: 2.70 (s, 3H), 7.89 (d, 1H, J = 5.7), 8.57 (d, 1H, J = 5.7), 8.85 (bs, 1H), 9.66 (s, 1H), 13.84 (bs, 1H); ^{1}H NMR (CD_3CO_2D) d: 2.84 (s, 3H), 8.41 (d, 1H, J = 6.5), 8.77 (d, 1H, J = 6.5), 8.91 (s, 1H), 9.84 (s, 1H); ^{13}C NMR (CD_3CO_2D) d: 19.09, 117.06, 120.52, 123.76, 123.96, 132.86, 134.63, 137.18, 139.01, 143.08, 143.20;

Elemental analysis: C: 50.54, H: 3.04, N: 15.78; $C_{11}H_8BrN_3$ requires C: 50.41, H: 3.08, N: 16.03%.

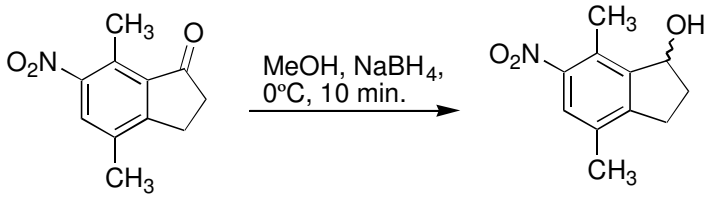


(109) (110)

2,3-Dihydro-4,7-dimethyl-6-nitro-1H-indene-1-one **(110)**

A cooling bath was prepared by adding enough dry ice to 1% pentane in carbon tetrachloride to bring the temperature to -20°C. A magnetic stir bar and fuming 90% nitric acid (29 mL, 625 mmol, 40 eq.) were placed into a 50 mL Erlenmeyer flask and stirred in the bath until cold. Over five minutes, the flask was charged with 2,3-dihydro-4,7-dimethyl-1H-indene-1-one **(109)** (2.502 g, 15.6 mmol, 1 eq.), mp. 76-76.5°C (lit. mp. 76-77°C)[74]; IR: 3019, 2985, 2922, 1704s, 1585s, 1497, 1442, 1412, 1379s, 1327s, 1246s, 1226, 1084, 1036, 1009, 990, 898, 832s, 729, 705, 667; ^{1}H NMR d: 2.30 (s, 3H), 2.60 (s, 3H), 2.65 (t, 2H, J = 5.9), 2.95 (t, 2H, J=5.9), 7.01 (d, 1H, J = 7.4), 7.23 (d, 1H, J = 7.4); ^{13}C NMR d: 17.32, 17.90, 24.23, 36.61, 129.15, 132.74, 134.15, 134.33, 135.90, 154.70, 208.29.

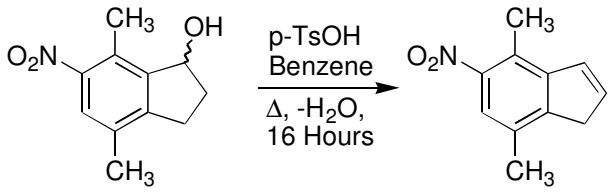
After an additional five minutes, the reaction mixture was poured over ice and extracted with 1:1 ethyl acetate/heptane (3 x 100 mL). The combined extracts were washed with saturated sodium bicarbonate until the washings remained basic, then they were washed with brine, dried and evaporated to produce a red-brown solid (3.7 g). This was purified on a 4 by 9 cm column using chloroform to obtain an orange solid (2.1058 g, 66% yield). Recrystallization from isopropanol gave dark yellow needles, mp. 111.5-112.5°C (lit. mp. 92.5-94°C)[75]; IR: 3095, 3065, 2974, 2927b, 2878, 1716s, 1578, 1515s, 1476, 1378s, 1358s, 1258s, 1226, 1105s, 1022, 997, 901, 860, 833, 748, 693; ^{1}H NMR d: 2.40 (s, 3H), 2.67 (s, 3H), 2.75 (t, 2H, J = 6.0), 3.04 (t, 2H, J = 6.0), 7.79 (s, 1H); ^{13}C NMR d: 12.13, 16.90, 23.69, 36.68, 128.86, 130.43, 134.12, 134.83, 148.89, 159.01, 206.00.



(110) (111)

2,3-Dihydro-4,7-dimethyl-6-nitro-1H-indene-1-ol **(111)**

In a 25 mL round-bottomed flask containing a magnetic stir bar 2,3-dihydro-4,7-dimethyl-6-nitro-1H-indene-1-one **(110)** (0.2196 g, 1.07 mmol, 1 eq.) was dissolved in methanol (11 mL). The solution was stirred in an ice bath until cold and sodium borohydride (0.0607 g, 1.61 mmol, 1.5 eq.) added over two minutes. After ten minutes, the solvent was evaporated and water (10 mL) added. The aqueous mixture was extracted with ethyl acetate (2 x 15 mL) and the combined organic layers were washed with brine and poured through a filter containing anhydrous sodium sulfate, decolorizing carbon, and silica gel. The filtrate was evaporated to generate light yellow solid (0.2142 g, 97% yield), mp. 71-72°C; IR: 3245bs, 2965, 2933, 2852, 1580, 1518s, 1442s, 1346s, 1211, 1071, 1047s, 1022, 969s, 903, 860, 757; ^{1}H NMR d: 1.99 (bs, 1H), 2.09-2.18 (m, 1H), 2.28 (s, 3H), 2.35-2.49 (m, 1H), 2.56 (s, 3H), 2.81 (ddd, 1H, J = 17.1, 9.7, 2.7), 3.03-3.14 (m, 1H), 5.36 (d, 1H, J = 6.0), 7.68 (s, 1H); ^{13}C NMR d: 15.34, 18.45, 29.20, 34.62, 75.11, 125.68, 128.14, 132.60, 145.07, 148.54, 148.70.

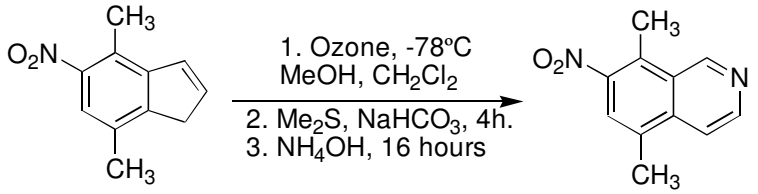


(111) (112)

4,7-Dimethyl-5-nitro-1H-indene **(112)**

Into a 25 mL round-bottomed flask containing a magnetic stir bar were placed 2,3-dihydro-4,7-dimethyl-6-nitro-1H-indene-1-ol **(111)** (0.2142 g, 1.03 mmol, 1 eq.), p-toluenesulfonic acid (0.0026 g, 0.01 mmol, 0.01 eq.) and benzene (2.5 mL). A Dean-Stark trap containing anhydrous calcium chloride pellets was placed on the flask and the reaction mixture was refluxed overnight.

The reaction mixture was allowed to cool and then mixed with ethyl acetate and water. The organic layer was washed with brine and evaporated to secure a light brown solid. The product was purified on a 2 by 11 cm column using 1:4 ethyl acetate/petroleum ether giving a light yellow solid (0.1895 g, 97% yield), mp. 62.5-63.5°C (lit. mp. 103-105°C)[75]; IR: 2932b, 2864, 1514s, 1453, 1382s, 1337bs, 1255, 1208, 1178, 1113, 1035, 947, 910, 866s, 755s, 691s, 620; ^{1}H NMR d: 2.37 (s, 3H), 2.59 (s, 3H), 3.36 (t, 2H, J = 2.0), 6.70 (dt, 1H, J = 5.7, 2.0), 7.03 (dt, 1H, J = 5.7, 2.0), 7.61 (s, 1H); ^{13}C NMR d: 15.63, 18.16, 38.72, 122.03, 123.03, 130.17, 131.00, 135.65, 145.62, 147.16, 148.75.

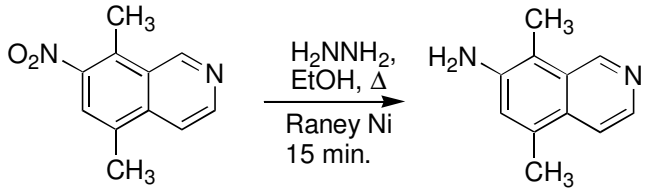


(112) (113)

5,8-Dimethyl-7-nitroisoquinoline **(113)**

Into a 250 mL ozonolysis flask were placed 4,7-dimethyl-5-nitro-1H-indene **(111)** (6.3083 g, 33.3 mmol), methanol (167 mL), and methylene chloride (167 mL). The flask was cooled in a dry ice/acetone bath with a stream of oxygen bubbles to provide mixing, and then ozone was bubbled through the solution until it turned blue. Oxygen was again bubbled through the solution until the blue color disappeared. The cold solution was poured into a 750 mL Erlenmeyer flask containing dimethyl sulfide (16.7 mL), sodium bicarbonate (3.33 g), and a magnetic stir bar. After stirring four hours at room temperature, concentrated aqueous ammonia (167 mL) was added and the mixture stirred overnight.

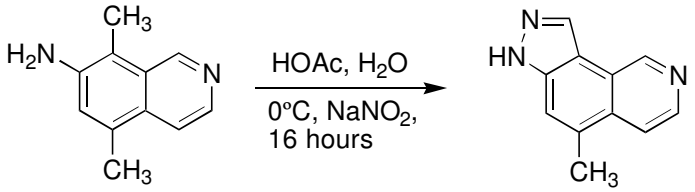
The mixture was poured into a 1 L round-bottomed flask and most of the organic solvents were evaporated until a yellow solid suspended in an aqueous solution remained. The suspension was extracted with chloroform (5 x 40 mL) and the combined organic layers were washed with brine, dried and evaporated to grant an orange-yellow solid (6.3196g, 94% yield). The product was recrystallized from ethyl acetate giving bright yellow needles, mp. 161-162°C (lit. mp. 144-145°C)[75]; IR: 3033b, 2966, 2931, 2858, 1937, 1890, 1842, 1755, 1652, 1608, 1580, 1521s, 1493, 1457, 1415, 1386s, 1365s, 1348s, 1308, 1285, 1218, 1172, 1078, 1041b, 989, 917, 879s, 824s, 815, 783, 768, 743, 721, 657, 610; ^{1}H NMR d: 2.69 (s, 3H), 2.88 (s, 3H), 7.79 (m, 2H), 8.73 (d, 1H, J = 6.0), 9.63 (d, 1H, J = 0.6); ^{13}C NMR d: 13.43, 18.32, 117.07, 124.32, 127.30, 128.63, 133.82, 136.82, 145.35, 147.67, 151.00.



(113) (114)

7-Amino-5,8-dimethylisoquinoline **(114)**

Into a 100 mL round-bottomed flask containing a magnetic stir bar were placed 5,8-dimethyl-7-nitroisoquinoline **(113)** (2.5535 g, 12.54 mmol, 1 eq.), absolute ethanol (75 mL), hydrazine monohydrate (3.77 g, 75 mmol, 6 eq.), and 80% Raney nickel in water (1.13 g, 15 mmol, 1.2 eq.), and the mixture was refluxed for 15 minutes. The reflux condenser was removed and most of the ethanol boiled away to remove the hydrazine. The mixture was cooled, ethyl acetate was added, and the mixture was filtered through celite. The filtrate was extracted twice with dilute hydrochloric acid, and the combined aqueous layers basified with sodium bicarbonate. The aqueous mixture was extracted three times with ethyl acetate, washed with brine, dried and evaporated giving an orange solid (1.9979 g, 92% yield). The product was recrystallized from methanol to create flat orange rods, mp. 201.5-202.5°C; IR: 3429, 3316b, 3197bs, 1645s, 1609s, 1572, 1493, 1447, 1386s, 1349, 1285, 1250, 1221, 1149, 1066, 1031, 996, 874s, 809s; ^{1}H NMR d: 2.45 (s, 3H), 2.56 (s, 3H), 3.88 (bs, 2H), 6.98 (s, 1H), 7.60 (d, 1H, J = 5.7), 8.35 (d, 1H, J = 5.7), 9.31 (s, 1H); ^{13}C NMR d: 10.62, 18.34, 110.63, 117.10, 122.96, 128.92, 130.27, 132.25, 139.45, 141.97, 147.83; Elemental analysis: C: 76.55, H: 6.97, N: 16.23; $C_{11}H_{12}N_2$ requires C: 76.71, H: 7.02, N: 16.27%.



(114) (115)

5-Methyl-3H-pyrazolo[3,4-*h*]isoquinoline **(115)**

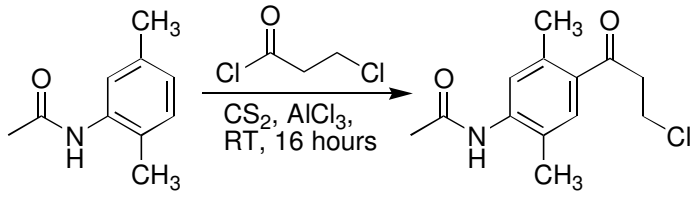
In a 50 mL round-bottomed flask containing a magnetic stir bar 7-amino-5,8-dimethylisoquinoline **(114)** (0.4516 g, 2.62 mmol, 1 eq.) was dissolved in glacial acetic acid (20.7 mL) and the yellow solution was placed in an ice bath. Before the solution froze (about two minutes) a solution of sodium nitrite (0.199 g, 2.88 mmol, 1.1 eq.) in water (2.62 mL) was added over four minutes. The ice bath was allowed to warm to room temperature overnight.

The dark red solution was diluted with water (50 mL) and basified using dilute aqueous ammonia causing a thick, fluffy, pinkish-yellow precipitate to appear. The mixture was extracted with methylene chloride (100 mL) and the resulting emulsion was patiently allowed to settle. The organic layer was dried and applied to a 2 by 8 cm column. The eluent from the column was used to extract the aqueous layer again, and this process was repeated until the aqueous layer had been extracted a total of ten times, all the solid had dissolved, and the extracts ceased to be yellow.

The column was eluted with chloroform (50 mL), 1% methanol/chloroform (50 mL), 2% methanol/chloroform (150 mL), 3% methanol/chloroform (100 mL), and 5% methanol/chloroform (50 mL). Starting material (18 mg, 4% recovery) was obtained, followed by a red impurity, and an orange solution of nearly pure product (0.401 g, 83% conversion, 87% yield based on recovered starting material) after that.

Sufficient methanol (1 mL) was added to the product in boiling chloroform (100 mL) to cause it to dissolve. No solid formed on cooling, so the clear red solution was boiled down until it became hazy (50 mL) and set in the freezer. The brownish yellow solid (0.2654 g, 55% conversion) was recrystallized from methanol to produce light brown needles which were further purified by sublimation at 155°C under high vacuum, mp 292-293°C (dec.); IR: 3201, 3168, 3118bs, 3066, 3036b, 2990, 2929, 2901s, 2848,

2818, 2800, 2788, 2778, 2727, 1611s, 1577, 1524, 1479, 1440, 1379, 1372, 1335, 1308, 1260s, 1209, 1155, 1090, 1070, 1038, 993, 936s, 868, 848s, 801, 768, 712; ^{1}H NMR (Me_2SO-d_6) d: 2.66 (s, 3H), 7.76 (s, 1H), 7.86 (d, 1H, J = 5.7), 8.57 (d, 1H, J = 5.7), 8.70 (s, 1H), 9.70 (s, 1H), 13.50 (bs, 1H); ^{1}H NMR (CD_3CO_2D) d: 2.58 (s, 3H), 7.76 (s, 1H), 8.08 (d, 1H, J = 6.4), 8.51 (s, 1H), 8.58 (d, 1H, J = 6.4), 9.55 (s, 1H); ^{13}C NMR (CD_3CO_2D) d: 20.04, 116.77, 122.47, 123.06, 124.05, 132.83, 135.16, 135.98, 138.21, 141.24, 142.49; Elemental analysis: C: 72.21, H: 4.91, N: 23.12; $C_{11}H_9N_3$ requires C: 72.11, H: 4.95, N: 22.94%.



(116) (117)

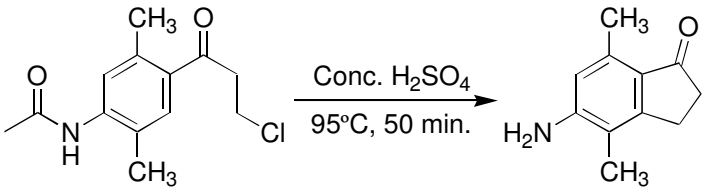
4-Acetamido-2,5-dimethyl-3'-chloropropiophenone **(117)**

In the hood, a 1 L round-bottomed flask containing a heavy duty magnetic stir bar was filled with 2,5-dimethylacetanilide **(116)** (25.05 g, 153 mmol, 1 eq.), mp. 141-142°C (lit. mp. 139°C)[76]; IR: 3275bs, 1657s, 1579, 1536s, 1491, 1453b, 1412, 1368, 1290s, 1269, 1125, 1038, 967, 878, 808s, 715, 610s; ^{1}H NMR d: 2.14 (s, 3H), 2.17 (s, 3H), 2.28 (s, 3H), 6.88 (d, 1H, J = 7.5), 7.03 (d, 1H, J = 7.8), 7.29 (bs, 1H), 7.46 (s, 1H); ^{13}C NMR d: 17.25, 20.93, 23.96, 124.40, 126.13, 126.76, 130.14, 135.33, 136.18, 168.53.

Carbon disulfide (475 mL), reused from a previous batch of this reaction when possible, and aluminum chloride (61.4 g, 460 mmol, 3 eq.) were added. A reflux condenser was placed on the flask and 3-chloropropionyl chloride (22.0 mL, 230 mmol, 1.5 eq.) added through it over a minute with stirring. A drying tube was attached to the top of the condenser. After a while, the stirring stopped because of the viscous paste forming in the flask.

The next day the solvent was decanted from the gummy brown tar and saved the next batch. Crushed ice (500 mL) and concentrated hydrochloric acid (200 mL) were cautiously added to the tar and the flask was slowly rotated on the rotary evaporator in a warm water bath without vacuum for a few hours, until all the clumps broke up and a fine gray solid was suspended in the flask. The suspension was poured onto a Buchner funnel and washed with water (a gallon). Care was taken to avoid draining the last liquid from the funnel until finished washing to prevent the solid from cracking and fluid passing through the cracks from then on. The solid was left in a warm place to dry. The chalky yellow-gray solid (35.51 g, 91% yield) was recrystallized from water to give a white fluff, mp. 161-161.5°C (lit. mp. 156-157°C)[6]; IR: 3283bs, 3184, 3127, 2974, 2927, 2860, 2767b, 1754, 1674s, 1660s, 1571s, 1522, 1494, 1447, 1420, 1391, 1369, 1350, 1302,

1275s, 1210, 1193, 1113, 1042, 1031, 1000, 964, 955, 881, 874, 850, 796, 780, 748, 701, 689, 667s, 629, 609; ^{1}H NMR d: 2.22 (s, 3H), 2.28 (s, 3H), 2.50 (s, 3H), 3.35 (t, 2H, J = 6.7), 3.89 (t, 2H, J = 6.7), 7.09 (bs, 1H), 7.50 (s, 1H), 7.88 (bs, 1H); ^{1}H NMR (Me_2SO-d_6) d: 2.08 (s, 3H), 2.23 (s, 3H), 2.36 (s, 3H), 3.43 (t, 2H, J = 6.3), 3.88 (t, 2H, J = 6.3), 7.49 (s, 1H), 7.68 (s, 1H), 9.33 (s, 1H); ^{13}C NMR (Me_2SO-d_6) d: 17.52, 20.99, 23.70, 50.14, 43.12, 126.80, 127.74, 131.78, 132.84, 135.92, 139.79, 168.66, 199.46.



(117) (118)

5-Amino-2,3-dihydro-4,7-dimethyl-1H-indene-1-one **(118)**

Into a 1 L round-bottomed flask were placed 4-acetamido-2,5-dimethyl-3'-chloropropiophenone **(117)** (14.286 g, 56.3 mmol, 1 eq.), concentrated sulfuric acid (500 mL, 9.38 mol, 167 eq.) and a magnetic stir bar. The flask was swirled to mix the reagents and an air condenser was placed on the flask to keep out water vapor. The flask was lowered into a stirring 95°C water bath and stirred for 50 minutes. Using a higher concentration of reactant caused a sharp decrease in the yield.

A 4 L Erlenmeyer flask was filled with ice and placed in the hood in a plastic pan full of ice. While wearing thick gloves and goggles and a lab coat, the hot green solution was added through a funnel into the flask of ice. A mechanical stirrer was mounted, inserting the stirrer through the funnel on the flask. Preweighed sodium hydroxide (737 g, 18.42 mol, 327 eq.) was added portionwise. As the ice surrounding the flask melted, the water was siphoned away and replaced with fresh ice. It didn't seem to do any harm to let the flask reach 65°C or so.

The reaction mixture darkened and became purplish when half of the sodium hydroxide had been added. Once certain this point had passed, the reaction mixture was cooled to about 40°C and recycled chloroform (200 mL) was added. This chloroform was previously collected in the receiver of a rotary evaporator with the aspirator running. This step was necessary to lower the R_f of the impurities during the column to come. Care was taken not to add the recycled chloroform before adding at least half of the sodium hydroxide because the neutralization of sulfuric acid is much more exothermic than the neutralization of bisulfate. When this precaution was not taken the chloroform boiled violently, causing a purple volcano to erupt.

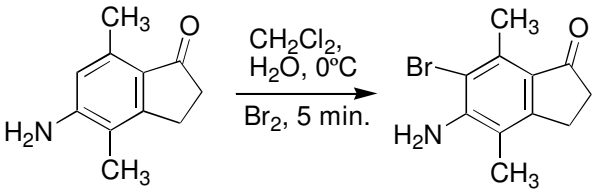
When almost all of the sodium hydroxide had been added, the remaining sodium hydroxide was dissolved in a little water and added to the solution in small portions. The

pH of the reaction mixture was measured between additions and the addition of sodium hydroxide solution stopped before the aqueous layer became basic. The neutralization was finished with sodium carbonate solution until reaching a pH of 8. If this point was overshot and an emulsion formed, it was acidified with a little sulfuric acid and again neutralized with sodium carbonate solution.

The mixture was kept warm to prevent the precipitation of sodium sulfate. If sodium sulfate did precipitate, the mixture was heated on a hot plate, swirling occasionally, until it dissolved.

A 4 by 12 cm column was packed using recycled chloroform and a 2 cm layer of anhydrous sodium sulfate placed on top. Once the chloroform extract of the product settled the aqueous layer was decanted in 800 mL portions and each portion extracted with recycled chloroform (3 x 150 mL). The organic layers were applied to the column and the eluent from the column used for further extraction. Upon extracting all of the aqueous layer and applying all extract to the column, the column was eluted with a few more liters of recycled chloroform until the product finished eluting from the column. As long as all the chloroform to be distilled had been previously recycled, it was more efficient to seal the rotary evaporator and turn the aspirator off once a vacuum had been established. It saved time to collect the eluent in one 1 L round-bottomed flask while a second was occupying the rotary evaporator.

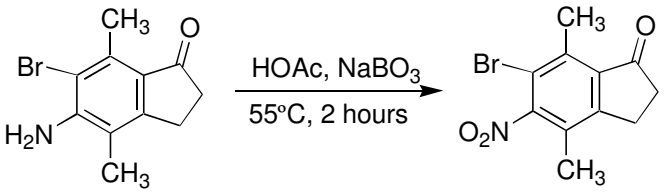
The bright yellow solid (7.2764 g, 74% yield) was recrystallized overnight from boiling methanol (250 mL) to give giant, highly pure dark yellow plates. Second and third crops were also very pure, mp. 200-201.5°C (lit. mp. 197-198°C)[6]; IR: 3449b, 3349b, 3228b, 1668s, 1630s, 1596bs, 1337s, 1269s, 1229, 1150, 1140, 1058, 1008, 987, 834; ^{1}H NMR d: 2.06 (s, 3H), 2.53 (s, 3H), 2.58-2.63 (m, 2H), 2.87-2.92 (m, 2H), 4.11 (bs, 2H), 6.38 (s, 1H); ^{13}C NMR d: 11.30, 18.18, 24.47, 36.99, 114.35, 115.85, 125.73, 137.97, 149.77, 156.98, 206.15.



(118) (119)

5-Amino-6-bromo-2,3-dihydro-4,7-dimethyl-1H-indene-1-one **(119)**

In a 125 mL Erlenmeyer flask containing a magnetic stir bar, 5-amino-2,3-dihydro-4,7-dimethyl-1H-indene-1-one **(118)** (0.9973 g, 5.69 mmol, 1 eq.) was dissolved in methylene chloride (60 mL). Water (10 mL) was added and the rapidly stirring mixture cooled in an ice bath. In dim light a solution of bromine (1.046 g, 6.55 mmol, 1.15 eq.) in methylene chloride (10 mL) was added over one minute to the yellow suspension. The excess bromine was quenched after five minutes by adding a saturated aqueous solution of sodium bisulfite to the flask. Enough saturated aqueous potassium carbonate solution was added to the mixture to make the aqueous layer strongly basic. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 100 mL). The combined organic layers were dried and the solvent was evaporated to obtain yellow solid (1.4432 g, 100% yield) which was further purified by chromatography using recycled chloroform and gave bright yellow needles from methanol, mp. 203-203.5°C (lit. mp. 189-190°C; 197-198°C)[6,14]; IR: 3476b, 3355bs, 3208b, 2955, 2930, 1679s, 1619s, 1590, 1550s, 1470, 1438, 1328s, 1250s, 1227, 1158, 1077, 1028, 990, 948, 871, 822, 758b, 684, 643; ^{1}H NMR d: 2.14 (s, 3H), 2.61-2.66 (m, 2H), 2.72 (s, 3H), 2.84-2.89 (m, 2H), 4,71 (bs, 2H); ^{13}C NMR d: 12.68, 17.44, 23.98, 36.99, 113.13, 115.09, 125.55, 137.62, 146.74, 154.53, 205.49.



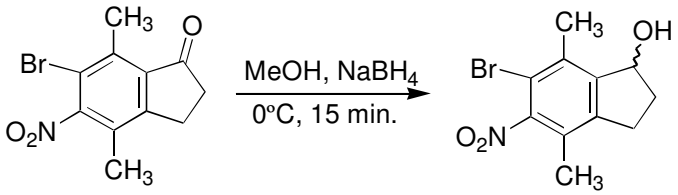
(119) (120)

6-Bromo-2,3-dihydro-4,7-dimethyl-5-nitro-1H-indene-1-one **(120)**

Into a 2 L Erlenmeyer flask with a magnetic stir bar was placed 5-amino-6-bromo-2,3-dihydro-4,7-dimethyl-1H-indene-1-one **(119)** (4.5043 g, 17.7 mmol, 1 eq.) and glacial acetic acid (266 mL). The stirring mixture was heated to 55°C in a water bath and sodium perborate tetrahydrate (16.36 g, 106 mmol, 6 eq.) added over one minute.

After two hours, ethyl acetate (250 mL) and water (1 L) were added to the reaction mixture. The aqueous layer was separated and extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with water (3 x 500 mL) and once with saturated aqueous sodium bicarbonate solution. The bicarbonate layer was washed once with ethyl acetate (100 mL) and the combined organic layers were washed with brine, dried and evaporated.

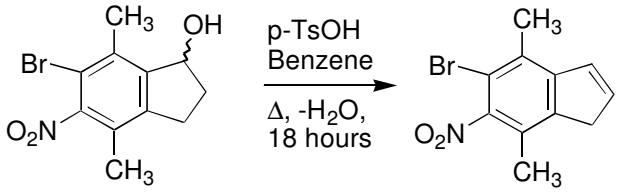
The impure product (4.09 g, 81% yield) was recrystallized from methanol to give dark yellow needles (1.0544g, 21% yield), mp. 180-181°C (lit. mp. 177-178°C)[6]; IR: 1713s, 1532s, 1441s, 1406, 1380s, 1312, 1279, 1227, 1106, 998, 946, 868s, 829, 790, 743; ^{1}H NMR d: 2.28 (s, 3H), 2.76 (s, 3H), 2.75-2.81 (m, 2H), 2.97-3.02 (m, 2H); ^{13}C NMR d: 13.17, 16.91, 24.13, 36.79, 114.92, 125.75, 135.20, 138.60, 144.18, 155.00, 205.45.



(120) (121)

6-Bromo-2,3-dihydro-4,7-dimethyl-5-nitro-1H-indene-1-ol **(121)**

In a 250 mL round-bottomed flask containing a magnetic stir bar, 6-bromo-2,3-dihydro-4,7-dimethyl-5-nitro-1H-indene-1-one **(120)** (1.9058 g, 6.71 mmol, 1 eq.) was suspended in methanol (67 mL). The stirring flask was cooled in an ice bath and sodium borohydride (0.3807 g, 10.06 mmol, 1.5 eq.) added over 30 seconds. TLC verified that the reaction was complete after 15 minutes. The stir bar was removed and the solvent evaporated with gentle heating. Water (50 mL) was added to the flask and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried and evaporated with gentle warming. The light yellow solid (1.8607 g, 97% yield) gave large yellow crystals from methanol, mp. 139-139.5°C (lit. mp. 139-141°C)[14]; IR: 3282bs, 2940b, 1533s, 1439, 1377s, 1202, 1073, 1045, 969, 908s, 877s, 732s; ^{1}H NMR d: 1.73 (bd, 1H, J = 6.1), 2.07-2.19 (m, 1H), 2.20 (s, 3H), 2.38-2.53 (m, 1H), 2.50 (s, 3H), 2.79 (ddd, 1H, J = 16.8, 9.1, 3.3), 2.99-3.12 (m, 1H), 5.35 (bs, 1H); ^{13}C NMR d: 14.40, 18.94, 29.28, 34.63, 75.78, 113.20, 124.48, 134.69, 143.58, 144.93, 152.59.

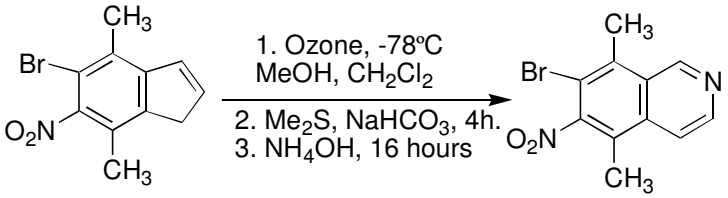


(121) (122)

5-Bromo-4,7-dimethyl-6-nitro-1H-indene **(122)**

In a 250 mL round-bottomed flask containing a magnetic stir bar, 6-bromo-2,3-dihydro-4,7-dimethyl-5-nitro-1H-indene-1-ol **(121)** (2.575 g, 9.00 mmol, 1 eq.) was dissolved in benzene (100 mL), and p-toluenesulfonic acid monohydrate (0.342 g, 1.80 mmol, 0.2 eq.) was added. A Dean-Stark trap and reflux condenser were attached to the flask in such a manner that the condensate passed through a bed of anhydrous calcium chloride before returning to the flask. After 18 hours, water (75 mL) was added to the dark mixture and the aqueous layer and tar in the flask were extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried and evaporated with gentle warming to obtain yellow-brown solid (2.390 g, 99% yield).

The product was dissolved in ethyl acetate, silica gel (12 mL) was added, and the solvent was evaporated with gentle warming. Heptane was added and the mixture evaporated to strip all ethyl acetate away from the silica. The dry powder was loaded onto a 4 by 6 cm column and eluted with 1:10 ethyl acetate/petroleum ether to obtain yellow solid (2.106 g, 87% yield) which was recrystallized from isopropanol to give fluffy yellow needles, mp. 133-135°C (lit. mp. 132-135°C)[14]; IR: 1524s, 1436s, 1381s, 1346s, 1248, 1190, 1111, 967, 950, 884s, 790s, 749, 712, 687, 661; ^{1}H NMR d: 2.27 (s, 3H), 2.48 (s, 3H), 3.30 (t, 2H, J = 1.6), 6.73 (dt, 1H, J = 5.6, 1.9), 6.94 (dt, 1H, J = 5.6, 1.8); ^{13}C NMR d: 14.26, 19.08, 39.01, 113.04, 123.27, 129.29, 130.28, 137.34, 142.15, 145.30, 149.54.

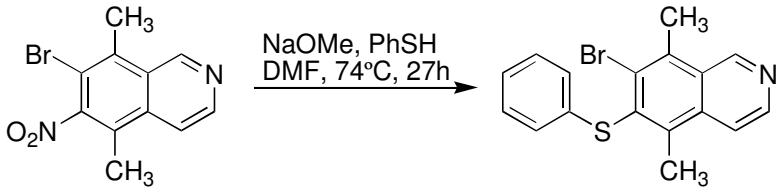


(122) (123)

7-Bromo-5,8-dimethyl-6-nitroisoquinoline **(123)**

In a 100 mL ozonolysis flask containing a magnetic stir bar, 6-bromo-4,7-dimethyl-5-nitro-1H-indene **(122)** (2.001 g, 7.46 mmol) was dissolved in methanol (37 mL) and methylene chloride (37 mL). The flask was cooled in a dry ice/acetone bath with stirring. Ozone was bubbled through the solution even if it had started precipitating. Once the solution had turned deep blue and all solid had dissolved, the solution was purged with oxygen until all blue color was gone before pouring it into a 250 mL round-bottomed flask containing sodium bicarbonate (0.75 g), dimethyl sulfide (3.7 mL), and a magnetic stir bar. A cork was placed in the flask and the mixture was stirred in the hood for four hours. Concentrated aqueous ammonia (37 mL) was added to the flask and the stirring was continued overnight.

The stir bar was removed from the flask and the contents were evaporated until a thin paste remained. Water (100 mL) and methylene chloride (100 mL) were added to the flask and the aqueous layer was extracted with methylene chloride (2 x 50 mL). The combined organic layers were washed with brine, dried and evaporated to produce yellow solid (1.9116 g, 91% yield) which was recrystallized from isopropanol to give light yellow crystals, mp. 196.5-198°C (lit. mp. 194-195°C)[6]; IR: 3079, 2933, 1603, 1532s, 1458b, 1424, 1384s, 1356s, 1299, 1273, 1217, 1078, 1036, 997, 909s, 820s, 797, 744, 712b, 621s; ^{1}H NMR d: 2.52 (s, 3H), 2.86 (s, 3H), 7.74 (d, 1H, J = 3.7), 8.68 (d, 1H, J = 4.0), 9.46 (s, 1H); ^{13}C NMR d: 13.37, 18.22, 112.13, 117.53, 124.21, 126.86, 134.14, 136.09, 144.56, 149.66, 151.71.



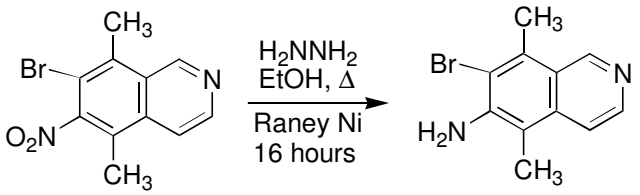
(123) (124)

7-Bromo-5,8-dimethyl-6-(thiophenyl)isoquinoline **(124)**

A stir bar and 7-bromo-5,8-dimethyl-6-nitroisoquinoline **(123)** (0.3850 g, 1.37 mmol, 1 eq.) were placed into a 25 mL Erlenmeyer flask and DMF (9.6 mL), thiophenol (0.281 mL, 2.74 mmol, 2 eq.), and sodium methoxide (0.111 g, 2.05 mmol, 1.5 eq.) were added. The flask was corked and stirred in a 100°C oil bath for six hours.

The hazy brown solution was poured into water (100 mL) and extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with aqueous sodium carbonate and brine, dried and evaporated. The residue was eluted from a 2 by 12 cm column using 1:1 petroleum ether/ethyl acetate giving a white solid with a yellow impurity (0.442 g, 94% yield), very pure by NMR. The product was recrystallized from isopropanol to produce yellow crystals, mp. 128-129°C; IR: 3053b, 3014, 2922b, 2860b, 1930b, 1878b, 1737, 1595, 1580s, 1538, 1477s, 1438s, 1379s, 1355, 1286, 1211, 1155, 1082, 1022, 978, 863s, 821, 741s, 690; ^{1}H NMR d: 2.86 (s, 3H), 2.87 (s, 3H), 6.98 (d, 2H, J = 7.3), 7.08 (t, 1H, J = 7.2), 7.17 (t, 2H, J = 7.4), 7.73 (d, 1H, J = 5.9), 8.61 (d, 1H, J = 5.9), 9.47 (s, 1H); ^{13}C NMR d: 18.55, 19.70, 117.65, 125.36, 126.46, 127.72, 128.92, 132.17, 134.27, 134.33, 135.32, 136.78, 139.89, 143.57, 149.77.

The product gave a positive Beilstein test, a silver bromide precipitate, a lead sulfide precipitate, and converted fluorescein to eosin after sodium fusion and oxidation by lead dioxide.

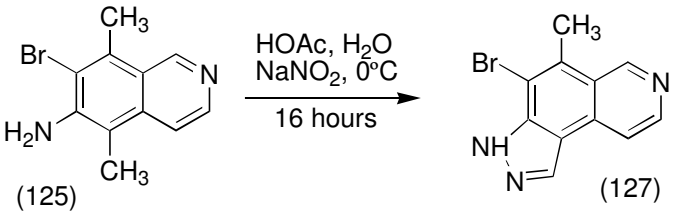


(123) (125)

6-Amino-7-bromo-5,8-dimethylisoquinoline **(125)**

Into a 10 mL round-bottomed flask were placed 7-bromo-5,8-dimethyl-6-nitroisoquinoline **(123)** (0.1217 g, 0.433 mmol, 1 eq.), hydrazine monohydrate (0.13 g, 2.60 mmol, 6 eq.), 50% Raney nickel in water (0.011 g, 0.15 mmol, 0.35 eq.), absolute ethanol (3 mL), and a magnetic stir bar. A reflux condenser was placed on the flask and it was heated to reflux with stirring. The reaction time varied depending on the amount of nickel and its activity, and more of the product debrominated to form **(126)** the longer the reaction ran. TLC was used to monitor the progress of the reduction, which was usually complete overnight. The stir bar was removed and the solvent evaporated.

The residue was dissolved in 3% methanol/methylene chloride, filtered through a 2 cm plug of silica in a pipette, and the solvent evaporated to reveal yellow solid (0.1045 g, 96% yield) which was recrystallized from ethyl acetate to give dark yellow powder, mp. 154.5-156°C (lit. mp 128°C; 153.5-156°C)[6,14]; IR: 3458b, 3390, 3329b, 3204b, 3067, 3010, 2921b, 2859, 2720, 1922, 1877, 1830, 1774, 1726, 1599s, 1565, 1489, 1432b, 1394, 1364s, 1355s, 1272s, 1258, 1200, 1155, 1101, 1073, 1032, 1014, 926, 812s, 773, 752, 660s; ^{1}H NMR d: 2.35 (s, 3H), 2.81 (s, 3H), 4.66 (bs, 2H), 7.52 (d, 1H, J = 6.0), 8.40 (bd, 1H, J = 5.1), 9.24 (bs, 1H); ^{13}C NMR d: 12.07, 18.54, 109.72, 115.48, 116.60, 122.62, 133.85, 135.09, 142.68, 142.97, 149.20.

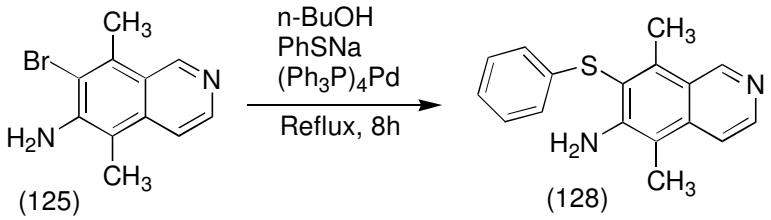


6-Bromo-5-methyl-3H-pyrazolo[4,3-*f*]isoquinoline **(127)**

Into a 25 mL round-bottomed flask were placed 6-amino-7-bromo-5,8-dimethylisoquinoline **(125)** (0.0600g, 0.24 mmol, 1 eq.), glacial acetic acid (1.89 mL) and a magnetic stir bar. The flask was cooled in an ice bath about 30 seconds, then a solution of sodium nitrite (0.0181 g, 0.26 mmol, 1.1 eq.) in water (0.24 mL) was added dropwise over another 30 seconds. Over this time the solution turned from yellow to orange. The flask was stoppered and the ice bath was allowed to warm to room temperature overnight.

The reaction mixture was added to sufficient concentrated aqueous ammonia to basify it and the mixture was allowed to cool before being extracted with methylene chloride (2 x 50 mL). The combined organic layers were extracted with dilute hydrochloric acid (3 x 200 mL) and the combined aqueous layers were basified with aqueous sodium carbonate. The aqueous layer was extracted with methylene chloride (2 x 50 mL) and chloroform (2 x 50 mL), and the combined extracts were dried, filtered, and evaporated to expose an orange-yellow solid (0.047g)

The product was eluted from a 2 by 7 cm column using chloroform (25 mL) and 1% methanol/chloroform (150 mL) to recover starting material (0.0214g, 36% recovery). Further elution with 1.5% methanol/chloroform provided a pure yellow solid (0.008 g, 13% conversion, 20% yield based on recovered starting material), mp. 305.5-307°C (dec.); IR: 3185, 3127, 3075b, 3010b, 2956b, 2847b, 2767bs, 2531, 1614s, 1595, 1569, 1521b, 1448, 1373, 1328b, 1302, 1259b, 1190, 1152, 1051s, 1039, 1008, 932s, 861b, 819s, 801, 780, 687s, 606; ^{1}H NMR (CD_3CO_2D) d: 2.95 (s, 3H), 8.59 (d, 1H, J = 6.2), 8.88 (d, 1H, J = 6.2), 8.96 (s, 1H), 9.72 (s, 1H); ^{13}C NMR d: 18.27, 112.98, 116.89, 121.18, 126.41, 135.00, 136.07, 136.85, 138.11, 143.84, 144.78; Elemental analysis: C: 50.54, H: 3.03, N: 15.80; $C_{11}H_8BrN_3$ requires C: 50.41, H: 3.08, N: 16.03%.



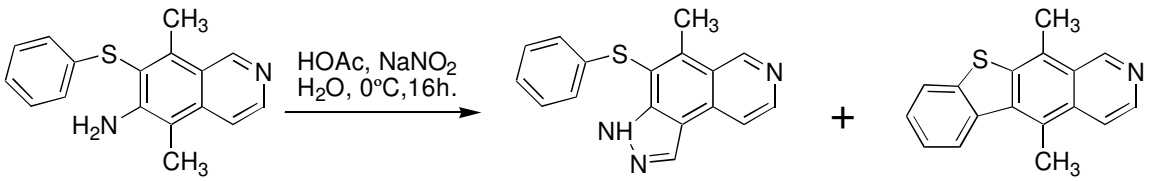
6-Amino-5,8-dimethyl-7-(thiophenyl)isoquinoline **(128)**

A magnetic stir bar and 6-amino-7-bromo-5,8-dimethylisoquinoline **(125)** (0.4938 g, 1.97 mmol, 1 eq.) were placed into a 25 mL round-bottomed flask, and a solution of sodium n-butoxide (7.7 mL, 0.64M, 4.92 mmol, 2.5 eq.), made by dissolving sodium in dry n-butanol, was added. Distilled thiophenol (0.303 mL, 2.95 mmol, 1.5 eq.) was injected from a syringe and tetrakis(triphenylphosphine)palladium(0) (0.114 g, 0.098 mmol, 0.05 eq., fresh from Lancaster) was added. An air reflux condenser having a greased joint was installed on the flask and the system was purged with argon before being heated to reflux with stirring.

After eight hours, the mixture was muddy greenish-black, and TLC verified the reaction to be complete. The flask was cooled, ethyl acetate (10 mL) and silica gel (4 mL) were added and thoroughly mixed, and the solvent was evaporated , using a gentle stream of air to remove the last butanol. The greenish silica was applied to a 2 by 12 cm column and eluted with ethyl acetate to obtain mostly pure product (0.356 g, 65% yield), impure product (0.127 g, 23% yield), and 6-amino-5,8-dimethylisoquinoline **(126)** (0.031 g, 9% yield).

A second 2 by 12 cm column of the almost pure product and impure product using ethyl acetate provided mostly pure product (0.391 g, 71% yield), impure product (0.064 g, 12% yield), and additional 6-amino-5,8-dimethylisoquinoline **(126)** (0.010 g, 3% yield). The almost pure product was recrystallized from ethyl acetate to slowly produce large yellow crystals (0.232 g, 42% yield), mp. 159.5-160.5°C; 3482b, 3439b, 3374b, 3308b, 3194b, 3071, 3056, 3013, 2956, 2921b, 2871b, 2729, 2604, 2513, 2457, 1929b, 1878b, 1795, 1773, 1733, 1599s, 1581s, 1553, 1477s, 1439s, 1429, 1411, 1375, 1365, 1349, 1275, 1257, 1215, 1198, 1156, 1099, 1080, 1070, 1036, 1024, 998, 937, 899, 815, 779, 739bs, 715, 689s, 669, 616; ^{1}H NMR d: 2.34 (s, 3H), 2.92 (s, 3H), 4.98 (s, 2H), 6.97 (d,

2H, J = 7.3), 7.09 (t, 1H, J = 7.3), 7.18 (t, 2H, J = 7.4), 7.57 (d, 1H, J = 6.0), 8.42 (d, 1H, J = 6.1), 9.30 (s, 1H); ^{13}C NMR d: 11.91, 16.65, 108.75, 115.39, 119.01, 122.46, 125.47, 125.89, 129.08, 135.77, 136.87, 141.69, 143.80, 146.69, 150.13; Elemental analysis: C: 72.55, H: 5.80, N: 10.07; $C_{17}H_{16}N_2S$ requires C: 72.82, H: 5.75, N: 9.99%.



(128) (129) 25% yield (130) 60% yield

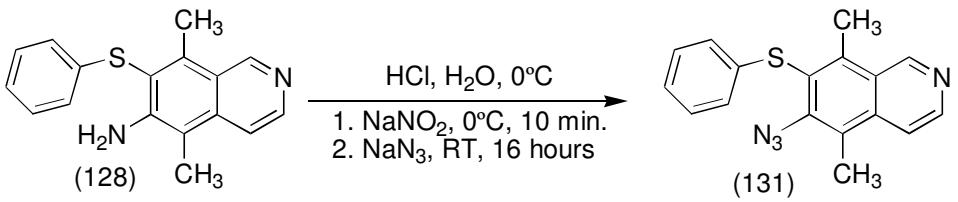
5-Methyl-6-thiophenyl-3H-pyrazolo[4,3-*f*]isoquinoline **(129)** and 5,11-Dimethyl[1]benzothieno[3,2-*g*]isoquinoline (Isothiaellipticine) **(130)**

Into a 10 mL round-bottomed flask were place 6-amino-5,8-dimethyl-7-(thiophenyl)isoquinoline **(128)** (0.0330 g, 0.12 mmol, 1 eq.) and a magnetic stir bar, and glacial acetic acid (0.93 mL) was added. The flask was purged with argon and stoppered. Once the amine dissolved the yellow solution was stirred in an ice bath for 20 seconds before a solution (0.12 mL) of sodium nitrite (0.0089 g, 0.13 mmol, 1.1 eq.) in water was added over 30 seconds. The solution turned reddish-orange within a minute. The ice bath was allowed to warm to room temperature overnight. When more sodium nitrite was added on a separate occasion, it seemed to destroy the product.

The reaction mixture was poured into sufficient dilute aqueous ammonia to basify it and the mixture was extracted with chloroform (3 x 30 mL). The combined extracts were washed with brine, dried and evaporated.

The orange-brown oil was eluted from a 2 by 6 cm column of basic alumina using methylene chloride (75 mL), 2% methanol/methylene chloride (50 mL), and 10% methanol/methylene chloride (10 mL). The only pure fraction, which was recrystallized as yellow fluff from heptane, was the 5,11-dimethyl[1]benzothieno[3,2-*g*]isoquinoline **(130)** (0.0114 g, 37% conversion, 60% yield based on recovered starting material), mp. 153-154°C (lit. mp. 146-149°C)[77]; IR: 3060b, 2920b, 2860, 1900b, 1651b, 1586, 1575, 1564, 1482, 1446s, 1425, 1381s, 1368s, 1324, 1299, 1269, 1237, 1174, 1157, 1143, 1071, 1038b, 982, 878, 808s, 782, 761s, 732s, 715, 606; ^{1}H NMR d: 2.84 (s, 3H), 3.02 (s, 3H), 7.46 (dt, 1H, J = 7.3, 1.4), 7.51 (dt, 1H, J = 7.2, 1.2), 7.84 (dd, 1H, J = 7.1, 1.5), 7.96 (d, 1H, J = 6.1), 8.40 (d, 1H, J = 7.4), 8.54 (d, 1H, J = 6.2), 9.50 (s, 1H); ^{13}C NMR d: 15.69, 16.59, 116.00, 122.74, 124.47, 124.98, 125.66, 126.63, 127.47, 127.72, 132.72, 135.57, 136.50, 138.75, 140.61, 141.15, 148.87.

The remaining mixture was eluted from a 2 by 10 cm column of silica using 1% methanol/methylene chloride (50 mL), 1.5% methanol/methylene chloride (100 mL), and 2% methanol/methylene chloride (100 mL). Impure fractions were eluted again on the same column using 1.5% methanol/methylene chloride (100 mL) and 2% methanol/methylene chloride (100 mL) to affect nearly complete separation of recovered starting material **(128)** (0.0129 g, 39% recovery) and traces of the other product, 5-methyl-6-thiophenyl-3H-pyrazolo[4,3-*f*]isoquinoline **(129)** (0.0052 g, 15% conversion, 25% yield based on recovered starting material). The latter product was dissolved in ethyl acetate, evaporated onto silica, and eluted from a 2 by 5 cm column. The pure fraction, which gave light brown disc-shaped crystal clumps from ethanol/chloroform, was a yellow solid, mp. 253-257°C (dec.); IR: 3171, 3111b, 3060b, 3011b, 2948b, 2924b, 2851, 2828, 2772b, 2660b, 1936b, 1727b, 1691b, 1613s, 1581s, 1514b, 1477s, 1439, 1410, 1373, 1329, 1305, 1262, 1191, 1157, 1083, 1050, 1038, 1023, 1012, 933s, 882, 829, 810, 785, 738s, 722, 697, 687s, 665, 615; ^{1}H NMR d: 3.04 (s, 3H), 7.08 (dd, 2H, J = 6.7, 1.6), 7.12-7.28 (m, 3H), 8.05 (dd, 1H, J = 5.5, 0.8), 8.50 (s, 1H), 8.76 (d, 1H, J = 5.5), 9.52 (s, 1H), 10.77 (bs, 1H); ^{1}H NMR (CD_3CO_2D) d: 3.10 (s, 3H), 7.16-7.27 (m, 5H), 8.67 (d, 1H, J = 6.3), 8.90 (s, 1H), 8.91 (d, 1H, J = 6.6), 9.83 (s, 1H); ^{13}C NMR (CD_3CO_2D) d: 16.74, 116.96, 121.06, 121.22, 126.29, 127.79, 128.81, 130.55, 135.37, 136.38, 137.77, 138.04, 143.51, 144.64, 145.44; HRMS: Found by EI at 70eV, m/z 291.0829 (M^+); $C_{17}H_{13}N_3S$ required 291.0830.

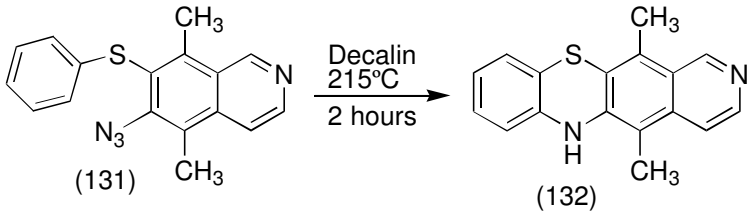


6-Azido-5,8-dimethyl-7-(thiophenyl)isoquinoline **(131)**

Concentrated hydrochloric acid (6.5 mL) was diluted with water (350 mL) and portions of the solution were used to dissolve 6-amino-5,8-dimethyl-7-(thiophenyl)isoquinoline **(128)** (0.279 g, 0.99 mmol, 1 eq.) with heating. The bright yellow solution was decanted into a 500 mL Erlenmeyer flask containing a magnetic stir bar. The stirring solution was cooled to 4°C in an ice bath, by which time a precipitate sometimes formed, and a solution of sodium nitrite (0.103 g, 1.49 mmol, 1.5 eq.) in water (4 mL) was added in one portion. The solution turned red and then darkened to brownish-red.

After ten minutes, during which any precipitate redissolved, a solution of sodium azide (1.293 g, 19.9 mmol, 20 eq.) in water (10 mL) was added over 10 seconds. The solution foamed slightly and lightened in color to orange-yellow. The flask was stoppered and protected from light. The ice bath was allowed warm to room temperature overnight.

Ethyl acetate (70 mL) was added to the apple juice color solution, and the aqueous layer was basified with aqueous sodium carbonate. The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic layers were washed with brine. The organic layer was filtered, dried, and evaporated and the residue was eluted from a 2 by 8 cm column using 1:1 ethyl acetate/petroleum ether. The yellow oil darkened on standing and was better stored in the freezer, where it slowly produced a crystalline mass (0.181 g, 59% yield), mp. 78.5-80.5°C; IR: 3067b, 3019, 2954b, 2923, 2867, 2261b, 2113s, 1599s, 1581, 1544, 1478s, 1440s, 1419, 1361, 1333bs, 1271b, 1211, 1163, 1081b, 1024, 997, 916, 818, 739s, 688, 640; ^{1}H NMR d: 2.64 (s, 3H), 2.99 (s, 3H), 7.03 (dd, 2H, J = 7.3, 0.7), 7.14 (t, 1H, J = 7.2), 7.22 (t, 2H, J = 7.3), 7.76 (d, 1H, J = 5.9), 8.63 (d, 1H, J = 5.9), 9.50 (s, 1H); ^{13}C NMR d: 13.65, 16.67, 117.12, 125.26, 125.82, 126.04, 126.59, 127.56, 129.15, 136.57, 136.79, 141.61, 141.89, 144.55, 150.36.

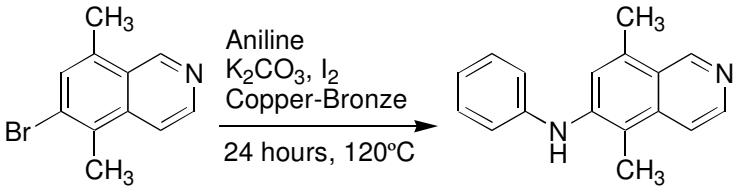


(131) (132)

5,12-Dimethyl-6H-pyrido[4,3-*b*]phenothiazine **(132)**

A magnetic stir bar and decalin (36 mL) were placed into a 100 mL round-bottomed flask. A reflux air condenser was attached to the flask and an addition funnel was attached to the condenser. A solution of 6-azido-5,8-dimethyl-7-(thiophenyl)isoquinoline **(131)** (0.2795 g, 0.91 mmol) in decalin (26 mL), was placed in the addition funnel, and the system was purged with argon. The stirring flask was heated to 155°C in an oil bath and the solution added from the addition funnel over 20 minutes. The addition funnel was rinsed with decalin (11 mL), the temperature of the oil bath was increased to 215°C, and the reaction was cooked for two hours.

The hazy orange suspension was allowed to cool and it was eluted from a 2 by 7 cm column using petroleum ether (70 mL), chloroform (45 mL), and 1% methanol/chloroform (200 mL). It required compressed air to force the decalin through the column so that the other solvents could be applied. Some of the product was impure (0.091 g) and contained decalin. The almost pure fractions gave a yellow-orange solid (0.195 g, 77% yield). The solid became impure if left sitting, but was more stable when recrystallized from 15% ethyl acetate/methanol to produce dark, copper colored flakes, mp. 217-218.5°C; IR (KBr): 3430, 3340b, 3278b, 3206, 3117, 3060, 2956, 2813, 2577, 1908, 1768, 1636, 1602, 1585, 1570s, 1552, 1523, 1478s, 1449b, 1403s, 1388, 1372, 1345s, 1305, 1279s, 1257, 1194, 1159, 1130b, 1086, 1064, 1041, 1033, 954, 928, 849, 836, 816, 807, 772, 741s, 733, 718, 698, 655; ^{1}H NMR d: 2.35 (s, 3H), 2.62 (s, 3H), 6.24 (bs, 1H), 6.65 (d, 1H, J = 7.8), 6.85 (t, 1H, J = 7.4), 7.03 (t, 1H, J = 7.9), 7.05 (d, 1H, J = 7.6), 7.47 (d, 1H, J = 5.9), 8.34 (d, 1H, J = 5.9), 9.12 (s, 1H); ^{13}C NMR d: 10.87, 14.47, 108.86, 115.06, 116.00, 117.95, 121.65, 122.79, 125.09, 126.61, 127.51, 129.23, 135.68, 139.28, 139.52, 143.21, 148.40; Elemental analysis: C: 73.28, H: 5.00, N: 9.96; $C_{17}H_{14}N_2S$ requires C: 73.35, H: 5.07, N: 10.06%.



(133) (134)

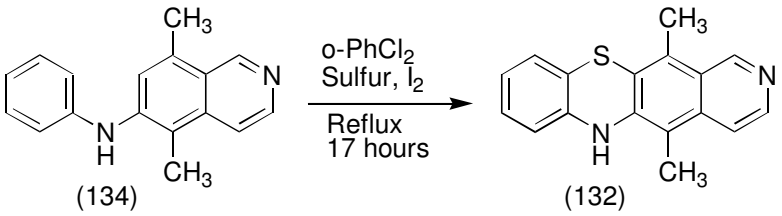
6-Anilino-5,8-dimethylisoquinoline **(134)**

Into a 100 mL round-bottomed flask were placed a magnetic stir bar, aniline (2.62 g, 28.2 mmol, 10 eq.), copper bronze (0.358 g, 5.63 mmol, 2 eq.), ground potassium carbonate (0.778 g, 5.63 mmol, 2 eq.), iodine (0.0088 g, 0.035 mmol, 0.01 eq.), and 6-bromo-5,8-dimethylisoquinoline **(133)** (0.6650 g, 2.82 mmol, 1 eq.), mp. 113-114°C (lit. mp. 111.5-112.5°C)[34]; IR: 3074, 3041, 2979, 2950, 2921, 2861b, 2817, 1725b, 1603s, 1577, 1490, 1455, 1440, 1406, 1381s, 1359, 1303, 1271, 1241s, 1212, 1194, 1168, 1094, 1070, 1031, 1025, 961, 922, 864s, 811s, 765, 723, 644s; ^{1}H NMR d: 2.66 (s, 3H), 2.68 (s, 3H), 7.48 (s, 1H), 7.70 (d, 1H, J = 6.0), 8.57 (d, 1H, J = 6.0), 9.34 (s, 1H); ^{13}C NMR d: 17.77, 17.86, 117.19, 126.49, 126.84, 130.62, 131.83, 134.50, 136.09, 143.84, 149.66. The flask was purged with argon, stoppered, and allowed to stir in a 120°C oil bath for 24 hours.

The oil bath was allowed to cool below 100°C, water (50 mL) was added to the flask, and the temperature of the oil bath was increased. Half the water was distilled away with rapid stirring to remove aniline. The flask was cooled and the contents were extracted with ethyl acetate (3 x 12 mL). The extracts were filtered through sodium sulfate (1.5 cm) upon silica gel (3.5 cm) in a pipette and the cola colored filtrate was evaporated to deposit brown solid (0.710 g).

The product was eluted from a 2 by 8 cm column using chloroform (400 mL) to obtain product (0.101 g, 14% yield) as dark yellow crystals, a mixture of product and starting material (0.366 g, approximately 53% yield/recovery), and recovered starting material (0.149 g, 22% recovery). Starting material could be separated from the mixture either by recrystallization from ethyl acetate or by fractional sublimation at 100°C under high vacuum. The product was recrystallized from isopropanol or ethyl acetate giving

clumps of orange needles, mp. 194-196°C (lit. mp. 194-195°C)[34]; IR: 3252b, 3186b, 3092, 3025b, 2947, 2913, 2866b, 1921, 1847, 1837, 1774, 1733, 1612s, 1597s, 1527, 1496s, 1481, 1466s, 1442, 1408, 1396, 1381, 1347, 1296, 1275s, 1265, 1220, 1188, 1176, 1155, 1128, 1116, 1077, 1066, 1035, 997, 958, 917b, 894, 871, 841, 816, 780, 748s, 725, 700, 661b, 634; ^{1}H NMR d: 2.46 (s, 3H), 2.68 (s, 3H), 5.84 (bs, 1H), 7.01 (t, 1H, J = 7.3), 7.05 (d, 2H, J = 7.6), 7.29-7.35 (m, 3H), 7.70 (d, 1H, J = 6.0), 8.48 (bd, 1H, J = 2.9), 9.28 (bs, 1H); ^{13}C NMR d: 11.70, 18.54, 115.73, 116.54, 118.90, 120.94, 121.86, 124.24, 129.46, 134.33, 137.10, 141.80, 142.69, 143.19, 149.12

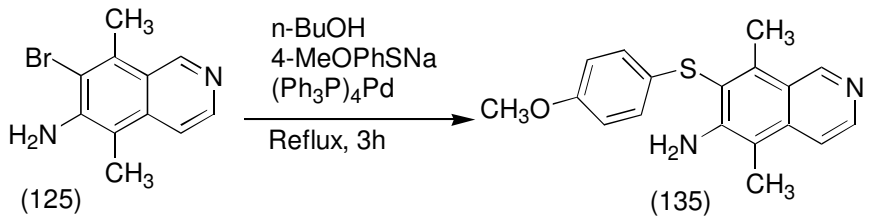


(134) (132)

Attempted Synthesis of 5,12-Dimethyl-6H-pyrido[4,3-*b*]phenothiazine **(132)**

Into a 25 mL round-bottomed flask were placed 6-anilino-5,8-dimethylisoquinoline **(134)** (0.160 g, 0.64 mmol, 1 eq.), finely powdered sulfur (0.0415 g, 0.16 mmol of S_8, 2 eq. of S), iodine (0.0164 g, 0.064 mmol, 0.1 eq.), o-dichlorobenzene (1.62 mL) and a magnetic stir bar. The mixture was refluxed under argon with rapid stirring for 17 hours.

The flask was allowed to cool, ethyl acetate (10 mL) was added, and the aqueous layer was basified with aqueous potassium carbonate. TLC, eluting with ethyl acetate, was used to verify that there was no desired product in the organic layer by comparing with the authentic sample of product obtained previously. The organic layer was eluted from a 2 by 7 cm column using ethyl acetate to recover mostly pure starting material (0.086 g, 54% recovery).

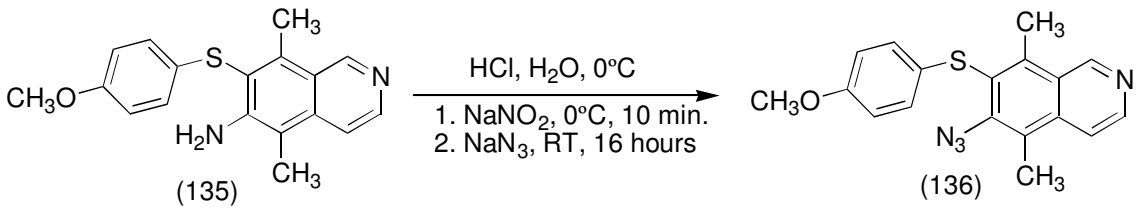


6-Amino-5,8-dimethyl-7-(4'-methoxythiophenyl)isoquinoline **(135)**

A magnetic stir bar and 6-amino-7-bromo-5,8-dimethylisoquinoline **(125)** (0.3494 g, 1.39 mmol, 1 eq.) were placed into a 25 mL round-bottomed flask, and a solution of sodium n-butoxide (5.4 mL, 0.64M, 3.48 mmol, 2.5 eq.), made by dissolving sodium in dry n-butanol, was added. A syringe was used to inject 4-methoxythiophenol (0.257 mL, 2.09 mmol, 1.5 eq.), and tetrakis(triphenylphosphine)palladium(0) (0.804 g, 0.070 mmol, 0.05 eq., fresh from Lancaster) was added. An air reflux condenser having a greased joint was attached to the flask and the system was purged with argon before being heated to reflux with stirring.

After three hours, the mixture had lightened in color to a medium brown, and the reaction was complete according to TLC. The flask was allowed to cool, and the solvent was evaporated using a gentle stream of air. The product was suspended in boiling chloroform, and the cooled mixture was eluted from a 2 by 16 cm column using a 0-5% methanol/chloroform gradient. Some 6-amino-5,8-dimethylisoquinoline **(126)** side product separated, but the impure product had to be eluted again from a 2 by 8 cm column using chloroform (50 mL), 3% methanol/chloroform (100 mL), and 5% methanol/chloroform (50 mL). The product (0.405 g, 94% yield) was almost pure, but together with the combined side product (0.0806 g, 34% yield) weighed too much. The previous chromatography column was reused to further purify the side product, eluting with chloroform (50 mL) and 5% methanol/chloroform (125 mL). The product (0.397 g, 92% yield) and side product (0.057g, 24% yield) obtained were dried thoroughly to expel any retained solvent, but still the theoretical yield was exceeded. The product was recrystallized from ethyl acetate to form large orange rods (0.201 g, 47% yield), mp. 158.5-159°C; IR: 3434, 3297b, 3193b, 3071, 3046, 3000, 2934b, 2831, 2731, 2612, 2520, 2386, 2292, 2229, 2040, 1919, 1867, 1838, 1775, 1738, 1706, 1598s, 1568, 1533, 1493s,

1453b, 1431, 1420, 1411, 1374, 1365, 1351, 1287, 1276s, 1258, 1243s, 1196, 1174, 1156, 1119, 1105, 1085, 1035s, 1006, 938, 817s, 779, 756b, 718, 704, 669, 636, 625; ^{1}H NMR d: 2.34 (s, 3H), 2.96 (s, 3H), 3.72 (s, 3H), 5.00 (bs, 2H), 6.76 (dt, 2H, J = 8.9, 2.2), 7.00 (dt, 2H, J = 8.9, 2.2), 7.57 (dd, 1H, J = 6.2, 0.5), 8.41 (d, 1H, J = 6.1), 9.29 (s, 1H); ^{13}C NMR d: 11.94, 16.76, 55.26, 108.75, 114.89, 115.42, 120.60, 122.53, 126.34, 128.29, 136.79, 141.24, 143.72, 146.68, 150.12, 158.14; Elemental analysis: C: 69.43, H: 5.92, N: 9.01; $C_{18}H_{18}N_2OS$ requires C: 69.65, H: 5.84, N: 9.02%.

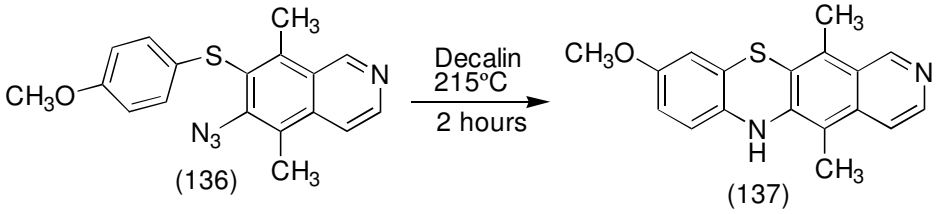


6-Azido-5,8-dimethyl-7-(4'-methoxythiophenyl)isoquinoline **(136)**

Concentrated hydrochloric acid (4.6 mL) was diluted with water (300 mL), and portions of the resulting solution were used to dissolve 6-amino-5,8-dimethyl-7-(4'-methoxythiophenyl)isoquinoline **(135)** (0.2184 g, 0.704 mmol, 1 eq.) with heating. The resulting yellow-orange solution was decanted into a 500 mL round-bottomed flask containing a magnetic stir bar. The solution was cooled to 4°C with stirring in an ice bath, by which time a precipitate sometimes formed, and a solution of sodium nitrite (0.0728 g, 1.06 mmol, 1.5 eq.) in water (1 mL) was added.

During the next ten minutes any solid redissolved, and the solution became deep red-brown. A solution of sodium azide (0.915 g, 14.1 mmol, 20 eq.) in water (5 mL) was added in one portion. The color lightened as the solution foamed gently. The flask was stoppered and protected from light. The ice bath was allowed to warm to room temperature overnight.

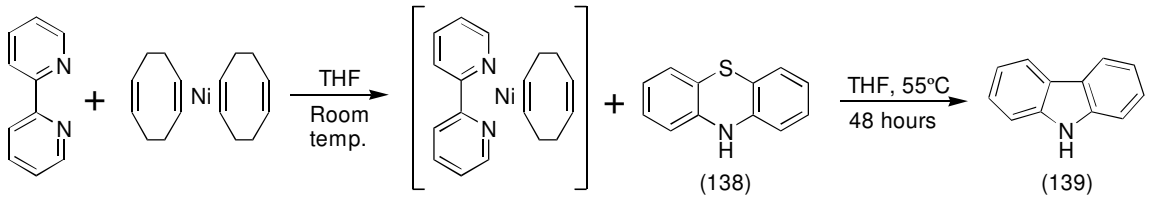
Ethyl acetate (50 mL) was added to the yellow emulsion and the aqueous layer was basified with aqueous sodium carbonate. The aqueous layer was extracted with ethyl acetate (2 x 75 mL) and the combined organic layers were washed with brine, dried, filtered, and evaporated. The product was eluted from a 2 by 6 cm column using 1:1 ethyl acetate/petroleum ether (200 mL) to obtain nearly pure yellow oil (0.134 g, 57% yield), IR: 3066b, 3003b, 2938b, 2835, 2533b, 2484b, 2420b, 2370b, 2328b, 2260b, 2113s, 1928b, 1883b, 1599s, 1573, 1544, 1493s, 1461b, 1419, 1361, 1334, 1286s, 1245s, 1212, 1174, 1105, 1076, 1032, 997, 916, 821s, 674, 641; ^{1}H NMR d: 2.60 (s, 3H), 2.99 (s, 3H), 3.73 (s, 3H), 6.76 (d, 2H, J = 8.8), 7.05 (d, 2H, J = 8.8), 7.71 (d, 1H, J = 5.9), 8.58 (d, 1H, J = 5.9), 9.45 (s, 1H); ^{13}C NMR d: 13.55, 16.66, 55.19, 114.79, 117.00, 125.06, 125.93, 127.06, 129.06, 129.26, 136.22, 141.02, 141.28, 144.25, 150.18, 158.34.



5,12-Dimethyl-9-methoxy-6H-pyrido[4,3-*b*]phenothiazine **(137)**

A magnetic stir bar and decalin (20 mL) were placed into a 100 mL round-bottomed flask and a reflux air condenser was installed. An addition funnel containing a solution of 6-azido-5,8-dimethyl-7-(4'-methoxythiophenyl)isoquinoline **(136)** (0.134 g, 0.40 mmol, 1 eq.) in decalin (6 mL) was placed on the condenser, the system was purged with argon, and the flask was heated to 155°C in an oil bath. The solution from the addition funnel was added over 15 minutes. The addition funnel was rinsed with decalin (5 mL) and the oil bath was heated to 215°C.

After two hours, the suspension of orange crystals was allowed to cool and then eluted from a 2 by 7 cm column using petroleum ether (70 mL), chloroform (70 mL), and 1% methanol/chloroform (180 mL). Pressurized air was necessary to force the decalin through the silica. Impure product (0.029 g) containing some decalin was obtained, along with almost pure orange-brown solid (0.094 g, 76% yield). The crude product formed an impurity of low R_f on standing in air, but was more stable after recrystallization. The purer fraction was recrystallized from chloroform to give orange flakes, mp. 227-229°C; IR: 3276b, 3185b, 3060b, 2998b, 2943b, 2833, 2063, 1897, 1873, 1605, 1591, 1576, 1555, 1498s, 1481s, 1452, 1440, 1410s, 1388, 1368, 1344, 1293, 1276s, 1260, 1230s, 1220s, 1182, 1142b, 1073, 1062, 1038, 953b, 821, 807, 758b, 701b, 666b, 640b; ^{1}H NMR d: 2.35 (s, 3H), 2.65 (s, 3H), 3.75 (s, 3H), 6.13 (s, 1H), 6.61 (d, 2H, J = 1.3), 6.66 (s, 1H), 7.48 (d, 1H, J = 6.0), 8.34 (d, 1H, J = 6.0), 9.13 (s, 1H); ^{13}C NMR d: 10.94, 14.61, 55.72, 108.50, 111.77, 113.35, 115.72, 115.97, 118.86, 121.05, 124.77, 129.27, 132.84, 135.58, 140.05, 143.13, 148.40, 155.59; The structure was verified by single crystal X-ray analysis - see Appendix B.

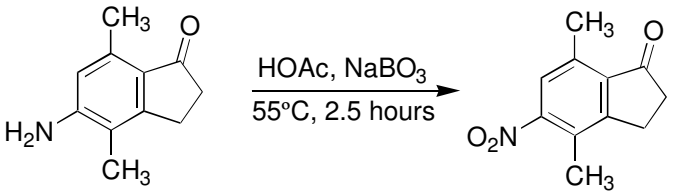


Attempted Conversion of Phenothiazine **(138)** to Carbazole **(139)**

A bottle of fresh, yellow bis(cyclooctadienyl)nickel(0) was purchased from Strem[78] and placed in the freezer of a helium filled glove box as soon as it arrived. The reagent (0.1223 g, 0.44 mmol, 2.2 eq.) was transferred in the glove box using a ceramic scoop to a 5 mL ampule containing a magnetic stir bar which was cleaned of any adhering metal using nitric acid. A septum was placed in the ampule, the ampule was removed from the glove box, and the darkening reactant was carefully removed from the neck of the ampule using a tissue. The atmosphere in the ampule was replaced with argon and the ampule was stoppered with a clean septum and protected from light. Into separate oven-dried 10 mL pointed flasks were placed 2,2'-dipyridyl (0.0694 g, 0.44 mmol, 2.2 eq.) and phenothiazine **(138)** (0.0403 g, 0.20 mmol, 1 eq.). The flasks were purged with argon and stoppered. As soon as possible, before the $Ni(COD)_2$ had a chance to darken, which happened unpredictably but sometimes within hours, freshly distilled THF (0.8 mL) was injected into the ampule, and it was allowed to stir. After fifteen minutes, THF (1.6 mL) was used to dissolve and transfer the dipyridyl to the ampule using a syringe. After the opaque purple liquid in the ampule had stirred for 30 minutes, THF (0.2 mL) was used to dissolve and transfer the phenothiazine to the ampule, and more THF (0.2 mL) to rinse the two flasks into the ampule by syringe. The ampule was lowered into an oil bath preheated to 55°C in the dark. This low temperature was easier to set by plugging the variac powering the nichrome in the oil bath into a second variac, both set at 37 volts.

After 48 hours, the ampule was allowed to cool and glacial acetic acid (0.8 mL) was injected into the mixture of nearly colorless liquid and black solid. The contents of the ampule were transferred to a round-bottomed flask, using ethyl acetate to rinse the ampule, and the solvent was evaporated. The residue was basified using dilute aqueous ammonia and extracted with ethyl acetate (30 mL). The organic layer was washed with

brine, dried and evaporated. According to NMR the residue contained dipyridyl, cyclooctadiene, phenothiazine **(138)** (67% yield) and carbazole **(139)** (33% yield). This was the highest conversion for the five reactions attempted.

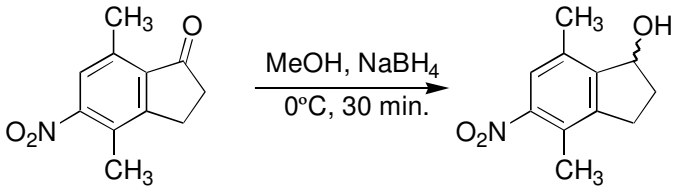


(118) (140)

2,3-Dihydro-4,7-dimethyl-5-nitro-1H-indene-1-one **(140)**

Into a 2 L Erlenmeyer flask were placed 5-amino-2,3-dihydro-4,7-dimethyl-1H-indene-1-one **(118)** (2.0075 g, 11.5 mmol, 1 eq.), glacial acetic acid (172 mL), and a magnetic stir bar. The flask was heated to dissolve the solid and then placed in a 55°C water bath with stirring. Over one minute sodium perborate tetrahydrate (10.576 g, 68.7 mmol, 6 eq.) was added.

After two and a half hours, ethyl acetate (300 mL) and water (800 mL) were added to the flask and the aqueous layer was extracted again with ethyl acetate (2 x 75 mL). A solid impurity remained undissolved. The combined organic layers were washed with water, aqueous sodium bicarbonate, and brine, and these three washings were back extracted with ethyl acetate. The combined organic extracts were dried, filtered, and evaporated to produce bright yellow solid (1.75 g, 74% yield). The product was recrystallized from methanol to furnish yellow fluff, mp. 115-116°C; IR: 2930b, 1707s, 1576, 1521s, 1437, 1390, 1356s, 1323, 1247s, 1094, 992, 895, 848s, 831, 761s, 752, 637; ^{1}H NMR d: 2.45 (s, 3H), 2.65 (s, 3H), 2.78 (t, 2H, J = 5.9), 3.08 (t, 2H, J = 5.8), 7.56 (s, 1H); ^{13}C NMR d: 14.07, 17.77, 24.88, 36.89, 124.77, 127.37, 136.64, 137.23, 152.44, 157.00, 206.61; Elemental analysis: C: 64.29, H: 5.33, N: 6.97; $C_{11}H_{11}NO_3$ requires C: 64.38, H: 5.40, N: 6.83%.

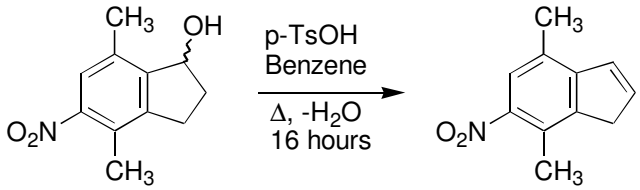


(140) (141)

2,3-Dihydro-4,7-dimethyl-5-nitro-1H-indene-1-ol **(141)**

A 250 mL round-bottomed flask containing 2,3-dihydro-4,7-dimethyl-5-nitro-1H-indene-1-one **(140)** (1.1871 g, 5.78 mmol, 1 eq.) in methanol (58 mL) was warmed until the solid dissolved. A magnetic stir bar was added and the flask was cooled in an ice bath. Over 30 seconds sodium borohydride (0.328 g, 8.68 mmol, 1.5 eq.) was added to the cold, stirring mixture.

After 30 minutes, any starting material which precipitated had redissolved into a clear orange solution. The solvent was evaporated without heating, ethyl acetate (50 mL) and water (150 mL) were added to the flask, and the aqueous layer was extracted again with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried and evaporated. The solid was dissolved in methanol, filtered through glass wool in a pipette to remove insoluble solid, and evaporated to provide product (1.1747 g, 98% yield) pure by TLC. The product was recrystallized from methanol to form rods, mp. 121.5-122°C; IR: 3249bs, 2966, 2927b, 2850b, 2737, 1761, 1618b, 1526s, 1475, 1449, 1430, 1382, 1347bs, 1296, 1264, 1252, 1211, 1199, 1179, 1158, 1067, 1046, 1017, 959s, 902s, 881, 866s, 822, 790, 761, 750, 702b, 615; ^{1}H NMR d: 2.03-2.13 (m, 1H), 2.16 (bs, 1H), 2.39 (s, 3H), 2.42 (s, 3H), 2.42-2.51 (m, 1H), 2.82 (ddd, 1H, J = 16.5, 9.0, 3.7), 3.02-3.15 (m, 1H), 5.30 (bd, 1H, J = 0.6), 7.56 (s, 1H); ^{13}C NMR d: 15.70, 17.78, 29.42, 34.65, 75.06, 124.40, 126.63, 133.50, 145.46, 147.04, 149.75.

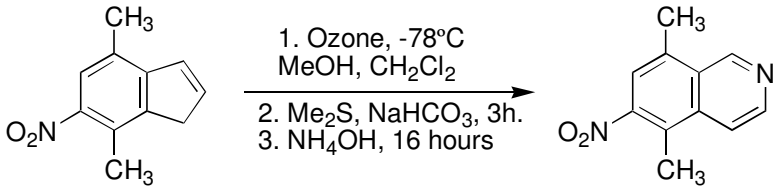


(141) (142)

4,7-Dimethyl-6-nitro-1H-indene **(142)**

Into a 100 mL pear shaped flask were placed 2,3-dihydro-4,7-dimethyl-5-nitro-1H-indene-1-ol **(141)** (1.4786 g, 7.14 mmol, 1 eq.), benzene (88 mL), p-toluenesulfonic acid (0.271 g, 1.43 mmol, 0.2 eq.), and a magnetic stir bar. The mixture was heated to boiling and 10 mL of the solvent distilled to remove most of the water. A Dean-Stark trap loaded with calcium chloride was attached to the flask and reflux was allowed to continue overnight.

Water (15 mL) was added to the cooled mixture and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to bestow yellow solid (1.2998 g, 96% yield). The product was evaporated onto silica (12 mL) and eluted from a 4 by 8 cm column using 1:10 ethyl acetate/petroleum ether (350 mL) to provide yellow solid (1.1353 g, 84% yield). This was recrystallized from isopropanol to form fluffy yellow needles, mp. 75-76.5°C; IR 3068, 3052, 2980, 2918b, 2862, 1576, 1552, 1507s, 1457, 1393, 1377s, 1360s, 1331s, 1318s, 1210, 1131, 1107, 1077, 1036b, 952, 913, 902, 873, 763, 755, 745, 695s, 667, 630; ^{1}H NMR d: 2.41 (s, 3H), 2.51 (s, 3H), 3.34 (bs, 2H), 6.80 (dt, 1H, J = 5.6, 1.9), 6.96 (dt, 1H, J = 5.6, 1.7), 7.73 (s, 1H); ^{13}C NMR d: 16.16, 17.86, 39.31, 124.59, 126.06, 128.14, 129.91, 138.60, 144.26, 146.20, 147.90; Elemental analysis: C: 69.89, H: 5.83, N: 7.49; $C_{11}H_{11}NO_2$ requires C: 69.83, H: 5.86, N: 7.40%.



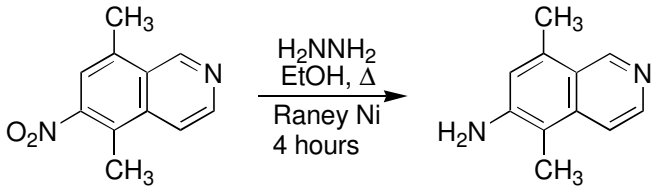
(142) (143)

5,8-Dimethyl-6-nitroisoquinoline **(143)**

Pure 4,7-dimethyl-6-nitro-1H-indene **(142)** (1.1353 g, 6.00 mmol) was dissolved in methylene chloride (30 mL) and methanol (30 mL) in a 100 mL ozonolysis flask. The solution was cooled in a dry ice/acetone bath using oxygen bubbles to churn it. Once cold, ozone was bubbled through the solution until it turned deep blue and any precipitate redissolved. The solution was purged with oxygen until the blue color was gone and it became yellow, and then it was poured into a 250 mL round-bottomed flask containing sodium bicarbonate (0.6 g), dimethyl sulfide (3 mL), and a magnetic stir bar. The flask was corked and allowed to warm to room temperature while stirring. After three hours, concentrated aqueous ammonia (30 mL) was added to the flask, which brought the color from yellow to brown-orange. The mixture was allowed to stir overnight.

The organic solvent was evaporated from the bright orange mixture, water (100 mL) was added to the pasty solid remaining, and the mixture was extracted with methylene chloride (3 x 100 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to create orange solid (1.1212g, 92% yield). The product was dissolved in ethyl acetate and evaporated onto silica (12 mL). The product was eluted from a 4 by 5 cm column using 1:1 ethyl acetate/petroleum ether (200 mL) and ethyl acetate (300 mL) to produce nearly pure product (1.0212 g, 84% yield) which was recrystallized from isopropanol to make yellow powder, mp. 128.5-129.5°C; IR: 3064b, 3036, 2957, 2931, 2860b, 1931, 1896, 1783b, 1610, 1583, 1521s, 1488, 1465, 1432, 1421, 1383s, 1365s, 1350s, 1277, 1245, 1205, 1172, 1078, 1040, 927, 890s, 819s, 766, 747, 723, 653, 607; ^{1}H NMR d: 2.73 (s, 3H), 2.81 (s, 3H), 7.64 (s, 1H), 7.93 (dd, 1H, J = 6.0, 0.8), 8.73 (d, 1H, J = 6.0), 9.50 (d, 1H, J = 0.7); ^{13}C NMR d: 13.57, 18.28, 118.31,

121.67, 126.22, 127.88, 135.63, 136.04, 144.74, 149.82, 149.91; Elemental analysis: C: 65.13, H: 4.87, N: 13.92; $C_{11}H_{10}N_2O_2$ requires C: 65.34, H: 4.98, N: 13.85%.



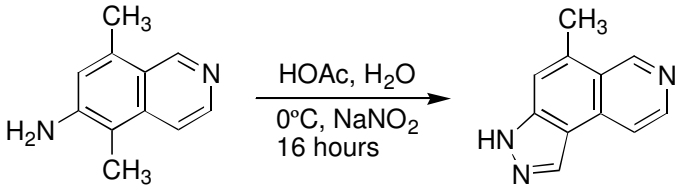
(143) (126)

6-Amino-5,8-dimethylisoquinoline **(126)**

Into a 50 mL round-bottomed flask were placed 5,8-dimethyl-6-nitroisoquinoline **(143)** (0.8782 g, 4.34 mmol, 1 eq.), absolute ethanol (23.9 mL), hydrazine monohydrate (1.304 g, 26.06 mmol, 6 eq.), W-2 Raney nickel (0.23 g, 1.96 mmol, 0.45 eq.), and a magnetic stir bar. A reflux air condenser was inserted into the flask and the contents were refluxed gently with stirring.

After four hours, the reaction was confirmed to be complete by TLC. The solvent was evaporated and the residue was dissolved in 10% methanol/chloroform and filtered through a plug of silica in a pipette. The filtrate was evaporated using a stream of air.

The crude solid was dissolved in chloroform, the organic layer was extracted twice with dilute hydrochloric acid, the combined aqueous layers were back extracted with chloroform, and this last organic layer was back extracted with dilute hydrochloric acid. The combined aqueous layers were basified using sodium carbonate and extracted with chloroform. The organic layer was dried, filtered, and evaporated to manifest a yellow solid (0.7368 g, 98% yield). Recrystallization from ethyl acetate/heptane produced yellow needles, mp. 149.5-150°C (lit. mp. 149°C (vac.))[38]; IR: 3463, 3440, 3399, 3334b, 3190b, 3076, 2947, 2911, 2863, 1920, 1735b, 1652, 1609s, 1595s, 1577, 1490, 1468s, 1443, 1405s, 1387s, 1348, 1280, 1260, 1195, 1155b, 1032, 1001, 922, 905, 876, 868, 821s, 797, 752, 719, 680, 646b; ^{1}H NMR d: 2.29 (s, 3H), 2.64 (s, 3H), 4.11 (bs, 2H), 6.78 (s, 1H), 7.56 (d, 1H, J = 6.0), 8.40 (d, 1H, J = 6.0), 9.17 (s, 1H); ^{13}C NMR d: 10.64, 18.21, 108.35, 115.67, 119.71, 122.78, 134.43, 137.00, 143.09, 144.91, 148.81.



(126) (144)

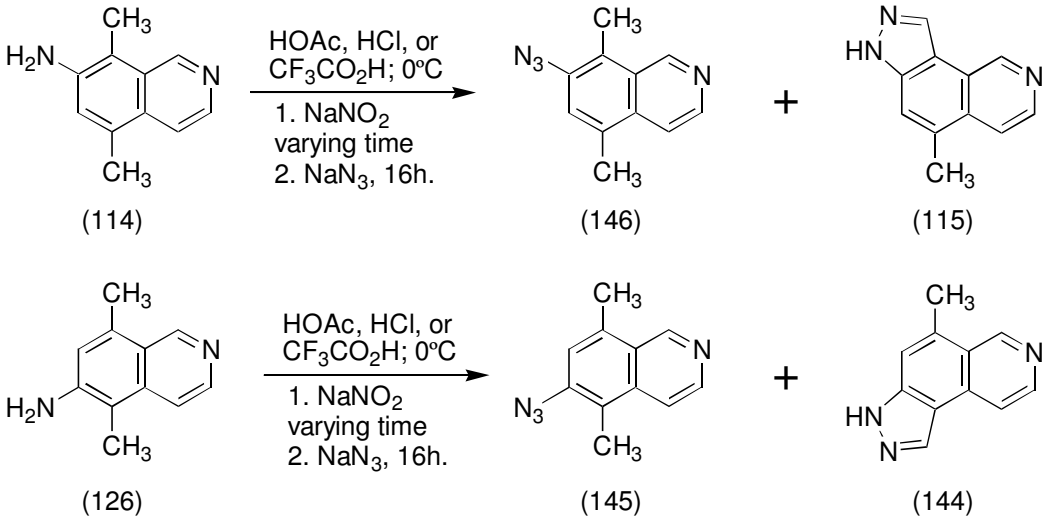
5-Methyl-3H-pyrazolo[4,3-*f*]isoquinoline **(144)**

In a 25 mL round-bottomed flask containing a magnetic stir bar, 6-amino-5,8-dimethylisoquinoline **(126)** (0.1831 g, 1.063 mmol, 1 eq.) was dissolved in glacial acetic acid (8.4 mL). The flask was cooled in an ice bath with stirring, and after about 30 seconds, a solution of sodium nitrite (0.0807 g, 1.169 mmol, 1.1 eq.) in water (1.1 mL) was added over 30 seconds. The ice bath was allowed warm to room temperature overnight.

The reaction solution was poured into sufficient dilute ammonia to make a basic suspension, and this was extracted three times with methylene chloride. The combined organic layers were extracted four times with dilute hydrochloric acid, and the combined aqueous layers were basified with sodium bicarbonate and then extracted four times with methylene chloride. The combined organic layers were washed with brine, dried and evaporated to render yellow solid (0.1512 g, 78% yield) with a red contaminant.

The product was purified on a 4 by 8 cm column using chloroform (200 mL), 2% methanol/chloroform (200 mL), 3% methanol/chloroform (200 mL), and 4% methanol/chloroform (400 mL) to obtain mostly pure product (0.0814 g, 42% yield). To obtain further purification, a solution of the product was evaporated onto neutral alumina and eluted from a 2 by 6 cm column of neutral alumina using chloroform (100 mL), 1% methanol/chloroform (100 mL) and 2% methanol/chloroform (50 mL). The product, which was recrystallized from methanol, was a yellow solid, mp. 272-275°C (dec.); IR: 3147, 3088b, 3025, 2960, 2831, 2770s, 2726, 2673, 2536, 1620s, 1587, 1513, 1480, 1437, 1416, 1371, 1341, 1307, 1264, 1192, 1163, 1069, 1038s, 966, 937s, 873, 845, 829s, 822, 814s, 789, 757, 687, 653, 637, 608; ^{1}H NMR (CD_3CO_2D) d: 2.72 (s, 3H), 7.64 (s, 1H), 8.41 (d, 1H, J = 6.3), 8.60 (s, 1H), 8.68 (d, 1H, J = 6.3), 9.44 (s, 1H); ^{13}C NMR

(CD_3CO_2D) d: 19.89, 116.76, 117.98, 121.67, 125.76, 135.60, 136.62, 137.62, 138.04, 143.38, 143.69; Elemental analysis: C: 71.81, H: 4.90, N: 22.76; $C_{11}H_9N_3$ requires C: 72.11, H: 4.95, N: 22.94%.



Measurement of the Rate of Cyclization of:

6-Amino-5,8-dimethylisoquinoline **(126)** in acetic acid (6A)

6-Amino-5,8-dimethylisoquinoline **(126)** in hydrochloric acid (6H)

6-Amino-5,8-dimethylisoquinoline **(126)** in trifluoroacetic acid (6T)

7-Amino-5,8-dimethylisoquinoline **(114)** in acetic acid (7A)

7-Amino-5,8-dimethylisoquinoline **(114)** in hydrochloric acid (7H)

7-Amino-5,8-dimethylisoquinoline **(114)** in trifluoroacetic acid (7T)

6-Azido-5,8-dimethylisoquinoline **(145)** and 7-Azido-5,8-dimethylisoquinoline **(146)**

For reaction 6A or 7A, either 6-amino-5,8-dimethylisoquinoline **(126)** or 7-amino-5,8-dimethylisoquinoline **(114)** (92.7 mg, 0.54 mmol, 1 eq.) was dissolved in glacial acetic acid (4.25 mL) in a 15 mL pointed flask and water (0.62 mL) was added to prevent the acetic acid from freezing. For reaction 6H or 7H, the same amount of either amine was dissolved in concentrated hydrochloric acid (3.23 mL) and water (1.64 mL). For reaction 6T or 7T the same amount of either amine was dissolved in trifluoroacetic acid (4.25 mL) and water (0.62 mL). Although the measured weights of the two amines for these six reactions were very close but not identical, they will be scaled to one weight for simplification in this report.

A syringe was used to transfer one ninth of one of the above solutions to each of nine numbered vials. A tiny stir bar was placed in each of the first four vials. The vials

were cooled in an ice bath on a magnetic stirrer and 20% aqueous sodium nitrite (23 mL, 4.53 mg, 0.066 mmol, 1.1 eq.) was quickly injected into each vial, followed by a quick injection of 20% sodium azide (58 mL, 11.67 mg, 0.18 mmol, 3 eq.) into the first eight vials after the following delays: Vial #1 - 1 sec., Vial #2 - 4 sec., Vial #3 - 16 sec., Vial #4 - 64 sec., Vial #5 - 256 sec., Vial #6 - 17.07 min., Vial #7 - 68.27 min., Vial #8 - 4.55 hours. Once the injections were complete, the ice bath was placed in the refrigerator overnight.

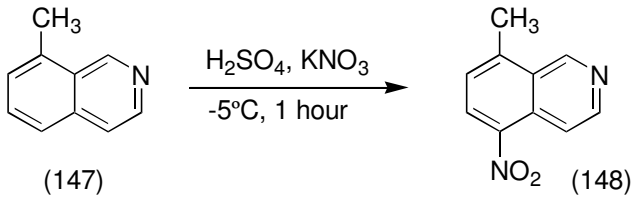
Concentrated aqueous ammonia (2 mL) was added to each vial, producing much heat, and each mixture was extracted with chloroform (3 x 1 mL or until all the solid dissolved). Each extract was filtered through sodium sulfate in a pipette and the filtrate was evaporated. Each residue was dissolved in deuterochloroform, methylene bromide (4.0 mL, 0.046 mmol, 0.8 eq.) was added, and the composition analyzed by NMR.

All samples of pure azide from reactions 6A, 6H, and 6T were combined, and samples from 7A, 7H, and 7T were separately combined, and the solvent was evaporated. The residue was dissolved in hot ethyl acetate and the cooled solution was filtered through silica gel (3 cm) in a pipette, removing most of the color. The filtrate was evaporated to about 4 mL, heated to dissolve precipitated solid, and set aside to crystallize.

6-Azido-5,8-dimethylisoquinoline **(145)** formed long, light yellow needles. These were recrystallized again from ethyl acetate to create large greenish-yellow prismatic needles (89 mg, 41% yield), mp. 149.5-150°C; IR: 3070, 3019, 2948, 2917, 2540, 2473, 2372, 2323, 2275, 2221, 2162, 2112s, 1608s, 1583, 1469, 1442, 1417, 1387, 1331, 1273s, 1200, 1168, 1100, 1078, 1028s, 929, 889, 876, 841, 814s, 733, 691, 662, 616s; ^{1}H NMR d: 2.44 (s, 3H), 2.76 (s, 3H), 7.15 (s, 1H), 7.66 (d, 1H, J = 5.9), 8.55 (d, 1H, J = 6.0), 9.34 (s, 1H); ^{13}C NMR d: 11.69, 18.41, 117.15, 118.64, 120.57, 125.09, 135.36, 136.62, 137.89, 143.86, 149.40; HRMS: Found by CI, m/z 199.0986 (MH^+); $C_{11}H_{11}N_4$ (MH^+) requires 199.0985.

7-Azide-5,8-dimethylisoquinoline **(146)** formed short, bright yellow needles. These were recrystallized again from ethyl acetate to forge bright yellow needles (86 mg, 35% yield), mp. 149.5-150.5°C; IR: 3029, 2991, 2942, 2910, 2868, 2501, 2440, 2382,

2339, 2323, 2266, 2217, 2155b, 2114s, 2082, 2025, 1923, 1885, 1843, 1750, 1605, 1595, 1573, 1494, 1466, 1441, 1409, 1388, 1382s, 1376, 1333s, 1291s, 1272, 1233, 1210, 1171, 1076, 1052, 1037, 997, 920, 879s, 856, 814s, 758b, 729, 691, 660, 637; ^{1}H NMR d: 2.57 (s, 3H), 2.65 (s, 3H), 7.29 (s, 1H), 7.68 (d, 1H, J = 5.8), 8.53 (d, 1H, J = 5.8), 9.38 (s, 1H); ^{13}C NMR d: 11.49, 18.48, 117.05, 121.41, 122.24, 128.37, 132.93, 133.55, 134.81, 142.26, 149.55. Found by CI, m/z 199.0989 (MH^+); $C_{11}H_{11}N_4$ (MH^+) requires 199.0985.

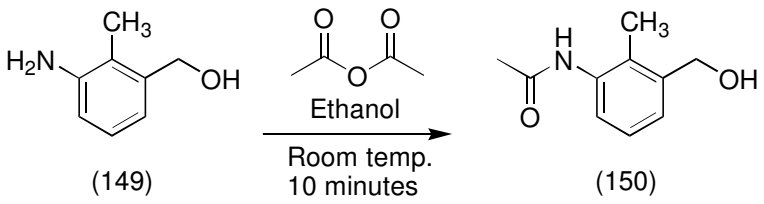


(147) (148)

8-Methyl-5-nitroisoquinoline **(148)**

Into a 50 mL pointed flask were placed sulfuric acid (1.1 mL) and a magnetic stir bar; it was submerged in an ice/salt bath at -5°C and then charged with 8-methylisoquinoline **(147)** (0.100 g, 0.64 mmol, 1 eq.), mp. 89.5-90°C (lit. mp. 87-88°C)[42]; IR: 3056, 3030, 3003b, 2972b, 2943b, 2913, 1778, 1778, 1631, 1582, 1558, 1494, 1446b, 1398s, 1387, 1361s, 1276, 1258, 1245b, 1217s, 1043, 1028, 980, 970, 956, 937, 890s, 838s, 801, 777, 645s, 636; ^{1}H NMR d: 2.54 (s, 3H), 7.43 (d, 1H, J = 8.3), 7.54-7.58 (m, 2H), 7.86 (d, 1H, J = 8.4), 8.47 (d, 1H, J = 5.8), 9.18 (s, 1H); ^{13}C NMR d: 22.04, 119.90, 125.31, 127.10, 127.35, 129.46, 136.03, 140.64, 143.04, 152.06.

A solution of potassium nitrate (0.0801 g, 0.79 mmol, 1.2 eq.) in sulfuric acid (1.1 mL) was added to the beige mixture. After one hour, the cooled, yellow solution was cautiously basified using dilute aqueous ammonia. The cooled mixture was extracted with methylene chloride (3 x 30 mL) and the combined organic layers were washed with brine, dried, filtered, and evaporated to provide brown crystals (0.1075 g, 83% yield), mp. 134.5-135.5°C; IR: 3078b, 3025b, 2967, 2936, 1890, 1846, 1789, 1631, 1588, 1565, 1514s, 1494, 1480, 1470, 1437, 1396, 1380, 1359s, 1346s, 1328, 1277, 1231, 1222, 1161, 1041, 1025, 1015, 925, 872, 825s, 813s, 803s, 770, 740, 713, 671, 645; ^{1}H NMR d: 2.55 (s, 3H), 7.48 (d, 1H, J = 8.4), 7.55 (dd, 1H, J = 6.0, 0.7), 8.00 (d, 1H, J = 8.4), 8.63 (d, 1H, J = 6.1), 9.25 (s, 1H); ^{1}H NMR (NOE): Irradiation at 2.55 ppm increased the integration at 7.48 ppm by 13%, but caused no measurable increase in integration at 9.25 ppm; ^{13}C NMR (APT), C and CH_2 d: 126.87, 127.52, 133.15, 145.88; CH and CH_3 d: 18.34, 113.88, 129.66, 130.16, 145.37, 152.03.

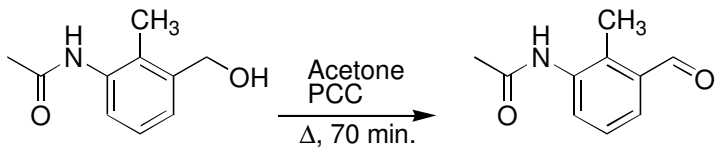


(149) (150)

3-Acetamido-2-methylbenzyl alcohol **(150)**

In a 250 mL round-bottomed flask, absolute ethanol (100 mL) was used to dissolve 3-amino-2-methylbenzyl alcohol **(149)** (2.0697 g, 15.1 mmol, 1 eq.), mp. 107.5-108°C (lit. mp. 106-108°C)[79]; IR: 3400, 3379, 3237bs, 3033b, 2898b, 2865b, 2664b, 2470b, 2426b, 1829b, 1753b, 1633b, 1590s, 1470s, 1364, 1306, 1286, 1253, 1198, 1166, 1145, 1087, 1058, 1016s, 988, 957, 903, 882, 874, 851bs, 811, 796, 770, 719s, 679b; ^{1}H NMR (CD_3OD) d: 2.12 (s, 3H), 4.56 (s, 2H), 4.84 (bs, 3H), 6.69 (dd, 1H, J = 7.9, 1.0), 6.75 (dd, 1H, J = 7.6, 0.6), 6.94 (t, 1H, J = 7.7); ^{13}C NMR (CD_3OD) d: 12.23, 64.07, 116.53, 120.02, 122.32, 126.99, 140.49, 146.49.

The purple solution was treated with acetic anhydride (4.27 mL, 45.3 mmol, 3 eq.) and the flask was swirled. After ten minutes, the solvent was evaporated with gentle heating and residual acetic anhydride and acetic acid were removed with a stream of air. After at least one hour, the residue was dissolved in boiling ethyl acetate (100 mL) and filtered through a plug of glass wool if necessary to remove any insoluble material. The filtrate was boiled down to 40 mL, or until crystals began to form, and set aside. After a few hours, the mother liquor was decanted and a little ethyl acetate was used to rinse the light purple crystals of 3-acetamido-2-methylbenzyl alcohol[43] (2.5003 g, 92% yield), mp. 133-133.5°C; IR: 3260bs, 3054b, 2880b, 2825b, 1662s, 1608, 1587, 1534s, 1471s, 1442bs, 1369s, 1303, 1283, 1190, 1167, 1095, 1030, 1012, 973, 905b, 791, 749, 725, 606b; ^{1}H NMR (CD_3OD) d: 2.14 (s, 3H), 2.19 (s, 3H), 4.62 (s, 2H), 7.02 (t, 1H, J = 7.9), 7.20 (dd, 1H, J = 7.5, 2.1), 7.28 (dd, 1H, J = 6.6, 2.3); ^{13}C NMR (CD_3OD) d: 13.24, 22.90, 63.58, 126.78, 126.81, 127.14, 132.97, 136.98, 141.53, 172.34.



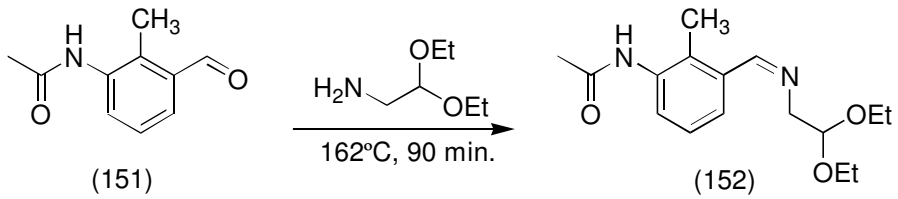
(150) (151)

3-Acetamido-2-methylbenzaldehyde **(151)**

In a 500 mL round-bottomed flask containing a magnetic stir bar, pyridinium chlorochromate (PCC) (3.909 g, 18.1 mmol, 1.3 eq.) was dissolved in acetone (125 mL), and a solution of 3-acetamido-2-methylbenzyl alcohol **(150)** (2.5003 g, 14.0 mmol, 1 eq.) in acetone (125 mL) was added. The darkening solution was refluxed under argon.

After 70 minutes, isopropanol (50 mL) was added to destroy remaining PCC, and reflux was continued another 65 minutes. The solution was allowed to cool, the stir bar was removed, silica gel (3.9 g) was added, and the solvent was evaporated. Ethyl acetate was added and the solvent was evaporated again to remove residual ethanol. The black solid was scraped from the sides of the flask, ground to a fine powder, and applied to a 4 by 5 cm column, eluting with a large volume of ethyl acetate.

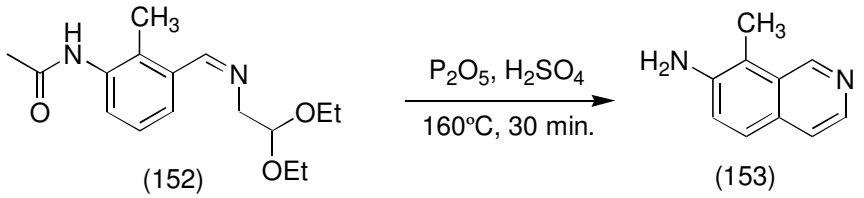
The faintly green solid was dissolved in hot ethyl acetate, evaporated onto silica (3.7 g), and eluted from a 4 by 7 cm column using ethyl acetate to give birth to a fluffy white solid (2.026 g, 82% yield) which was almost pure. Recrystallization from isopropanol produced crystals, mp. 128.5-129.5°C (lit. mp. 124-128°C)[51]; IR: 3265bs, 3192b, 3127b, 3036b, 2970, 2937b, 2863b, 2832b, 2731, 1696s, 1658s, 1599, 1584, 1533bs, 1467, 1440b, 1407, 1372s, 1306, 1282s, 1258, 1243, 1217, 1197, 1167, 1100, 1079, 1065, 1037b, 1017, 1062, 968, 910, 837, 821, 801, 780, 752, 720b, 666, 617; ^{1}H NMR d: 2.20 (s, 3H), 2.50 (s, 3H), 7.33 (t, 1H, J = 7.8), 7.58-7.64 (m, 2H), 7.78 (d, 1H, J = 7.8), 10.20 (s, 1H); ^{13}C NMR d: 12.71, 23.68, 126.29, 130.07, 130.53, 133.57, 134.81, 136.70, 169.22, 192.56.



3-(2,2-Diethoxyethyliminomethyl)-2-methylacetanilide **(152)**

Into a 10 mL round-bottomed flask were placed 3-acetamido-2-methylbenzaldehyde **(151)** (0.2249 g, 1.27, 1 eq.), aminoacetaldehyde diethyl acetal (0.369 mL, 2.54 mmol, 2 eq.), and a magnetic stir bar. A reflux condenser was placed on the flask and it was lowered into a 162°C oil bath with stirring. A metal clamp was used for the flask since plastic preferred to melt.

After 90 minutes, the flask was allowed to cool and a stream of air was used to remove remaining acetal. The solid was recrystallized from isopropanol to obtain bulky white fluff (0.2892 g, 78% yield), mp. 130.5-131°C; IR: 3268bs, 3205b, 3129b, 3041b, 2974s, 2928, 2886b, 1648s, 1583, 1541s, 1470, 1440, 1371s, 1354, 1300, 1280, 1251, 1230, 1125, 1073s, 1039, 1012, 969, 935, 907, 886, 849, 830, 802, 775, 718b, 615; ^{1}H NMR d: 1.20 (t, 6H, J = 7.0), 2.08 (s, 3H), 2.23 (s, 3H), 3.58 (dq, 2H, J = 9.3, 7.0), 3.73 (dq, 2H, J = 9.3, 7.0), 3.77 (d, 2H, J = 5.3), 4.79 (t, 1H, J = 5.3), 7.12 (t, 1H, J = 7.8), 7.36 (d, 1H, J = 7.7), 7.64 (d, 1H, J = 7.6), 8.08 (s, 1H), 8.50 (s, 1H); ^{13}C NMR d: 12.95, 15.13, 23.29, 62.46, 64.68, 101.83, 125.35, 125.80, 127.40, 131.82, 135.08, 135.79, 162.06, 169.11.



(152) (153)

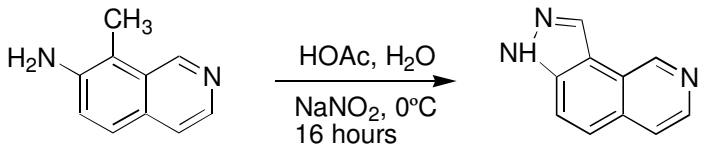
7-Amino-8-methylisoquinoline **(153)**

Into a 100 mL round-bottomed flask were placed phosphorous pentoxide (8.94 g), sulfuric acid (5 mL), and a magnetic stir bar. A reflux condenser was attached and the flask was placed in a 160°C oil bath. A metal clamp was used to secure the flask since plastic tended to melt, and care was taken to avoid exposure to the corrosive sulfur trioxide fumes which the flask evolved. Portions of sulfuric acid (45 mL) were used to dissolve 3-(2,2-diethoxyethyliminomethyl)-2-methylacetanilide **(152)** (1.30 g, 4.5 mmol, 1 eq.) and then added through the reflux condenser as rapidly as possible (about 25 minutes). The solution was allowed to react until 30 minutes after the addition was started.

The cooled black mire was poured onto ice (300 mL) and basified using sodium carbonate. The mixture was extracted with chloroform (3 x 50 mL) and the combined organic layers were extracted with 2% hydrochloric acid (2 x 100 mL). The combined aqueous layers were basified with aqueous sodium carbonate and the resulting mixture was extracted with chloroform (3 x 50 mL). The combined organic layers were dried and evaporated.

The brown residue was dissolved in chloroform and eluted from a 2 by 15 cm column using ethyl acetate. The product was bright yellow on TLC, just like all other aminoisoquinolines studied. The mostly pure fractions (0.079 g, 11% yield) were eluted from another 2 by 15 cm column using 0.5% concentrated aqueous ammonia and 2% methanol/chloroform to give nearly pure yellow solid (0.060 g, 8.5% yield), mp. 170-172°C; IR: 3361s, 3188bs, 3060, 3047, 2025b, 2867, 1891, 1659b, 1617s, 1598s, 1568, 1508, 1450, 1427, 1404s, 1377, 1330, 1286, 1268, 1223, 1159, 1146, 1086, 1049, 1027, 959, 871, 833s, 757b, 728, 699b; ^{1}H NMR d: 2.49 (s, 3H), 3.90 (bs, 2H), 7.15 (d, 1H, J = 8.7), 7.50 (d, 1H, J = 5.6), 7.54 (d, 1H, J = 8.8), 8.32 (d, 1H, J = 5.6), 9.34 (s, 1H); ^{13}C

NMR d: 10.87, 112.89, 120.69, 122.53, 125.53, 128.74, 130.70, 139.38, 142.57, 147.44; HRMS: Found by EI at 70eV, m/z 158.0845 (M^+); $C_{10}H_{10}N_2$ required 158.0844.

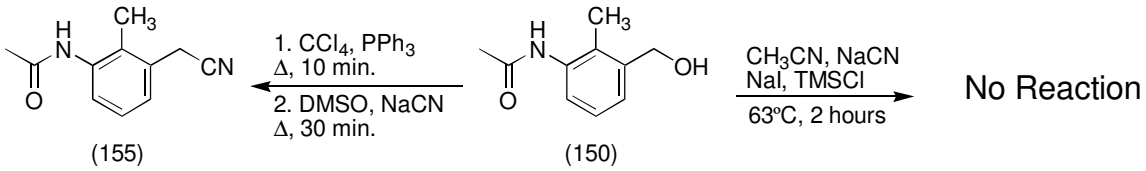


(153) (154)

3H-pyrazolo[3,4-*h*]isoquinoline **(154)**

Into a 10 mL round-bottomed flask were placed 7-amino-8-methylisoquinoline **(153)** (0.0236 g, 0.149 mmol, 1 eq.), glacial acetic acid (1.2 mL), and a magnetic stir bar. The flask was submerged, with stirring, into an ice bath. After 20 seconds, a solution of sodium nitrite (0.0113 g, 0.164 mmol, 1.1 eq.) in water (0.15 mL) was added over 20 seconds, turning the yellow solution orange. The flask was stoppered and the ice bath was allowed to thaw in the dark overnight.

The reaction mixture was poured into a separatory funnel, diluted with water and basified with concentrated aqueous ammonia. Once cool, the mixture was extracted with methylene chloride (3 x 50 mL), and the combined organic layers were dried and evaporated onto silica gel. The product was eluted from a 2 by 14 cm column using 0.5% concentrated aqueous ammonia and 3% methanol/methylene chloride (100 mL) and 0.5% concentrated aqueous ammonia and 5% methanol/methylene chloride (150 mL). The product came off the column right after a bright orange band to leave upon evaporation an off white to light orange solid (0.0243 g, 96% yield), mp. 244-244.5°C; IR: 3188, 3168, 3122bs, 3029b, 2966, 2937bs, 2855bs, 2788bs, 1692b, 1624, 1602, 1577, 1531, 1459, 1388, 1377, 1283, 1239, 1213, 1191, 1156, 1085, 1058, 938s, 865b, 828s, 780, 769; ^{1}H NMR (CD_3CO_2D) d: 7.92 (d, 1H, J = 9.3), 8.23 (d, 1H, J = 9.3), 8.28 (d, 1H, J = 6.3), 8.71 (d, 1H, J = 6.3), 8.81 (s, 1H), 9.86 (s, 1H); ^{13}C NMR (CD_3CO_2D) d: 117.74, 123.75, 123.93, 126.28, 127.54, 132.83, 135.37, 138.59, 141.41, 142.47; Elemental analysis: C: 70.94, H: 4.12, N: 24.79; $C_{10}H_7N_3$ requires C: 70.99, H: 4.17, N: 24.84%.



Attempted Syntheses of 3-Acetamido-2-methylphenylacetonitrile **(155)**

Into a 50 mL round-bottomed flask were placed 3-acetamido-2-methylbenzyl alcohol **(150)** (0.2027 g, 1.13 mmol, 1 eq.), triphenylphosphine (0.2967 g, 1.13 mmol, 1.0 eq.), carbon tetrachloride (3 mL), and a magnetic stir bar and the mixture was refluxed for ten minutes. A few drops of DMSO were added to dissolve the suspended solids, and after another three minutes, the rest of the DMSO (18 mL) was added, followed by sodium cyanide (0.095 g, 1.47 mmol, 1.3 eq.).

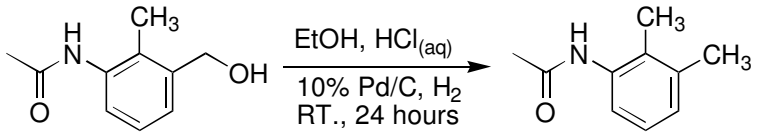
After 30 more minutes of reflux, the deep red-brown solution was allowed to cool, poured into a separatory funnel containing ice, and diluted with water and ethyl acetate. The mixture was gently shaken and the emulsion was patiently allowed to separate, adding brine to hasten the separation when patience ran short. The aqueous layer was extracted some more with methylene chloride (3 x 50 mL). The combined organic layers were dried, silica gel was added, and the mixture was filtered and evaporated.

The crystalline brown mass was eluted from a 2 by 7 cm column using ethyl acetate. An inseparable mixture containing nitrile, with an IR absorption around 2200, and triphenylphosphine oxide was isolated.

Into a 25 mL round-bottomed flask were placed 3-acetamido-2-methylbenzyl alcohol **(150)** (0.7008 g, 3.91 mmol, 1 eq.), powdered sodium cyanide (0.383 g, 7.82 mmol, 2 eq.), powdered sodium iodide (0.003 g, 0.020 mmol, 0.005 eq.), acetonitrile (5.2 mL), DMF (5.2 mL), and a magnetic stir bar. The flask was purged with argon and stoppered with a septum, and trimethylsilyl chloride (0.99 mL, 7.82 mmol, 2 eq.) was injected. The flask was placed in a 63°C oil bath with stirring.

After two hours, the mixture was allowed to cool and a stream of air and gentle warming with stirring IN THE HOOD were used to remove the solvent, with care to avoid inhaling hydrogen cyanide. Water (15 mL) was added to the residue and the

mixture was extracted with ethyl acetate (9 x 12 mL). The combined extracts were dried and filtered through silica gel (3 cm) in a pipette. The filtrates were evaporated and the solid was allowed to dry to leave fluffy white solid (0.730 g, >100% recovery) identical to starting material in every analysis. The starting material gave a mixture of needles and white clumps from ethyl acetate.

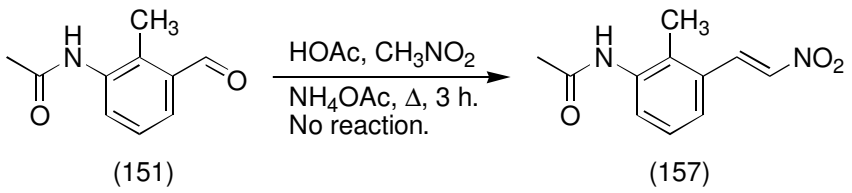


(150) (156)

2,3-Dimethylacetanilide **(156)**

Into a 50 mL round-bottomed flask with a 24/40 joint were placed 3-acetamido-2-methylbenzyl alcohol **(150)** (0.330 g, 1.84 mmol, 1 eq.), absolute ethanol (4.4 mL), concentrated hydrochloric acid (0.44 mL), 10% palladium/carbon (0.070 g, 0.066 mmol, 0.036 eq.), and an efficient magnetic stir bar. A septum was inserted into the flask, and a needle attached to a balloon of hydrogen was inserted through the septum. A syringe was used to withdraw gas (300 mL) from just above the liquid in the flask, causing the air in the flask to be displaced by hydrogen from the balloon. The mixture was stirred vigorously for 24 hours.

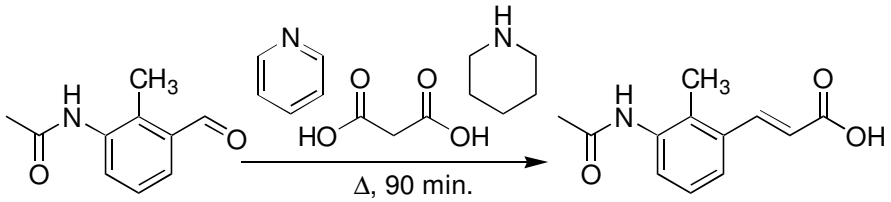
The reaction mixture was forced through a 4 cm plug of celite in a pipette using compressed air and the filtrate was evaporated using a stream of air. The residue was basified using aqueous sodium carbonate and extracted with ethyl acetate (4 x 10 mL). The organic layers were filtered through a 3 cm plug of silica gel in a pipette and the combined filtrates were evaporated to deliver a fluffy white solid (0.246 g, 82% yield). The product was recrystallized from ethyl acetate to form bulky white fluff, mp. 137.5-138°C (lit. mp. 135°C)[80]; IR: 3278bs, 3137, 3054b, 2974, 2937, 1655s, 1606, 1588, 1536s, 1472s, 1457s, 1426, 1368, 1302, 1283, 1253, 1190, 1164, 1095, 1020, 993, 970, 818, 780s, 748, 723b, 606; ^{1}H NMR d: 2.12 (s, 3H), 2.17 (s, 3H), 2.28 (s, 3H), 7.01 (d, 1H, J = 7.2), 7.08 (t, 1H, J = 7.7), 7.13 (bs, 1H), 7.37 (d, 1H, J = 7.6); ^{13}C NMR d: 13.79, 20.51, 23.95, 122.61, 125.80, 127.58, 135.22, 137.40, 144.18, 168.59.



(151) (157)

Attempted Synthesis of 3-Acetamido-2-methyl-b-nitrostyrene **(157)**

A solution of 3-acetamido-2-methylbenzaldehyde **(151)** (0.204 g, 1.15 mmol, 1 eq.), nitromethane (75 mL, 1.38 eq., 1.2 eq.) and ammonium acetate (0.018 g, 0.23 mmol, 0.2 eq.) in glacial acetic acid (1.3 mL) in a 10 mL round-bottomed flask containing a magnetic stir bar was refluxed for three hours, allowed to cool, and poured into water. The mixture was basified with sodium bicarbonate, extracted with chloroform (4 x 15 mL), and the combined orange organic layers were dried and evaporated to return only the starting material (0.210 g, 103% recovery).



(151) (158)

3-Acetamido-2-methylcinnamic Acid **(158)**

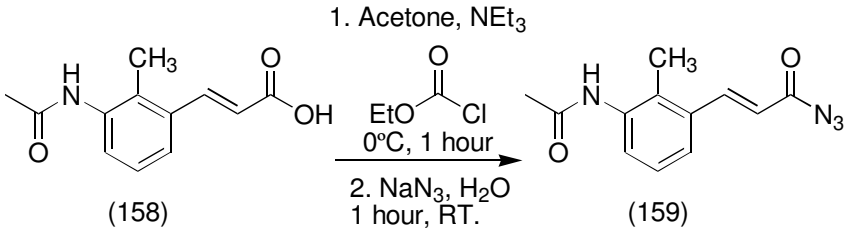
Into a pointed 50 mL flask were placed 3-acetamido-2-methylbenzaldehyde **(151)** (1.530 g, 8.64 mmol, 1 eq.), malonic acid (0.9436 g, 9.07 mmol, 1.05 eq.), piperidine (43 mL, 0.43 mmol, 0.05 eq.) and dry pyridine (14 mL). The flask was attached to a reflux air condenser, purged with argon, and heated to reflux without stirring. After 90 minutes, the reflux condenser was removed and the dark yellow solution was boiled until about 5 mL remained. The solution was allowed to cool and left under a stream of air overnight to dry.

The solid was dissolved in aqueous sodium carbonate, extracted with chloroform (3 x 10 mL) and the organic layers were filtered through sodium sulfate and silica gel in a pipette. The combined filtrates were evaporated, removing as much pyridine as possible, and the residue was dissolved in methanol and evaporated again. The residue was left under a stream of air for a few hours to dry.

The residue was dissolved in ethanol and the solvent was evaporated by leaving the residue under a stream of air overnight. This recovered starting material (0.853 g, 56% recovery) was mostly pure and didn't smell of pyridine.

The stirring, basic aqueous layer was placed under a stream of air for a few hours to remove organic solvent, and then it was acidified with dilute hydrochloric acid. The fine white precipitate was collected on a small Hirsch funnel, rinsed with water, and allowed to dry on the warm top of an oven. Care was taken not to generate a breeze that might blow away the resulting white tuft (0.7310 g, 39% conversion, 87% yield based on recovered starting material). The product was recrystallized from methanol (100 mL) to give glossy white fibers (0.506 g, 27% conversion, 60% yield), mp. 268-268.5°C (lit. mp. 265-267°C)[51]; IR (KBr): 3428b, 3267bs, 3020b, 2988, 2965, 2925, 2829b, 2723b, 2620,

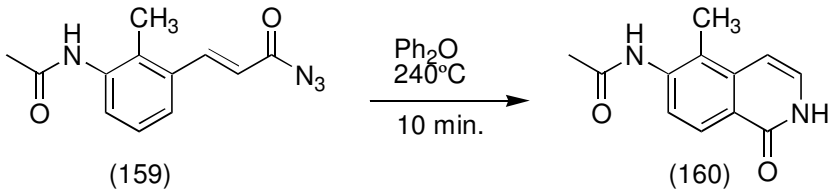
2565, 2528b, 2299, 2190, 2091, 1948, 1889, 1810b, 1692s, 1675s, 1651s, 1626s, 1597, 1577, 1529, 1473, 1448, 1438, 1421, 1380, 1370, 1334s, 1308, 1292, 1267, 1247, 1223, 1192, 1176, 1083, 1072, 1044, 1027, 1020, 974, 949b, 908, 872, 798, 764, 738, 714, 685, 643, 615; ^{1}H NMR (Me_2SO-d_6) d: 2.04 (s, 3H), 2.20 (s, 3H), 6.36 (d, 1H, J = 15.8), 7.19 (t, 1H, J = 7.8), 7.34 (d, 1H, J = 7.6), 7.50 (d, 1H, J = 7.6), 7.85 (d, 1H, J = 15.8), 9.46 (s, 1H), 12.45 (s, 1H); ^{13}C NMR (Me_2SO-d_6) d: 14.09, 23.27, 121.06, 124.02, 126.04, 127.61, 132.05, 134.19, 137.20, 141.82, 167.57, 168.49.



3-Acetamido-2-methylcinnamoyl Azide **(159)**

Into a 50 mL Erlenmeyer flask were placed crushed 3-acetamido-2-methylcinnamic acid **(158)** (0.7168 g, 3.27 mmol, 1 eq.), triethylamine (0.46 mL, 3.33 mmol, 1.02 eq.), acetone (8.8 mL) and a magnetic stir bar. The suspension was cooled in an ice bath with stirring and ethyl chloroformate (0.43 mL, 4.45 mmol, 1.36 eq.) was added over one minute, producing a temporary yellowing of the suspension. After one hour, a solution of sodium azide (0.319 g, 4.90 mmol, 1.5 eq.) in water (1.2 mL) was added over 30 seconds, causing the suspension to thicken into paste, and the ice bath was removed. After a few minutes, the paste was stirred manually to ensure homogeneity.

After another hour, the light pink paste was washed into water (90 mL), mixed, filtered, and dried to occasion fluffy white solid (0.5652 g, 71% conversion, 92% yield based on recovered starting material) which showed no decomposition at room temperature for weeks. The filtrate was acidified with 5% aqueous hydrochloric acid and, after an hour, the recovered starting material (0.1634 g, 23% recovery) was filtered out. Surprisingly, the azide cleanly survived recrystallization from boiling isopropanol to award pure white fluff, mp. 130°C (dec.) (lit. mp. 150°C (dec.))[51]; IR: 3281bs, 3039b, 2957b, 2333b, 2293b, 2152s, 1799b, 1685s, 1658s, 1619, 1580, 1534, 1472, 1435, 1371, 1283, 1247, 1211s, 1188s, 1102, 1016, 974, 876, 801, 725b, 611; ^{1}H NMR d: 2.21 (s, 3H), 2.28 (s, 3H), 6.31 (d, 1H, J = 15.7), 7.15-7.25 (m, 2H), 7.39 (d, 1H, J = 7.6), 7.61 (d, 1H, J = 7.8), 8.04 (d, 1H, J = 15.7); ^{13}C NMR d: 13.85, 23.96, 121.15, 124.58, 126.62, 127.20, 131.16, 134.06, 136.20, 144.33, 168.62, 171.89.



(159) (160)

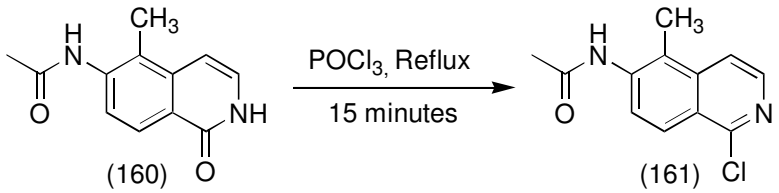
6-Acetamido-5-methylisoquinolin-1(2H)-one **(160)**

Into a 50 mL pointed flask, bearing a reflux air condenser, were placed 3-acetamido-2-methylcinnamoyl azide **(159)** (0.5652 g, 2.31 mmol, 1 eq.), triethylamine (0.58 mL, 2.45 mmol, 1.06 eq.), diphenyl ether (14 mL), and a magnetic stir bar, and the system was purged with argon. The stirring flask was plunged into an oil bath heated to 240°C and allowed to bake for ten minutes. The resulting yellow mixture was sometimes cloudy and sometimes clear. The flask was allowed to cool, and petroleum ether (30 mL) was added. The mixture was stirred thoroughly and the suspension was filtered with gravity. The impure product was washed generously with petroleum ether until no diphenyl ether remained, and the yellow solid (0.4815 g, 96% yield) was allowed to dry.

The crude product was dissolved in boiling methanol (200 mL) and allowed to sit overnight. The solution was filtered to remove light brown fluff, which was not product. The filtrate was boiled until 50 mL remained and allowed to crystallize overnight. The yellow powder obtained was recrystallized from boiling DMF and allowed to dry thoroughly.

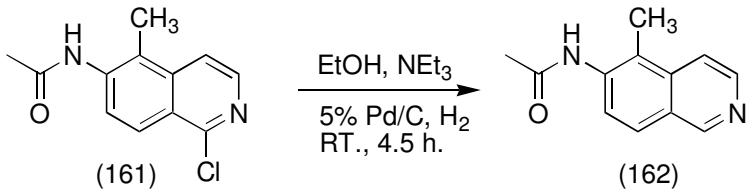
The mother liquor was evaporated onto silica gel (6 mL) and eluted from a 2 by 10 cm column using 10% methanol/chloroform (3 L). During the column, the silica on which the product was loaded was stirred to restore homogeneity and hasten dissolution. Much purification was achieved, giving a light yellow solid (0.305 g, 61% yield). The pure sample from DMF was a shiny off-white powder (0.1194 g, 24% yield, 85% yield total), mp. > 330°C (lit. mp. >320°C)[51]; IR 3460b, 3208b, 1678s, 1647s, 1618s, 1569, 1537bs, 1482b, 1432b, 1382, 1342, 1299b, 1232s, 1180, 1148, 1069, 983, 842b, 798s, 773, 702, 685, 644; ^{1}H NMR (Me_2SO-d_6) d: 2.09 (s, 3H), 2.30 (s, 3H), 6.60 (d, 1H, J = 7.4), 7.17 (bt, 1H, J = 6.0), 7.50 (d, 1H, J = 8.6), 8.00 (d, 1H, J = 8.5), 9.62 (s, 1H), 11.21

(bs, 1H); ^{13}C NMR (Me_2SO-d_6) d: 13.37, 23.21, 101.38, 123.32, 123.55, 124.39, 125.67, 128.81, 137.51, 139.48, 161.62, 168.33.



6-Acetamido-1-chloro-5-methylisoquinoline **(161)**

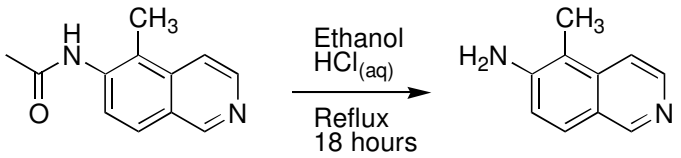
Into a 25 mL round-bottomed flask were placed 6-acetamido-5-methylisoquinolin-1(2H)-one **(160)** (0.1238 g, 0.57 mmol, 1 eq.), phosphorous oxychloride (12 mL, 132 mmol, 230 eq.), and a magnetic stir bar, and a reflux air condenser was attached. The system was purged with argon and the mixture was heated to reflux with stirring. After 15 minutes, the flask was allowed to cool, and the contents were added portionwise to a cooled, stirring solution of sodium carbonate (63 g, 598 mmol, 1045 eq.) in water (500 mL). The yellow mixture was extracted with ethyl acetate (3 x 75 mL), but a solid impurity remained undissolved. The combined organic layers were washed with brine, dried and evaporated. The residue was eluted from a 2 by 8 cm column using ethyl acetate to obtain a faintly yellow solid (0.088 g, 66% yield). Recrystallization from methanol produced white crystals, mp. 223-224°C; IR: 3261b, 3017b, 2871b, 1910b, 1776b, 1660s, 1612s, 1590, 1570, 1520s, 1479, 1360s, 1321s, 1284s, 1247, 1227, 1186, 1107, 1093, 1065, 1038, 1014, 971, 907, 861, 821, 803, 781, 750, 706b, 671, 631, 614, 603; ^{1}H NMR d: 2.27 (s, 3H), 2.42 (s, 3H), 7.58 (d, 1H, J = 5.7), 7.79 (bs, 1H), 7.86 (d, 1H, J = 8.9), 8.08 (d, 1H, J = 9.0), 8.19 (d, 1H, J = 5.8); ^{13}C NMR d: 13.02, 24.14, 117.13, 124.30, 125.06, 125.55, 137.32, 137.79, 141.70, 152.07, 168.71; ^{1}H NMR (CD_3OD) d: 2.24 (s, 3H), 2.53 (s, 3H), 7.78 (d, 1H, J = 9.1), 7.92 (dd, 1H, J = 6.0, 0.8), 8.17 (d, 1H, J = 9.1), 8.21 (d, 1H, J = 6.0); ^{13}C NMR (CD_3OD) d: 13.57, 23.20, 119.28, 125.40, 126.12, 128.49, 128.58, 139.41, 139.60, 142.24, 152.72, 172.25; HRMS: Found by EI at 70eV, m/z 234.0559 (M^+); $C_{12}H_{11}{}^{35}ClN_2O$ required 234.0560. The peak corresponding to $C_{12}H_{11}{}^{37}ClN_2O$ was 32% of the intensity of the peak for $C_{12}H_{11}{}^{35}ClN_2O$.



6-Acetamido-5-methylisoquinoline **(162)**

Into a 100 mL round-bottomed flask with a 24/40 joint were placed 6-acetamido-1-chloro-5-methylisoquinoline **(161)** (0.088 g, 0.38 mmol, 1 eq.), 5% palladium/carbon (0.040 g, 0.019 mmol, 0.05 eq.), triethylamine (105 mL, 0.76 mmol, 2 eq.), absolute ethanol (12.5 mL), and an efficient stir bar. A septum was placed on the flask and a needle attached to a balloon of hydrogen was inserted through the septum. A syringe was used to withdraw gas (300 mL) from just above the liquid in the flask, causing the air in the flask to be displaced by hydrogen from the balloon. The mixture was stirred vigorously at room temperature for 4.5 hours.

After making sure the reaction was complete according to TLC, the solvent was evaporated and the black residue was loaded onto a 2 by 6 cm column by boiling it with small amounts of ethyl acetate. A few drops of water were added to the residue during these extractions to dissolve triethylamine hydrochloride. The product was eluted using ethyl acetate (500 mL) to obtain sparingly soluble off-white solid (0.057 g, 75% yield). The column was further eluted using 5% methanol/chloroform (100 mL) and 10% methanol/chloroform (110 mL) and the eluent was evaporated. A few drops of water was added to the residue and it was extracted with ethyl acetate, dried and evaporated to yield further product (0.015 g, 20% yield, 95% yield total), mp. 203-204.5°C; IR: 3407b, 3324b, 3222b, 3170b, 3011b, 2898b, 2825b, 2266b, 1664s, 1617, 1598, 1581, 1524bs, 1484s, 1436b, 1412, 1386, 1369, 1328, 1295s, 1284s, 1276, 1243, 1223, 1175b, 1092, 1069, 1041, 1012b, 966, 936, 896, 868, 826s, 810, 785, 763b, 728, 668, 614, 609; ^{1}H NMR d: 2.26 (s, 3H), 2.46 (s, 3H), 7.68 (d, 1H, J = 5.8), 7.74 (d, 1H, J = 8.8), 7.84 (d, 1H, J = 8.8), 7.91 (bs, 1H), 8.48 (d, 1H, J = 5.6), 9.12 (s, 1H); ^{13}C NMR d: 12.53, 24.07, 116.98, 124.05, 124.79, 126.27, 126.66, 135.76, 136.53, 143.20, 152.48, 168.79.

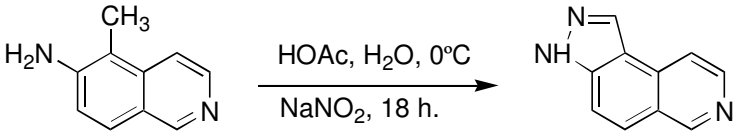


(162) (163)

6-Amino-5-methylisoqunoline **(163)**

Into a 50 mL pear shaped flask were placed 6-acetamido-5-methylisoquinoline **(162)** (0.072 g, 0.36 mmol, 1 eq.), ethanol (20 mL), concentrated hydrochloric acid (4 mL) and a magnetic stir bar. The flask was attached to a reflux air condenser, purged with argon, and heated to reflux in an oil bath. Within minutes, the colorless solution turned light yellow and gained a blue fluorescence.

After 18 hours, the yellow solution was allowed to cool and the solvent was evaporated until only water remained. Water (75 mL) was added and extracted with ethyl acetate (2 x 50 mL) and the organic layers were discarded. The aqueous layer was basified with concentrated aqueous ammonia (10 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to produce light yellow solid (0.051 g, 90% yield). The product was purified by column chromatography using 3% methanol/chloroform to obtain pure white solid, mp. 143-144°C; 3382, 3333b, 3205bs, 3025, 1910, 1777, 1731, 1611s, 1472s, 1421, 1394s, 1338, 1289, 1274s, 1224, 1191, 1175, 1136b, 1054b, 1026, 924, 897, 865, 822s, 778, 755b, 731b, 698, 671; ^{1}H NMR d: 2.34 (s, 3H), 4.12 (bs, 2H), 7.00 (d, 1H, J = 8.7), 7.59 (d, 1H, J = 6.1), 7.64 (d, 1H, J = 8.7), 8.39 (d, 1H, J = 6.1), 8.97 (s, 1H); ^{13}C NMR d: 10.91, 110.49, 115.51, 118.84, 123.70, 127.09, 136.55, 143.23, 145.36, 152.14; HRMS: Found by EI at 70eV, m/z 158.0851 (M^{+}); $C_{10}H_{10}N_2$ required 158.0844.



(163) (164)

3H-pyrazolo[4,3-*f*]isoquinoline **(164)**

A solution of 6-amino-5-methylisoquinoline **(163)** (0.031 g, 0.20 mmol, 1 eq.) in glacial acetic acid (1.55 mL) was prepared in a 5 mL round-bottomed flask containing a magnetic stir bar, and the solution was cooled with stirring in an ice bath. After 20 seconds, a solution (0.21 mL) of sodium nitrite (0.0149 g, 0.22 mmol, 1.1 eq.) in water was injected over 45 seconds. The flask was stoppered and the ice bath was allowed to warm to room temperature overnight.

The red solution was basified with dilute aqueous ammonia and extracted with chloroform (3 x 35 mL). The combined organic layers were dried and evaporated onto silica. The product was eluted from a 2 by 8 cm column using 0.5% concentrated aqueous ammonia and 3% methanol/methylene chloride (100 mL) followed by 0.5% concentrated aqueous ammonia and 5% methanol/methylene chloride. The solid obtained was redissolved in methylene chloride, filtered through sodium sulfate in a pipette, and evaporated to muster a red solid (0.0202 g, 61% yield), mp. 216-218.5°C; IR: 3244, 3206b, 3142b, 3100b, 3039b, 2981b, 2946b, 2908, 2876b, 2825b, 2759bs, 2539b, 2477b, 1622s, 1599, 1581, 1524b, 1490, 1469, 1449, 1412, 1388, 1375, 1319, 1298, 1243, 1213, 1181, 1168, 1079b, 1041, 1032, 933s, 882s, 822s, 806, 781, 741b, 699s; ^{1}H NMR (CD_3CO_2D) d: 8.07 (d, 1H, J = 9.2), 8.16 (d, 1H, J = 9.2), 8.61 (d, 1H, J = 6.4), 8.80 (d, 1H, J = 6.4), 8.86 (s, 1H), 9.60 (s, 1H); ^{13}C NMR (CD_3CO_2D) d: 117.63, 118.24, 121.28, 125.78, 129.22, 135.41, 136.77, 137.37, 143.22, 146.64; Elemental analysis: C: 71.01, H: 4.08, N: 24.70; $C_{10}H_7N_3$ requires C: 70.99, H: 4.17, N: 24.84%.

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Zollinger, Heinrich. Diazo Chemistry I: Aromatic and Heteroaromatic Compounds, Weinheim, New York: VCH, **1994**, p. 13.

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$$\frac{\frac{\$70}{5\text{ g Pd(OAc)}_2}\left(\frac{224.49\text{ g}}{\text{mole}}\right)\left(\frac{1\text{ mole}}{1\text{ mole ellipticine}}\right)}{\frac{\$50}{2\text{ g Ni(COD)}_2}\left(\frac{275.08\text{ g}}{\text{mole}}\right)\left(\frac{2\text{ moles}}{1\text{ mole ellipticine}}\right)} = .23 \text{ times as much.}$$

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Hope, H.; Moezzi, B. Chemistry Department, University of California, Davis.

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85. $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$; $Rw = \Sigma||F_o|-|F_c||\sqrt{w}/\Sigma|F_o|\sqrt{w}$

86. Goodness-of-Fit = $[\Sigma(w\cdot||F_o|-|F_c||^2)/(M-N)]^{½}$ where M is the number of observed reflections and N is the number of parameters refined.

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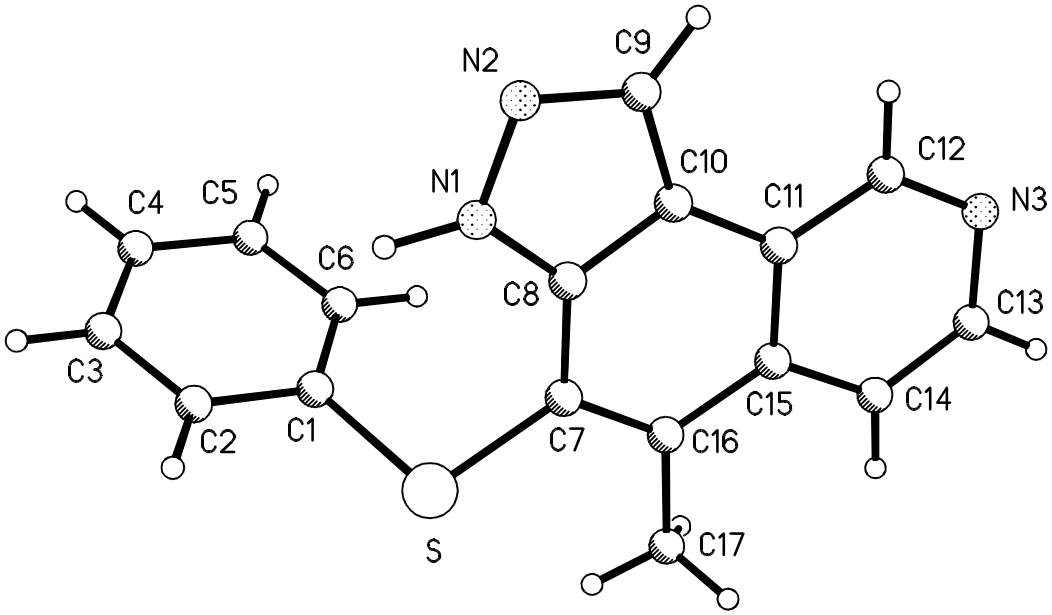
88. Refinement is based on F^2 for ALL reflections except for those with very negative F^2 or flagged by the user for potential systematic errors. Weighted R-factors wR and all goodnesses of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The observed criterion of $F^2 > 2\sigma(F^2)$ is used only for calculating R indices for observed data and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

89. Goodness-of-Fit = $[\Sigma[w(F_o^2-F_c^2)^2]/(M-N)]^{½}$
where M is the number of reflections and N is the number of parameters refined.

90. $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$; $wR2 = [\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{½}$

Appendix A



Structure of

5-methyl-6-thiophenyl-3H-pyrazolo[3,4-*h*]isoquinoline **(104)**

determined using X-ray crystallography[12]

Table 1. Crystal data for $C_{17}H_{13}N_3S$.

Identification code	mn531
Empirical Formula	$C_{17}H_{13}N_3S$
Color; Habit	Orange blocks
Crystal Size (mm)	0.30 x 0.35 x 0.50
Crystal System	Triclinic
Space Group	$P\bar{1}$
Unit Cell Dimensions	a = 7.907(2) Å a = 93.20(2)°
	b = 8.266(2) Å b = 95.90(2)°
	c = 10.506(2) Å c = 92.39(2)°
Volume	681.2(2) $Å^3$
Z	2
Formula Weight	291.4
Density(calc.)	1.421 Mg/m^3
Absorption Coefficient	2.063 mm^{-1}
F(000)	304

Table 2. Data Collection for $C_{17}H_{13}N_3S$.

Diffractometer Used	Syntex $P2_1$
Radiation	CuKa (l = 1.54178 Å)
Temperature (K)	130
Monochromator	Highly oriented graphite crystal
2q Range	0.0 to 114.0°
Scan Type	2q-q
Scan Speed	Constant; 29.30°/min. in w
Scan Range (2q)	1.20° plus Ka-separation
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 50.0% of total scan time
Standard Reflections	2 measured every 198 reflections
Index Ranges	$-8 \leq h \leq 8,\ -8 \leq k \leq 8,\ 0 \leq l \leq 11$
Reflections Collected	1844
Independent Reflections	1840 (R_{int} = 0.49%)
Observed Reflections	1688 (F > 4.0s(F))
Absorption Correction	XABS[82]
Range Transmission coefs	0.53 - 0.60

Table 3. Solution and Refinement for $C_{17}H_{13}N_3S$.

System Used	Siemens SHELXTL PLUS[83,84] (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o-F_c)^2$
Absolute Structure	N/A
Extinction Correction	N/A
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0025F^2$
Number of Parameters Refined	190
Final R Indices[85] (obs. data)	R = 3.83 %, Rw = 4.92 %
Goodness-of-Fit[86]	1.14
Largest and Mean Δ/σ	0.139, 0.025
Data-to-Parameter Ratio	8.9:1
Largest Difference Peak	0.26 eÅ^{-3}
Largest Difference Hole	-0.30 eÅ^{-3}

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^3$) for $C_{17}H_{13}N_3S$.

Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

	x	y	z	U(eq)
S	2124(1)	3571(1)	7741(1)	26(1)
N(1)	702(2)	208(2)	8671(2)	21(1)
N(2)	93(2)	-1322(2)	8856(2)	24(1)
N(3)	1935(3)	-3411(2)	3860(2)	25(1)
C(1)	3203(3)	3263(3)	9267(2)	20(1)
C(2)	2754(3)	4190(3)	10319(2)	22(1)
C(3)	3617(3)	4042(3)	11522(2)	26(1)
C(4)	4910(3)	2967(3)	11681(2)	25(1)
C(5)	5354(3)	2054(3)	10643(2)	24(1)
C(6)	4508(3)	2188(3)	9430(2)	22(1)
C(7)	2065(3)	1623(3)	6941(2)	20(1)
C(8)	1345(3)	275(3)	7527(2)	19(1)
C(9)	348(3)	-2224(3)	7820(2)	21(1)
C(10)	1145(3)	-1290(3)	6943(2)	18(1)
C(11)	1661(3)	-1568(3)	5691(2)	18(1)
C(12)	1530(3)	-3110(3)	5038(2)	22(1)
C(13)	2516(3)	-2112(3)	3270(2)	28(1)
C(14)	2744(3)	-570(3)	3821(2)	24(1)
C(15)	2329(3)	-233(3)	5081(2)	19(1)
C(16)	2560(3)	1373(3)	5725(2)	20(1)
C(17)	3330(3)	2719(3)	5041(2)	27(1)

Table 5. Bond lengths (Å) for $C_{17}H_{13}N_3S$.

S-C(1)	1.774(2)	S-C(7)	1.771(2)
N(1)-N(2)	1.366(3)	N(1)-C(8)	1.355(3)
N(2)-C(9)	1.322(3)	N(3)-C(12)	1.322(3)
N(3)-C(13)	1.358(3)	C(1)-C(2)	1.395(3)
C(1)-C(6)	1.393(3)	C(2)-C(3)	1.387(3)
C(3)-C(4)	1.386(4)	C(4)-C(5)	1.375(3)
C(5)-C(6)	1.390(3)	C(7)-C(8)	1.429(3)
C(7)-C(16)	1.382(3)	C(8)-C(10)	1.396(3)
C(9)-C(10)	1.415(3)	C(10)-C(11)	1.425(3)
C(11)-C(12)	1.408(3)	C(11)-C(15)	1.418(3)
C(13)-C(14)	1.367(4)	C(14)-C(15)	1.411(3)
C(15)-C(16)	1.451(3)	C(16)-C(17)	1.500(3)

Table 6. Bond angles (°) for $C_{17}H_{13}N_3S$.

C(1)-S-C(7)	103.0(1)	N(2)-N(1)-C(8)	111.4(2)
N(1)-N(2)-C(9)	106.2(2)	C(12)-N(3)-C(13)	115.8(2)
S-C(1)-C(2)	117.8(2)	S-C(1)-C(6)	122.3(2)
C(2)-C(1)-C(6)	119.9(2)	C(1)-C(2)-C(3)	119.7(2)
C(2)-C(3)-C(4)	120.2(2)	C(3)-C(4)-C(5)	120.0(2)
C(4)-C(5)-C(6)	120.6(2)	C(1)-C(6)-C(5)	119.5(2)
S-C(7)-C(8)	118.8(2)	S-C(7)-C(16)	122.6(2)
C(8)-C(7)-C(16)	118.4(2)	N(1)-C(8)-C(7)	130.0(2)
N(1)-C(8)-C(10)	106.7(2)	C(7)-C(8)-C(10)	123.3(2)
N(2)-C(9)-C(10)	110.8(2)	C(8)-C(10)-C(9)	104.9(2)
C(8)-C(10)-C(11)	118.9(2)	C(9)-C(10)-C(11)	136.1(2)
C(10)-C(11)-C(12)	122.8(2)	C(10)-C(11)-C(15)	118.4(2)
C(12)-C(11)-C(15)	118.8(2)	N(3)-C(12)-C(11)	124.8(2)
N(3)-C(13)-C(14)	124.6(2)	C(13)-C(14)-C(15)	120.2(2)
C(11)-C(15)-C(14)	115.8(2)	C(11)-C(15)-C(16)	121.4(2)
C(14)-C(15)-C(16)	122.9(2)	C(7)-C(16)-C(15)	119.6(2)
C(7)-C(16)-C(17)	121.9(2)	C(15)-C(16)-C(17)	118.6(2)

Table 7. Anisotropic displacement coefficients ($Å^2$ x 10^3) for $C_{17}H_{13}N_3S$.

The anisotropic displacement factor exponent takes the form:

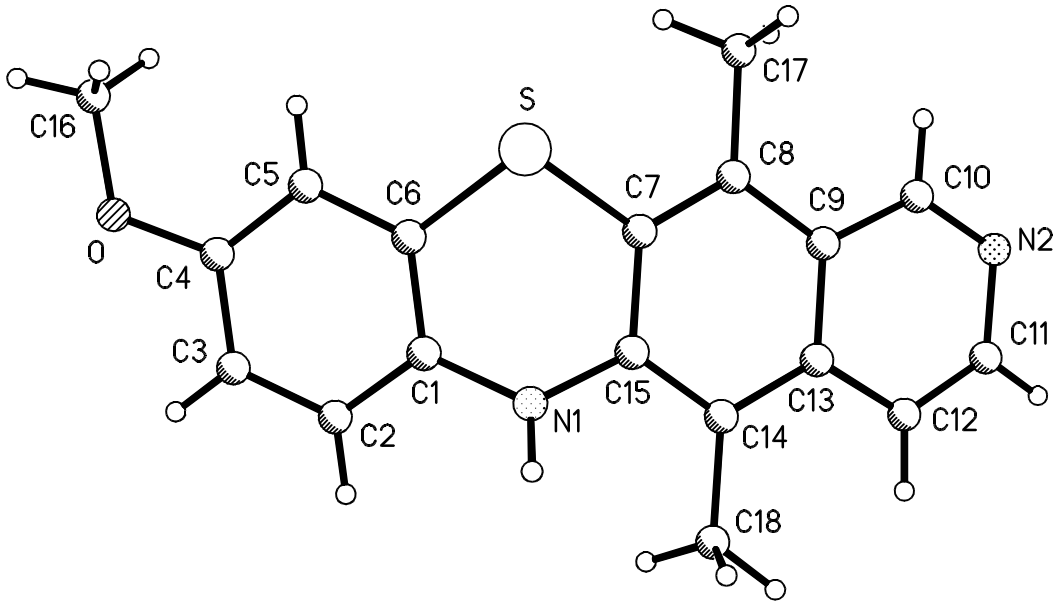
$-2p^2(h^2a^{*2}U_{11} + ... + 2hka^*b^*U_{12})$

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	32(1)	20(1)	24(1)	2(1)	-2(1)	1(1)
N(1)	21(1)	22(1)	21(1)	-2(1)	10(1)	1(1)
N(2)	21(1)	25(1)	26(1)	-3(1)	11(1)	0(1)
N(3)	21(1)	32(1)	24(1)	6(1)	6(1)	-1(1)
C(1)	17(1)	19(1)	25(1)	-4(1)	7(1)	4(1)
C(2)	20(1)	19(1)	29(1)	-3(1)	7(1)	-2(1)
C(3)	26(1)	25(1)	26(1)	-8(1)	8(1)	-3(1)
C(4)	25(1)	28(1)	23(1)	-6(1)	2(1)	5(1)
C(5)	18(1)	26(1)	27(1)	-1(1)	1(1)	3(1)
C(6)	17(1)	23(1)	26(1)	-3(1)	6(1)	1(1)
C(7)	14(1)	23(1)	23(1)	0(1)	1(1)	4(1)
C(8)	13(1)	24(1)	20(1)	2(1)	5(1)	2(1)
C(9)	15(1)	22(1)	26(1)	-2(1)	5(1)	-2(1)
C(10)	12(1)	24(1)	18(1)	1(1)	2(1)	-1(1)
C(11)	8(1)	26(1)	22(1)	2(1)	2(1)	2(1)
C(12)	18(1)	25(1)	24(1)	4(1)	3(1)	1(1)
C(13)	24(1)	41(2)	19(1)	10(1)	8(1)	-1(1)
C(14)	18(1)	34(1)	21(1)	5(1)	6(1)	6(1)
C(15)	10(1)	30(1)	18(1)	5(1)	2(1)	6(1)
C(16)	12(1)	24(1)	24(1)	1(1)	3(1)	5(1)
C(17)	28(1)	30(1)	24(1)	1(1)	6(1)	7(1)

Table 8. H-Atom coordinates (x 10^4) and isotropic displacement coefficients ($Å^2$ x 10^3) for $C_{17}H_{13}N_3S$.

	x	y	z	U
H(1)	701	1096	9358	35
H(2B)	1852	4927	10202	35
H(3B)	3314	4686	12246	35
H(4A)	5498	2859	12516	35
H(5A)	6256	1316	10758	35
H(6A)	4823	1554	8705	35
H(9A)	43	*3361	7682	35
H(12A)	1107	*4003	5479	35
H(13A)	2785	*2292	2404	35
H(14A)	3180	290	3351	35
H(17A)	3404	3701	5581	35
H(17B)	4449	2449	4849	35
H(17C)	2631	2872	4258	35

Appendix B



Structure for

9-methoxy-5,12-dimethyl-6H-pyrido[4,3-*b*]phenothiazine **(137)**

determined using X-ray crystallography[12]

Table 1. Crystal data for $C_{18}H_{16}N_2OS$.

Identification code	mn691
Empirical formula	$C_{18}H_{16}N_2OS$
Formula weight	308.39
Crystal size	0.46 x 0.22 x 0.08 mm
Crystal habit	plate
Crystal color	pale orange
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 8.5610(10) Å a = 90°
	b = 5.2190(10) Å b = 103.150(10)°
	c: = 16.623(3) Å c = 90°
Volume	723.2(2) $Å^3$
Z	2
Density (calculated)	1.416 $Mg•m^{-3}$
Absorption coefficient	0.227 mm^{-1}
F(000)	324
Absorption correction[87]	XABS2
Max. and min. transmission	0.986 and 0.959

Table 2. Data collection for $C_{18}H_{16}N_2OS$.

Diffractometer	Siemens R3m/v
Temperature	130(2) K
Radiation source	normal-focus sealed tube
Wavelength	0.71073 Å (MoKa)
Monochromator	graphite
q range for data collection	1.26 to 27.49°
Scan type	w
Index ranges	$-2 \leq h \leq 12$, $-2 \leq k \leq 7$, $-22 \leq l \leq 22$
Reflections collected	3226
Independent reflections	2422 (R_{int} = 0.0152)
Standard reflections	2
Percent decay of standards	< 1%

Table 3. Solution and refinement of $C_{18}H_{16}N_2OS$.

System for solution	SHELXTL 5.0 (Sheldrick, 1994)
Structure solution	direct
System for refinement	SHELXTL 5.0 (Sheldrick, 1994)
Refinement methods[88]	Full-matrix least-squares on F^2
Hydrogen atoms	riding except for methyl group of C18 (fixed)
Data / restraints / parameters	2422 / 1 / 201
Goodness-of-fit[89] on F^2	1.051
Weighting scheme	$w^{-1} = s^2(F_o^2) + (0.0444P)^2 + 0.2135P$, where $P = (F_o^2 + 2F_c^2)/3$
R indices (all data)[90]	R1 = 0.0366, wR2 = 0.0841
R indices calcd from obsd data	R1 = 0.0322, wR2 = 0.0808
Observed data (>2sigma(I))	2252
Absolute structure parameter	-0.01(8)
Largest diff. peak and hole	0.305 and -0.251 eÅ^{-3}

Table 4. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for $C_{18}H_{16}N_2OS$. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} **tensor**.

	x	y	z	U (eq)
S	32(1)	-2719(1)	6990(1)	22(1)
O	3093(2)	-416(4)	4737(1)	28(1)
N(1)	2018(2)	1500(4)	7871(1)	20(1)
N(2)	-4623(2)	2650(5)	9035(1)	26(1)
C(1)	2226(3)	1096(5)	7060(1)	19(1)
C(2)	3279(3)	2572(5)	6730(1)	21(1)
C(3)	3541(2)	2032(6)	5953(1)	22(1)
C(4)	2720(3)	36(5)	5488(1)	21(1)
C(5)	1589(3)	-1377(5)	5788(1)	21(1)
C(6)	1375(3)	-824(5)	6580(1)	19(1)
C(7)	-618(2)	-432(5)	7634(1)	17(1)
C(8)	-2146(3)	-605(5)	7764(1)	17(1)
C(9)	-2566(3)	1092(5)	8362(1)	18(1)
C(10)	-4107(3)	1047(5)	8537(1)	21(1)
C(11)	-3543(3)	4417(6)	9427(1)	26(1)
C(12)	-1997(3)	4565(5)	9337(1)	21(1)
C(13)	-1435(3)	2884(4)	8793(1)	18(1)
C(14)	142(3)	3027(5)	8645(1)	18(1)
C(15)	518(2)	1405(5)	8057(1)	16(1)
C(16)	2308(3)	-2568(6)	4272(1)	29(1)
C(17)	-3355(3)	-2494(6)	7291(1)	23(1)
C(18)	1351(3)	4947(6)	9091(1)	25(1)

Table 5. Bond lengths [Å] for $C_{18}H_{16}N_2OS$.

S-C(6)	1.767(2)	S-C(7)	1.775(2)
O-C(4)	1.377(2)	O-C(16)	1.440(3)
N(1)-C(15)	1.389(3)	N(1)-C(1)	1.415(3)
N(2)-C(10)	1.322(3)	N(2)-C(11)	1.362(3)
C(1)-C(6)	1.381(3)	C(1)-C(2)	1.390(3)
C(2)-C(3)	1.390(3)	C(3)-C(4)	1.389(3)
C(4)-C(5)	1.396(3)	C(5)-C(6)	1.400(3)
C(7)-C(8)	1.377(3)	C(7)-C(15)	1.431(3)
C(8)-C(9)	1.437(3)	C(8)-C(17)	1.514(3)
C(9)-C(10)	1.414(3)	C(9)-C(13)	1.418(3)
C(11)-C(12)	1.367(3)	C(12)-C(13)	1.420(3)
C(13)-C(14)	1.428(3)	C(14)-C(15)	1.385(3)
C(14)-C(18)	1.509(3)		

Table 6. Bond angles [°] for $C_{18}H_{16}N_2OS$.

C(6)-S-C(7)	100.20(11)	C(4)-O-C(16)	116.4(2)
C(15)-N(1)-C(1)	122.0(2)	C(10)-N(2)-C(11)	116.1(2)
C(6)-C(1)-C(2)	118.6(2)	C(6)-C(1)-N(1)	119.6(2)
C(2)-C(1)-N(1)	121.8(2)	C(3)-C(2)-C(1)	120.7(2)
C(2)-C(3)-C(4)	120.1(2)	O-C(4)-C(3)	116.1(2)
O-C(4)-C(5)	123.7(2)	C(3)-C(4)-C(5)	120.2(2)
C(4)-C(5)-C(6)	118.5(2)	C(1)-C(6)-C(5)	121.9(2)
C(1)-C(6)-S	119.2(2)	C(5)-C(6)-S	118.9(2)
C(8)-C(7)-C(15)	122.0(2)	C(8)-C(7)-S	119.3(2)
C(15)-C(7)-S	118.4(2)	C(7)-C(8)-C(9)	117.7(2)
C(7)-C(8)-C(17)	121.5(2)	C(9)-C(8)-C(17)	120.8(2)
C(10)-C(9)-C(13)	118.0(2)	C(10)-C(9)-C(8)	121.6(2)
C(13)-C(9)-C(8)	120.5(2)	N(2)-C(10)-C(9)	125.3(2)
N(2)-C(11)-C(12)	123.7(2)	C(11)-C(12)-C(13)	120.7(2)
C(12)-C(13)-C(9)	116.0(2)	C(12)-C(13)-C(14)	123.2(2)
C(9)-C(13)-C(14)	120.7(2)	C(15)-C(14)-C(13)	118.1(2)
C(15)-C(14)-C(18)	120.6(2)	C(13)-C(14)-C(18)	121.3(2)
C(14)-C(15)-N(1)	120.7(2)	C(14)-C(15)-C(7)	121.0(2)
N(1)-C(15)-C(7)	118.3(2)		

Table 7. Anisotropic displacement parameters [$Å^2$ x 10^3]

for $C_{18}H_{16}N_2OS$.

The anisotropic displacement factor exponent takes the form:

$-2p^2[(ha^*)^2U_{11} + ... + 2hka^*b^*U_{12}]$

	U11	U22	U33	U23	U13	U12
S	25(1)	18(1)	25(1)	-4(1)	10(1)	-5(1)
O	27(1)	36(1)	22(1)	-2(1)	7(1)	-7(1)
N(1)	13(1)	25(1)	19(1)	-3(1)	1(1)	-1(1)
N(2)	19(1)	31(1)	30(1)	0(1)	6(1)	-1(1)
C(1)	14(1)	22(1)	20(1)	-1(1)	2(1)	3(1)
C(2)	16(1)	21(1)	24(1)	-2(1)	-1(1)	-2(1)
C(3)	17(1)	25(1)	24(1)	5(1)	4(1)	-1(1)
C(4)	20(1)	25(1)	18(1)	3(1)	3(1)	2(1)
C(5)	21(1)	21(1)	21(1)	-1(1)	2(1)	0(1)
C(6)	15(1)	19(1)	21(1)	2(1)	3(1)	-1(1)
C(7)	19(1)	15(1)	16(1)	0(1)	2(1)	1(1)
C(8)	17(1)	16(1)	16(1)	1(1)	0(1)	-2(1)
C(9)	18(1)	19(1)	16(1)	4(1)	1(1)	2(1)
C(10)	18(1)	24(1)	22(1)	2(1)	2(1)	-2(1)
C(11)	27(1)	30(2)	21(1)	-2(1)	6(1)	5(1)
C(12)	21(1)	23(1)	18(1)	-1(1)	0(1)	-1(1)
C(13)	19(1)	21(1)	12(1)	4(1)	-1(1)	1(1)
C(14)	17(1)	20(1)	14(1)	1(1)	-2(1)	-1(1)
C(15)	13(1)	19(1)	16(1)	2(1)	-1(1)	-1(1)
C(16)	31(1)	35(2)	21(1)	-4(1)	5(1)	2(1)
C(17)	21(1)	22(1)	25(1)	-3(1)	1(1)	-5(1)
C(18)	24(1)	30(2)	19(1)	-8(1)	2(1)	-7(1)

Table 8. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for $C_{18}H_{16}N_2OS$.

	x	y	z	U(eq)
H(1)	2866(2)	1820(4)	8269(1)	24
H(2)	3826(3)	3966(5)	7039(1)	25
H(3)	4282(2)	3029(6)	5739(1)	26
H(5)	978(3)	-2683(5)	5462(1)	25
H(10)	-4830(3)	-241(5)	8275(1)	26
H(11)	-3883(3)	5613(6)	9782(1)	31
H(12)	-1291(3)	5806(5)	9642(1)	25
H(16A)	2678(15)	-2734(20)	3758(5)	44
H(16B)	1145(3)	-2298(16)	4141(9)	44
H(16C)	2567(16)	-4135(8)	4599(4)	44
H(17A)	-4404(5)	-1659(10)	7121(8)	35
H(17B)	-3440(14)	-3964(15)	7646(4)	35
H(17C)	-3004(10)	-3082(24)	6801(6)	35
H(18A)	2092	4022	9513	40
H(18B)	1786	5958	8707	40
H(18C)	1205	5939	9561	40