

TOTAL SYNTHESIS OF 2,4-DIOXYQUINOLINE ALKALOIDS<sup>#</sup>

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The various total syntheses available for this wide-spread alkaloid family are reviewed.

I. Introduction

The 2,4-dioxyquinoline alkaloids are common in nature, particularly in plants belonging to the rue family--the Rutaceae. Members of this group of alkaloids occasionally show potentially interesting pharmacological activity; for example, dictamnine causes smooth muscle contraction, increases the tone of heart muscle and contracts the uterus,<sup>1,2</sup> pteleatinium chloride is antimicrobial,<sup>3,4</sup> bucharaine suppresses aggressive tendencies,<sup>5</sup> dubinidine is sedative, hypothermic and antimicrobial,<sup>6,7</sup> evoxine is antimicrobial,<sup>7</sup> skimmianine is antimicrobial, sedative, hypothermic and antidiuretic,<sup>7,8,9</sup> hapliphyllidine and perforine are ataractic and sedative,<sup>10,11,12</sup> lunarine, lunacridine and lunamarine are transiently hypotensive,<sup>13</sup> foliosidine is antiarrhythmic,<sup>14</sup> and so on. No apparent medicinal use has been made of these properties, perhaps in part because administration and evaluation is greatly hindered

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<sup>#</sup>Dedicated to Dr. Ken'ichi Takeda on his seventieth birthday.

by the exceptionally poor water solubility of some of these alkaloids.

Chemical interest in this alkaloid family remains high and recent years have seen the isolation and characterization of numerous new bases.

The biosynthesis of these alkaloids is also becoming clearer and is briefly set out in chart 1 and chart 2. A full exposition is beyond the scope of this review.

[Charts 1 and 2]

The furoquinolines and their congeners (chart 1) are derived by condensation of anthranilic acid (1) and acetate to give 2<sup>15</sup> which is then prenylated at C<sub>3</sub> to give 3. Epoxidation of the side-chain double bond introduces optical assymetry (4) and prepares the molecule for further elaboration.<sup>16,17,18,19,20</sup> Protonation may then lead via glycol 5 to a large group of 2-oxo-4-methoxyquinolines with sidechains possessing oxygen atoms and double bonds in various arrangements (9). Alternately, participation of the lactam function in the protolysis of 4 would lead to tricyclic bases such as 6. These compounds are sometimes isolated from plants as such, but commonly three carbons are lost. This is thought to take place by stereospecific benzylic oxygenation (7) followed by a fragmentation reaction to produce the furoquinoline group represented by 8.<sup>22,23</sup> It is now generally agreed that hydroxylation of the aromatic ring occurs late -- probably after furan ring formation (8).<sup>24,25,26,27,28,29,30,31,32</sup>

The dihydrofuranquinoline group, represented in chart 2 by ifflaiamine and ravenoline, is considered to arise

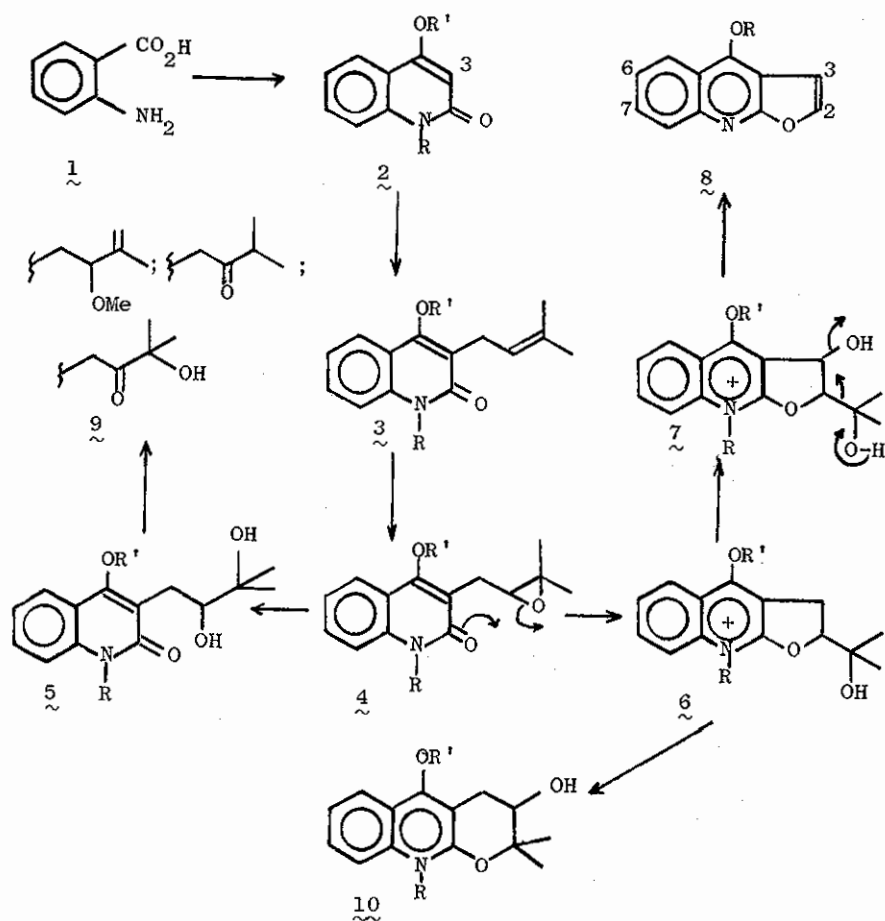


Chart 1. Proven or putative intermediates in the biosynthesis of furoquinoline alkaloids.

by prenylation of 2 on oxygen to give 11 (R=Me=ravenine<sup>33</sup>) followed by an electrocyclic rearrangement to 12.<sup>34,35</sup> Protonation could lead to formation of transient cyclopropane intermediate (13) which, on subsequent protonation of the C<sub>4</sub>-carbonyl, could rearrange in two manners. Migration of bond a would lead to carbocation 14 which could either lose a proton to form ravenoline,<sup>33</sup> or undergo cyclization to 15, which has been isolated from Flindersia ifflaiana.<sup>34</sup> Alternately, migration of bond b would lead to carbocation 16 which would undergo cyclization to ifflaiamine.<sup>36</sup> These proposals have received some experimental support.<sup>37</sup>

The 2,4-dioxyquinoline bases have deceptively simple structures so the reader might be surprised to learn that the first successful total syntheses are of comparatively recent origin. A number of syntheses are, however, now available. Because of the continuing interest in these substances and the fact that their synthesis has not been systematically reviewed, this account was prepared.

## II. Bicyclic Bases Lacking a Side Chain at C<sub>3</sub>

The simplest 2,4-dioxyquinoline alkaloids belong to this class. They are a relatively small group and their synthesis possesses technical rather than intellectual difficulties. Variation of the methods used for their construction is frequently employed as the first step in the preparation of more complex alkaloids.

The most commonly used method for construction of the ring system employs reaction between a primary or secondary aromatic amine (17) and a malonic ester.<sup>38</sup> Upon heating, amide

formation occurs (18) and continuing the thermolysis results in formation of the desired product (19) (chart 3). Brief

[chart 3]

reaction of the 4-hydroxy-2-quinolone with diazomethane results in selective ether formation at the 4-position (20) to complete the process. The aromatic ring must be suitably activated for this process to succeed and, of course, orientation ambiguities are possible in the cyclization step if the aromatic ring does not have rotational symmetry. In addition, other problems may be encountered. Use of a rather low temperature results in formation of uncyclized amide (18) and bisanilide (21).<sup>39</sup> Prolonged heating or use of higher temperatures results in low yields of 19 accompanied by pitch and the further reaction product 22.<sup>40</sup>

Despite these difficulties, when the appropriate aniline is readily available, this process represents the simplest and most convenient method for preparing these compounds and this overcomes the disadvantage of occasional poor yields.

An application of these methods in alkaloid synthesis is given in chart 4. Halfordamine is prepared by low

[chart 4]

temperature thermal amide-ester interchange between malonic acid<sup>41</sup> or malonic ester<sup>42</sup> and 2,4-dimethoxyaniline to give 24. In the latter case, the ester is hydrolyzed with base. Next, heating with polyphosphoric acid<sup>40</sup> gives the desired cyclization at the only open position and brief reaction with diazomethane leads to halfordamine.

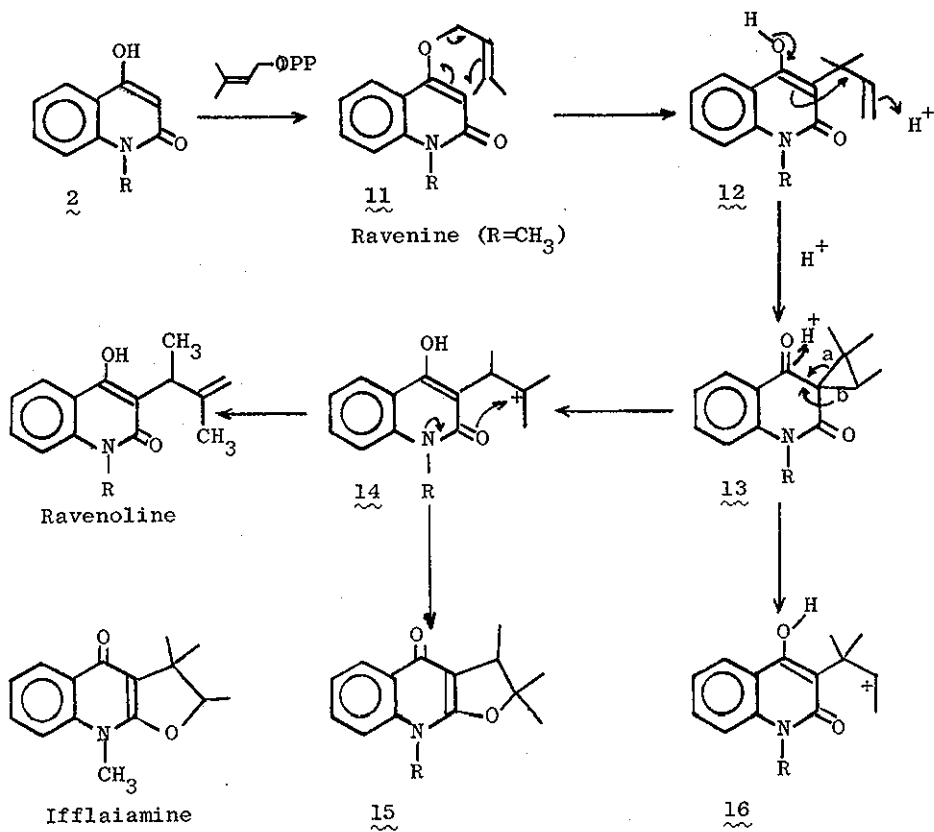


Chart 2. Proven or putative intermediates in the biosynthesis of dihydrofuranquinoline alkaloids.

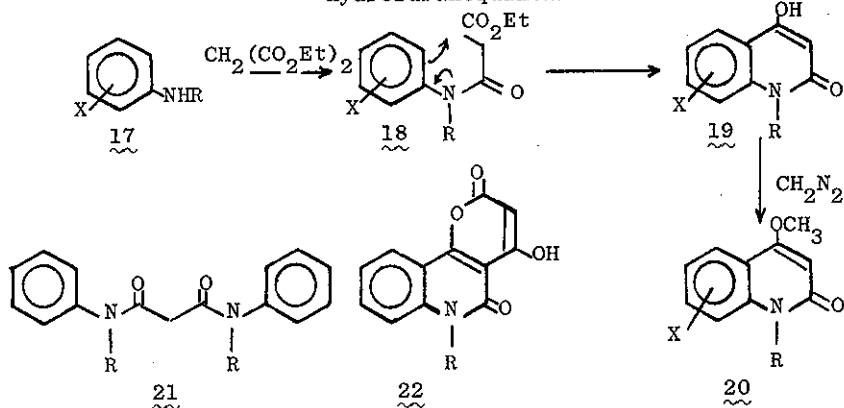


Chart 3. Synthesis of the unelaborated 2,4-dioxyquinoline system.

Recently, a C<sub>3</sub>-benzyl blocking group has been used to suppress over-reaction to side products such as

22. Edulitine (chart 5) was synthesized<sup>43</sup> by heating

[chart 5]

*o*-methoxyaniline with 2,4,6-trichlorophenyl benzylmalonate at 220° to give 25 in excellent yield. Removal of the benzyl group with aluminum chloride was accompanied by cleavage of the methoxy group to give 26. Treatment with diazomethane led to edulitine in relatively good overall yield.

### III. Angular tricyclic analogs of the 2,4-dioxyquinoline group

The 4-alkoxy-2-quinolone system is chemically more stable than the 2-alkoxy-4-quinolones as is revealed, for example, by the conversion of 27 to edulitine on treatment with 5% HCl.<sup>44</sup> (chart 6).

[chart 6]

The facile rearrangement of dictamnine to its angular analog (30, presumably via 28 and 29) upon warming with polyphosphoric acid (chart 7) is another illustration.<sup>45</sup> This would lead to potential uncertainty as to the structure of a

[chart 7]

substance cyclized in this fashion. These factors are of considerable importance in synthetic design and explain why the otherwise simple linear substances have been synthesized only comparatively recently. There are, however, a number of angularly substituted analogs of natural origin and their synthesis is comparatively easy and is considered in this section.

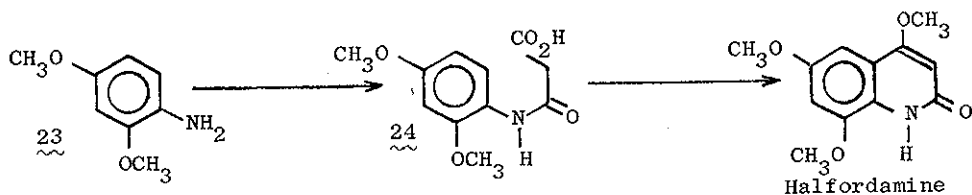


Chart 4. Synthesis of halfordamine.

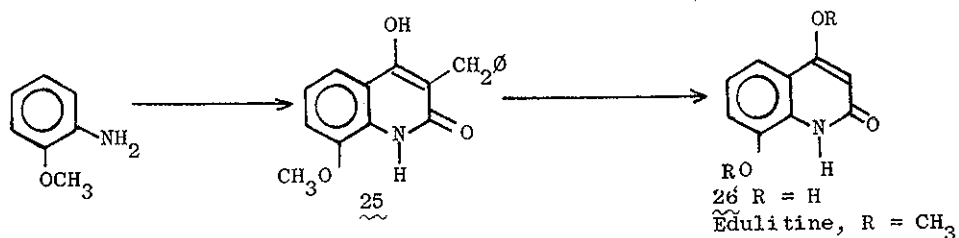


Chart 5. Synthesis of edulitine.

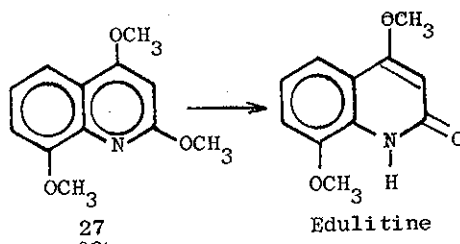


Chart 6. A simple preparation of edulitine.

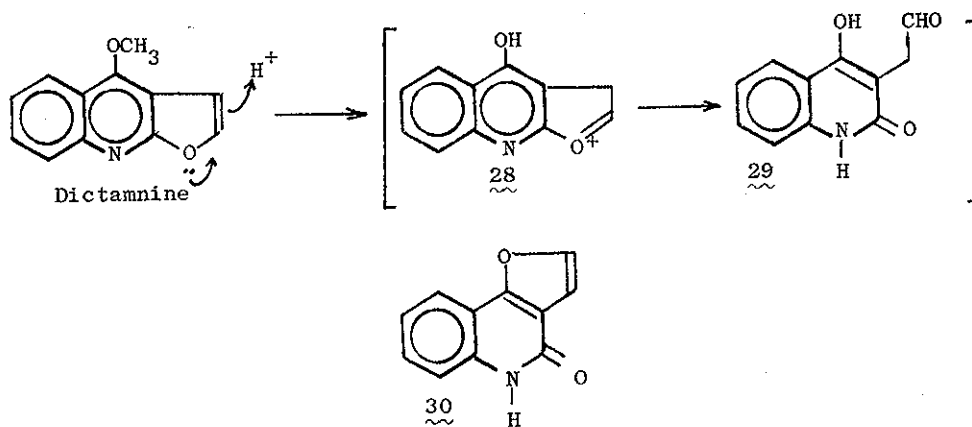


Chart 7. Rearrangement of dictamine under acidic conditions.



The synthesis of flindersine (chart 8), a 2,2-dimethyl-chromenoquinoline alkaloid, illustrates the problems inherent in preparation of angular tricyclics following direct alkylation of 4-hydroxy-2-quinolones.<sup>46</sup>

[chart 8]

Direct C-alkylation of 4-hydroxy-6-methoxy-2-quinolone (31) with 3,3-dimethylallyl bromide leads to preferential dialkylation (33), although a perceptible yield of the desired product (32) could be obtained.<sup>47,48</sup> Dehydrogenation of 32 with a high potential quinone (dicyanodichlorobenzoquinone) leads presumably to intermediate 34 which would undergo an electrocyclic rearrangement to 9-methoxyflindersine.

The dialkylation problem can be avoided (chart 9) by

[chart 9]

monobromination of 35 at C<sub>3</sub> (36), a high yield reaction, followed by alkylation in the usual way to give 37. The blocking group is then efficiently removed by brief treatment with zinc in acid to give the desired product (38).<sup>48</sup>

A more elegant process which has been used with particular effect by Grundon and his students, is illustrated in chart 10. In this particular application, oricine was synthesized by thermal reaction of 4-aminoveratrole with ethyl 3,3-dimethylallylmalonate to give 39 in moderately good yield. Oxidative cyclization with dicyanodichlorobenzoquinone was followed by

[chart 10]

N-methylation to complete the synthesis of oricine.<sup>49</sup> This converging synthesis is quite convenient and avoids the

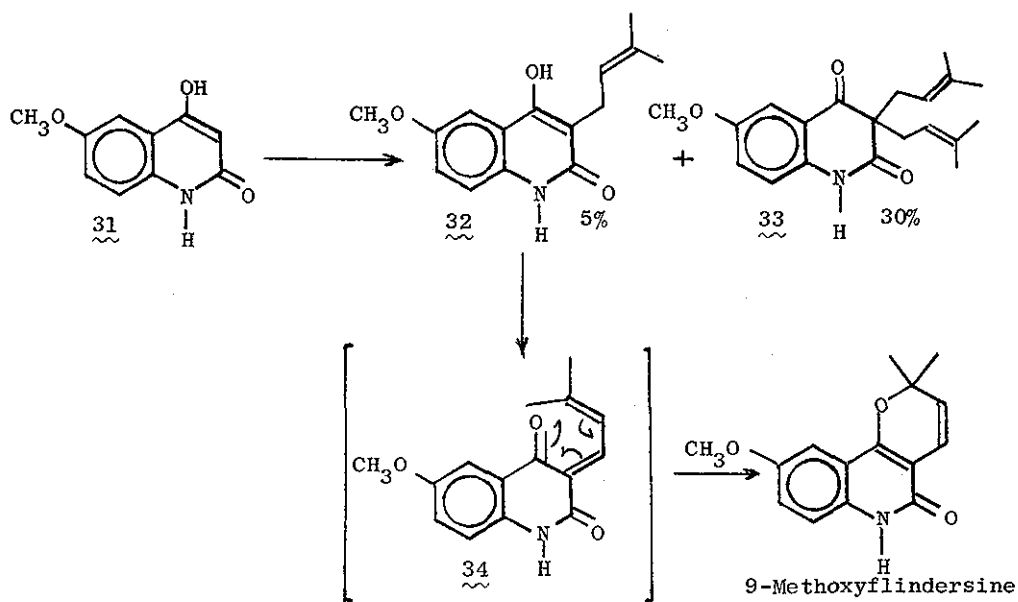


Chart 8. Synthesis of 9-methoxyflindersine by direct alkylation of a 2,4-dioxyquinoline derivative.

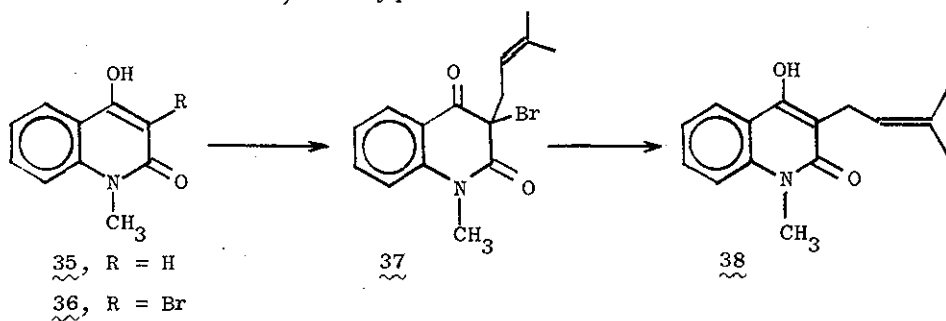


Chart 9. Use of bromine as a blocking agent in the synthesis of 3-alkyl-2,4-dioxyquinolines.

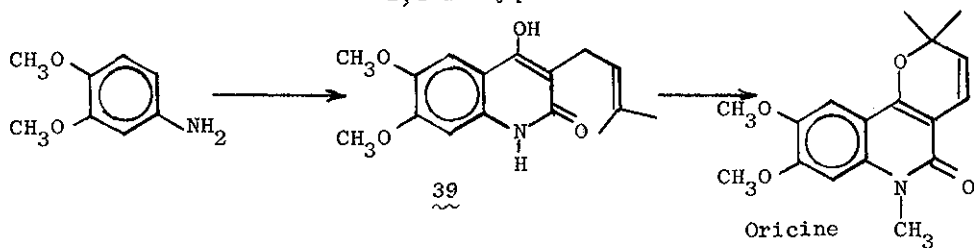


Chart 10. Grundon-type synthesis of oricine.

alkylation problems inherent in the previous syntheses.

An interesting synthesis of flindersine has been reported by the Grundon group and is summarized in chart 11.<sup>16,50,51</sup>

[chart 11]

Thermal reaction of aniline with the appropriately substituted malonate ester established the basic ring system (40). Prolonged treatment with diazomethane results in etherification of both oxygen atoms (41). Epoxidation to 42 occurs readily with perlauric acid, or with (+)-peroxycamphoric acid if optically active epoxide is desired. Treatment with base and a cosolvent (DMSO) leads efficiently to flindersine and analogs. The process can be considered to start with allylic opening of the epoxide to olefin 43. Next, nucleophilic aromatic displacement of the ether at the C<sub>4</sub> position (44) would lead to the 4-quinolone system of 45. This would undergo conjugative elimination of OH to produce quinone-methide 46 which would undergo an electrocyclic process to yield 47. It seems alternately possible that the oxanion generated with base from 42 would persist long enough to be the attacking species in a nucleophilic aromatic process. The intermediate so generated (48) would undergo elimination of methoxide to 47. Brief acid treatment of 47 leads to flindersine.

An interesting synthesis in which the reactants are at the desired final oxidation level is set out in chart 12.<sup>52</sup> This process depends upon the observation that thallos salts of non-chelated  $\beta$ -diketones react in high yield to form

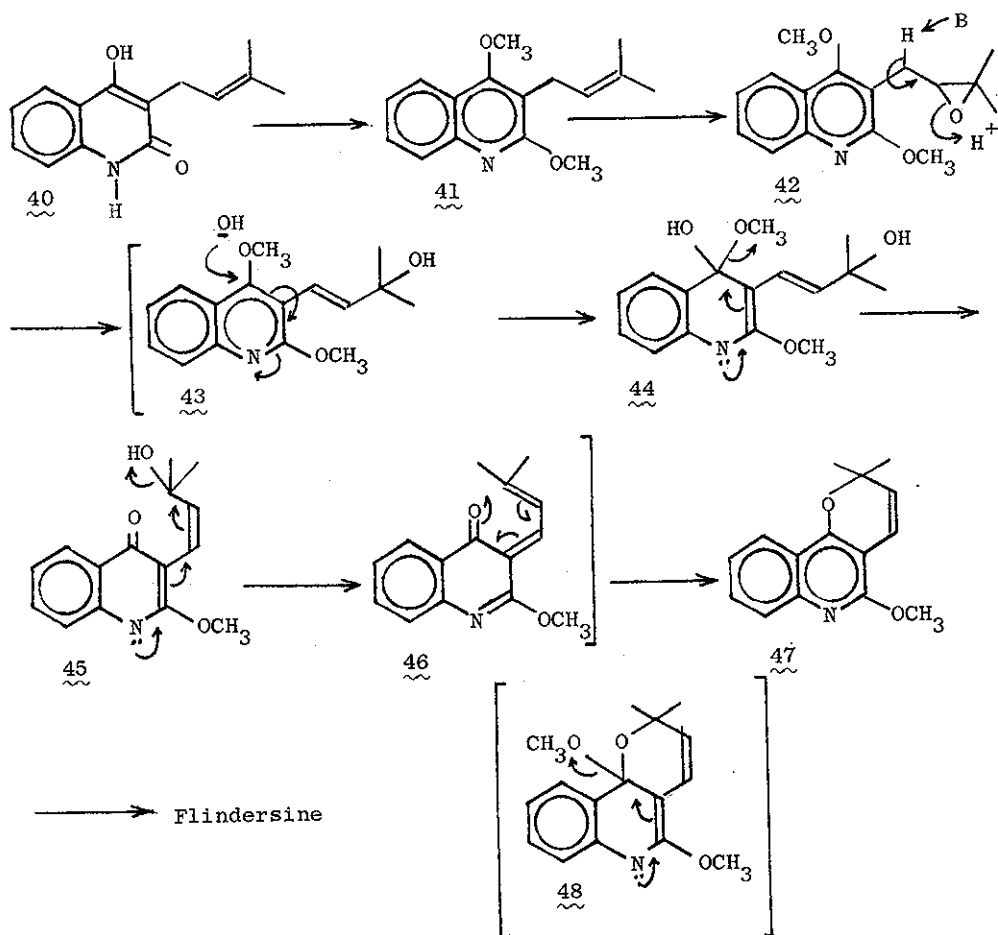


Chart 11. Grundon's synthesis of flindersine.

O-alkylated rather than C-alkylated products. Thus, quinolone 2 would react with the thallium salt derived from 3-chloro-3-methylbut-1-yne to give ether 49 which would undergo an

[chart 12]

o-Fries rearrangement to allene 50. The allene would then isomerize to 51 and on to flindersine. Because the thallium salt is ambident, the alternate possible product (52) was also isolated in the 8-methoxy series.

Another synthesis involving a Fries rearrangement has also been used to prepare flindersine (chart 13).<sup>53,54</sup> Acylation of 2,4-dioxyquinoline (2) with  $\beta,\beta$ -dimethylacroyl chloride gave

[chart 13]

enol ester 53. Treatment of 53 with  $AlCl_3$  resulted in a Fries rearrangement and the carbonyl group of 54 was reduced catalytically to give 55. Dehydration resulted in flindersine.

Huffman and his group attempted to modify this type of synthesis into a useful procedure for making linear tricyclics by using saturated branched acids (chart 14).<sup>55,56</sup>

[chart 14]

The product (56) from isovaleryl chloride was treated with diazomethane and, interestingly, did not produce the desired 4-OMe ether. Instead insertion and ring expansion occurred. Participation of the OH group at  $C_4$  led to presumed cyclopropane 57 via path a, which then rearranged to the major product 60 and its alkylation product 59. A percentage of the reaction product apparently resulted from participation of the electrons

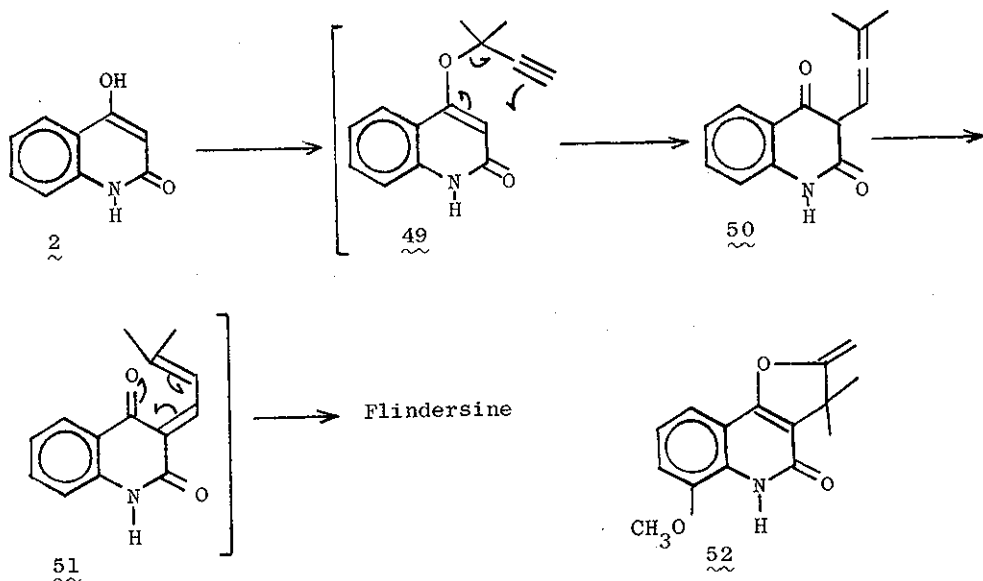


Chart 12. The Huffman synthesis of flindersine.

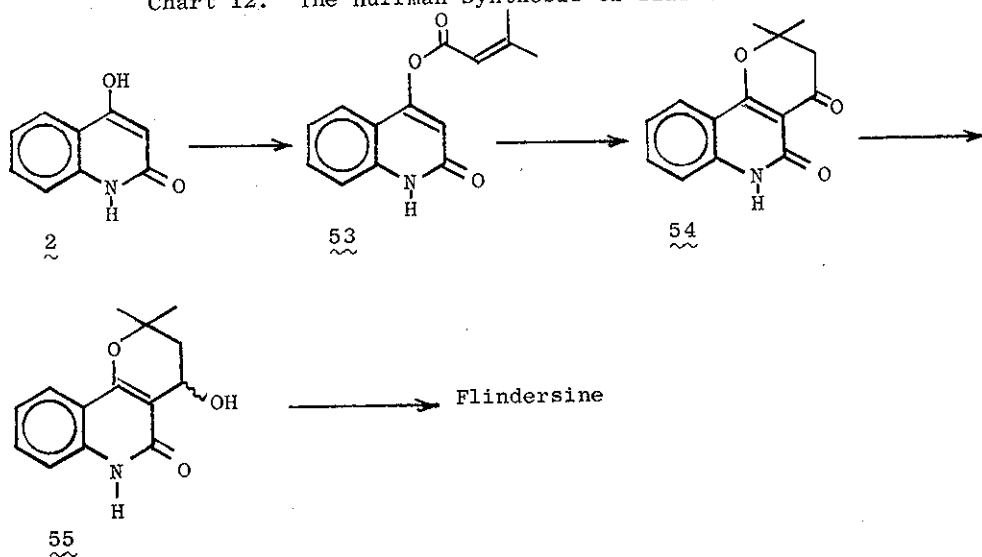


Chart 13. The Ritchie synthesis of flindersine.

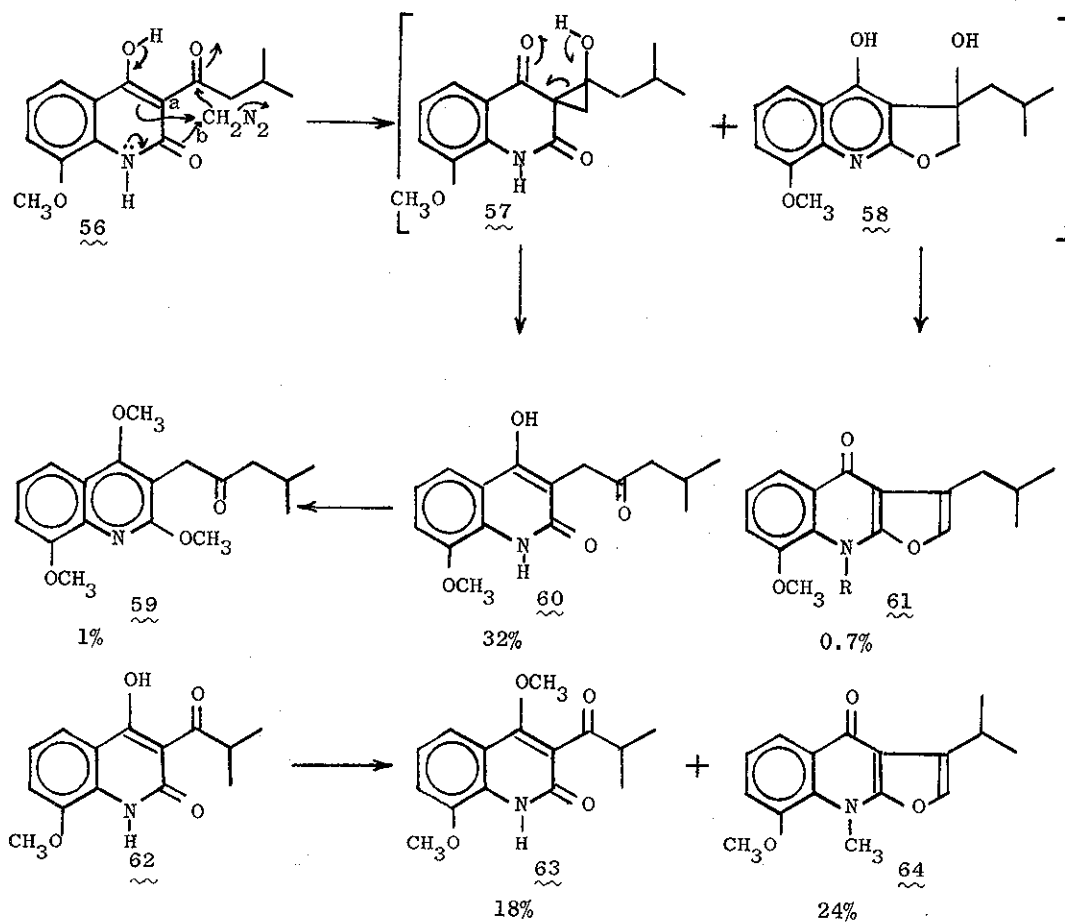


Chart 14. The Huffman approach to flindersine.

on  $N_1$ , via path b, to give alcohol 58. The latter dehydrated to 61 (R = H) and then reacted further with diazomethane to give 61 (R =  $CH_3$ ). Unfortunately, an attempt to turn this circumstance to advantage by using isobutyl ketone 62 instead, failed when homologation did not occur. In this case direct methylation did occur to give 63 and furan formation (64) was also significant. It appears that this otherwise promising approach had to be abandoned because of these difficulties.

Approaches to this system based on anthranillic acid derivatives have been reported (chart 15).<sup>57</sup> Amide ester 65 was cyclized at the only accessible center through the use of

[chart 15]

sodium dispersion to give 66. Ether cleavage with conc. HCl was followed by esterification at the vinylous acid position to give 67. Catalytic dehydrogenation led to iso-furoquinolone 68. An alternate procedure for angular furoquinolones starts with quinolone 2 and formylacetic acid (generated in situ from malic acid and concentrated  $H_2SO_4$ ). The resulting chromenoquinoline (69) added bromine and subsequent

[chart 16]

loss of HBr led to 70. The Perkin rearrangement led to the desired ring contraction to  $\alpha$ -carboxyfuran 71. Thermal decarboxylation to 72 finished the synthesis.<sup>59</sup>



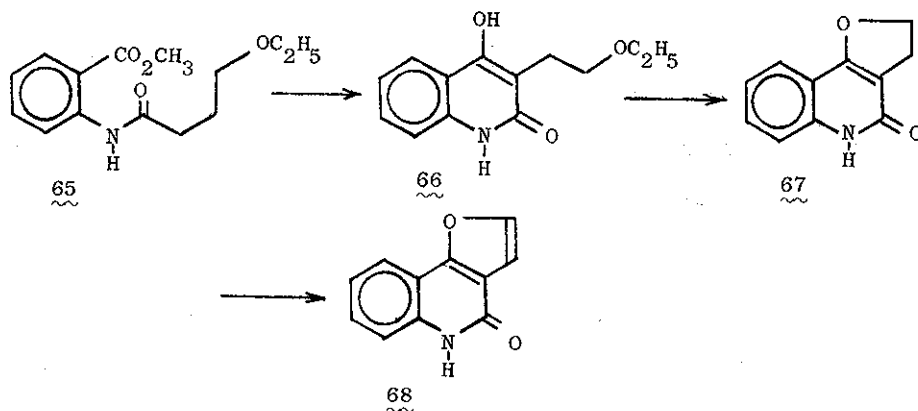


Chart 15. The first Ohta synthesis.

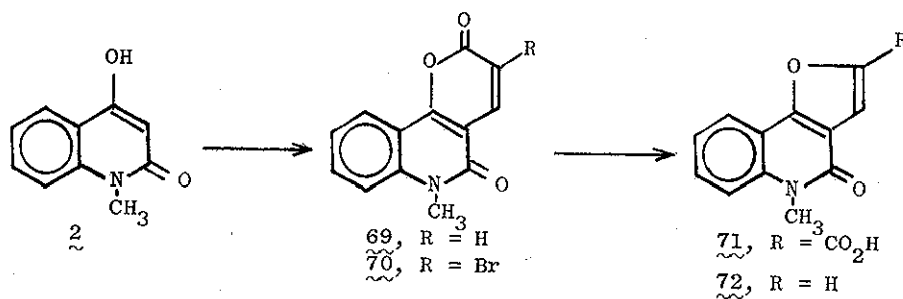


Chart 16. The second Ohta synthesis of angular furoquinolones.

#### IV. Linear Tricyclic analogs of the 2,4-dioxyquinoline group

It should be quite clear by now that synthesis of linear tricyclic 2,4-dioxyquinoline alkaloids present several problems in experimental design, however, several syntheses are now available which no longer make this a formidable task except in unusual circumstances. Most of the natural congeners belong to this group so these methods have the greatest intrinsic interest for the natural product chemist.

The first wholly dependable synthesis of the linear systems was that developed by Tuppy and Böhm (chart 17).<sup>60,61</sup> This general method requires an appropriate aniline and an isotetronic acid derivative (73). The latter are readily prepared<sup>62</sup> from sodiomalonic ester and chloroacetylchloride. An initial addition-elimination reaction (74) is followed by thermal ring closure to the desired linear derivative (75). The only possible ambiguity lies in the orientation of an aryl substituent if the aniline chosen does not have rotational symmetry. Yields may also be less satisfactory if the aniline

[chart 17]

ring is not sufficiently activated to promote closure. Reaction with  $\text{POCl}_3$  led to dichloride 76 but hydrogenolysis removes preferentially the wrong halogen to give 79. Treatment of 75 with diazomethane leads to a mixture of N (78) and Q (77) methylated products. If the Q-methyl product (77) is treated with  $\text{POCl}_3$  containing some water, chloride 80 results. Hydrogenolysis leads to dictamnine. This outcome is sufficiently

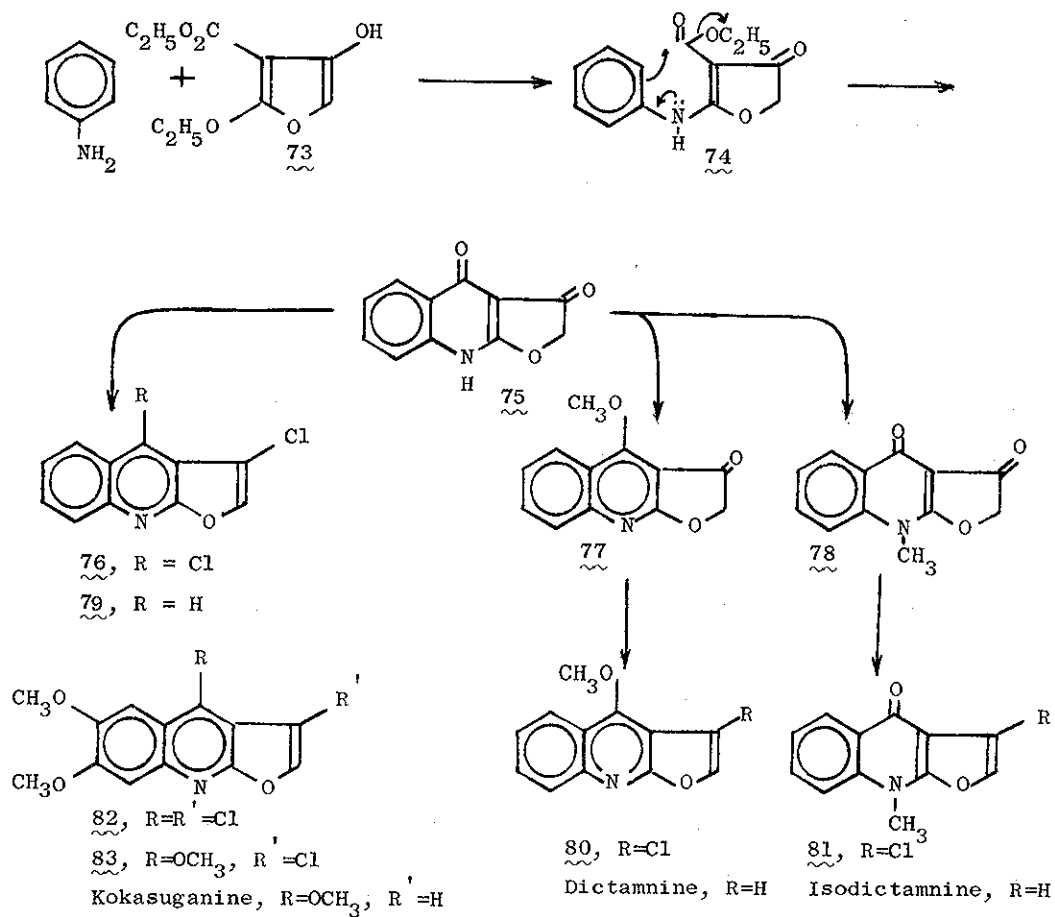


Chart 17. The Tuppy-Böhm Synthesis.

unambiguous that the process is accepted as proof of structure. When the N-methylated product (78) is treated with partially hydrolyzed  $\text{POCl}_3$ , preferential halogenation occurs at  $\text{C}_3$  (81). Hydrogenolysis leads to isodictamine.

This useful synthesis has been used widely and has undergone several useful modifications. For example, in the synthesis of kokasuganine,<sup>63</sup> 82, prepared essentially in the standard way, is reacted with  $\text{NaOMe}$  to give 83. This takes advantage of the greater reactivity of the 4-halogroups to nucleophilic displacement. Hydrogenolysis leads to kokasuganine.

The synthesis of medicosmine utilizes a cleverly conceived reduction to generate the desired furan system more directly (chart 18).<sup>64</sup> Reduction of 84 with borohydride in alkaline

[chart 18]

methanol results in reduction to the alcohol followed by elimination (85) and a prototropic shift (86) leads to the furan 87. Three standard steps complete the synthesis of medicosmine. In the synthesis of acronycidine by essentially the same means, the reduction step on 88 led not only to the desired furan (90), but also by hydrogenolysis to the undesired dihydrofuran (89).<sup>65</sup> Diazomethane treatment of 90 led to a mixture of acronycidine and isoacronycidine.

[chart 19]

The Grundon synthesis described earlier under angular tricyclics, is readily adapted to the synthesis of linear systems by timely ether formation with diazomethane (chart 20).

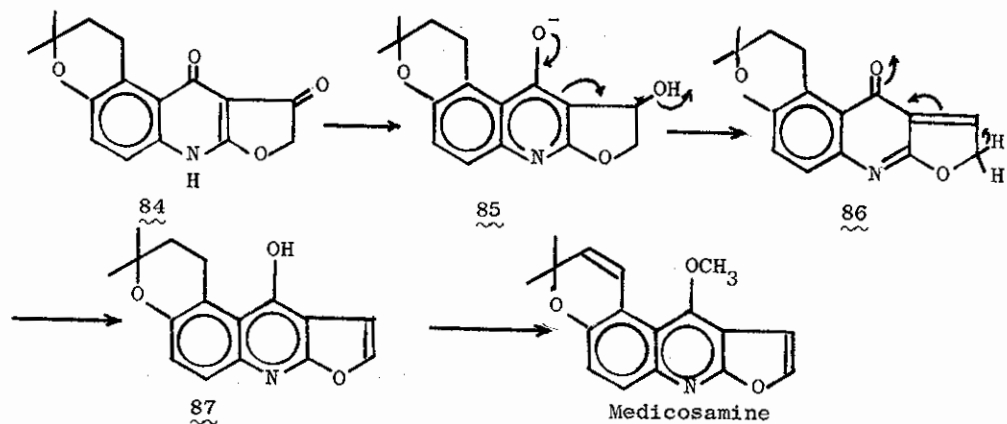


Chart 18. The Govindachari synthesis of medicosmine.

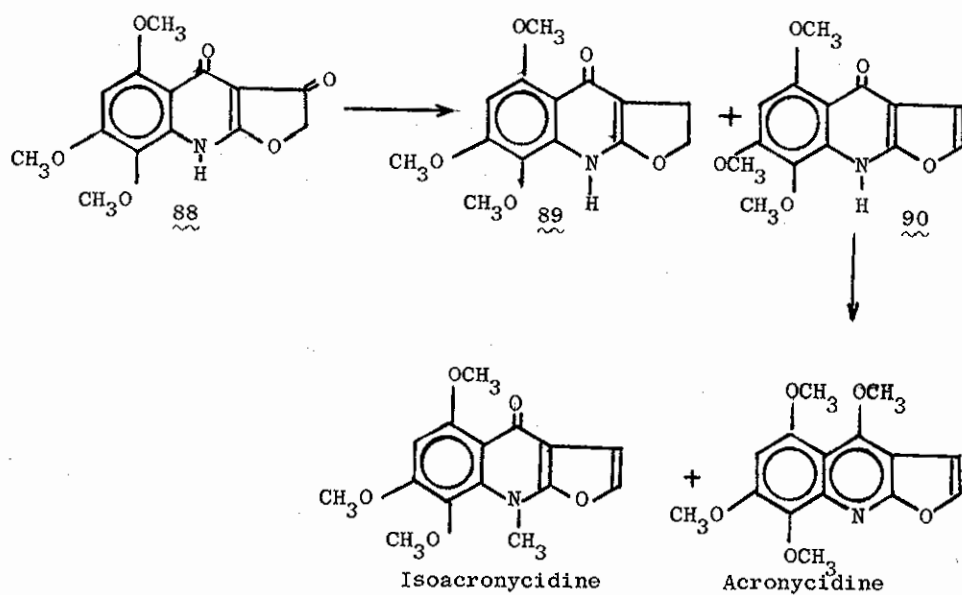


Chart 19. The Ramachandran synthesis of acronycidine.

This devise makes judicious use of the preference of 2,4-dioxyquinolines to form ethers at C<sub>4</sub>.<sup>66-71</sup> Once C<sub>4</sub> is blocked by a group which also extends the synthesis, ether formation can only take place at C<sub>2</sub> as desired. As an example, o-methoxy-N-methylaniline is condensed with substituted malonate 91 by strong heating in diphenylether and the product (92) is etherified by brief diazomethane treatment to give 94. Epoxidation can be carried out with an optically active reagent to give asymmetric induction, or with perlauric acid, for example. If no base is added, the mixture is sufficiently acidic to promote acidic opening of the epoxide (93) with participation of the lactam electrons to give quaternary salt 95. Heating in pyridine leads to O-demethylation (96).

If the synthesis is carried forward with O-methoxyaniline instead, intermediate 97 undergoes epoxide opening and gives 98 directly, along with significant quantities of the pyranoanalogs.<sup>72</sup>

The Grundon process is capable of useful extension to a wide variety of interesting products. For example, if the end products (99) are treated with acetic anhydride and pyridine, ring expansion to pyrans (101) occurs.<sup>73,74</sup> It is presumed that some sort of cyclic electron flow occurs as

[chart 20]

suggested in formula 100. Saponification to 102 completes the process.

[chart 21]

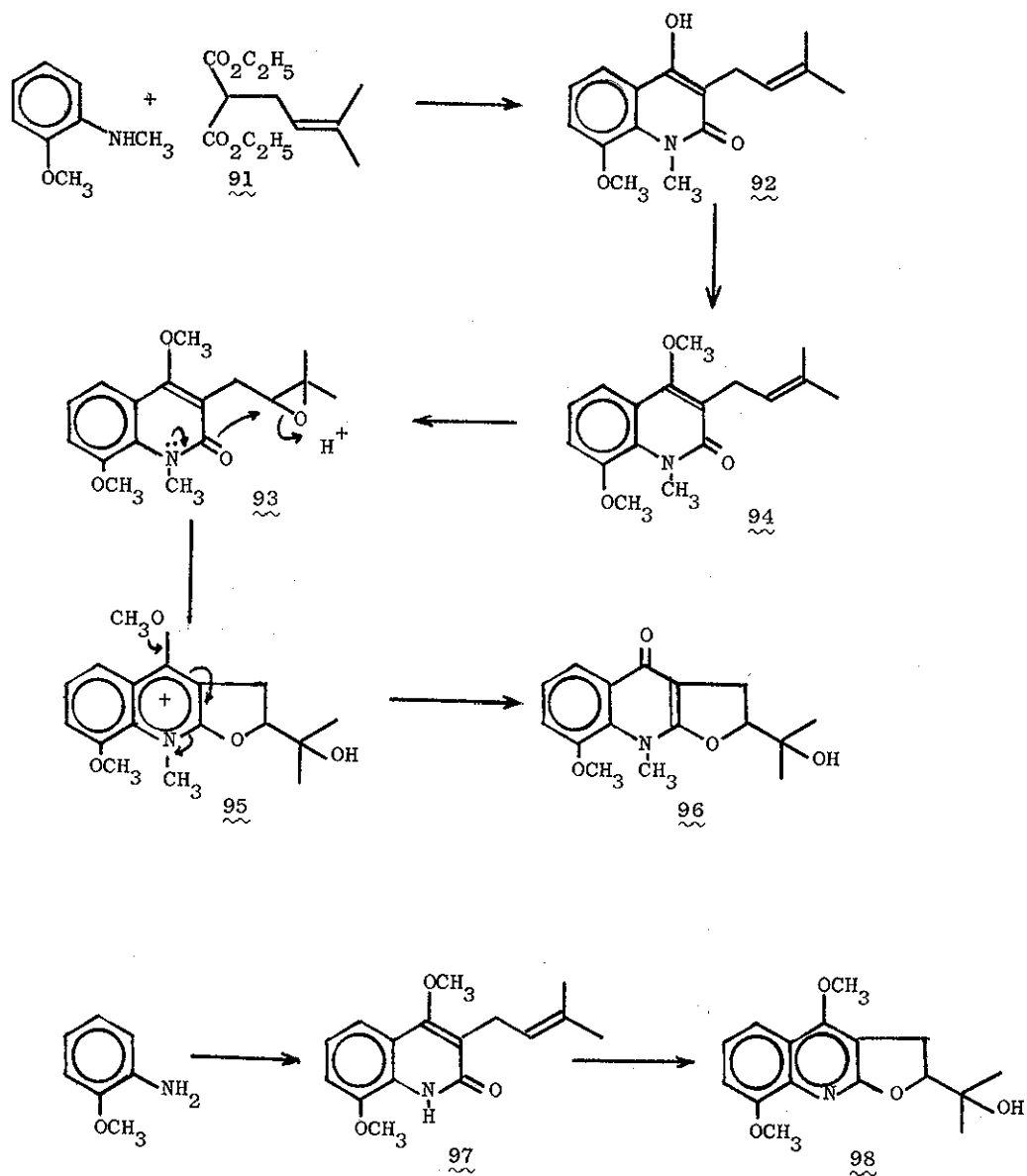


Chart 20. The Grundon synthesis of Linear tricyclic 2,4-dioxyquinolines

Cleavage to furans can also be accomplished. For example,<sup>75</sup> treatment of platydesmine with lead tetracetate,

[chart 22]

calcium carbonate and iodine using irradiation (the latter to generate I as an initiator) presumably leads to lead ester 103 followed by free radical scission to 104 which would collapse to oxonium ion 105 which would undergo hydrogen loss to give dictamnine. The overall yield is 34%. Alternately,<sup>45</sup> 3 can be ozonized or subjected to Lemieux-Von Rudloff reaction

[chart 23]

to give aldehyde 106 which cyclizes in acid to provide an efficient process for dictamnine.

In another variation (chart 24)<sup>19</sup> epoxide 107 undergoes diborane reduction in an anti-Markownikoff sense to alcohol 108. Selective hydrolysis gives lactam 109 which is N-methylated with diazomethane to give 110. This undergoes a

[chart 24]

a thermal rearrangement to give lunacridine. These reactions not only provide access to the deoxy series represented by lunacridine but also, when optically active epoxide 107 was prepared, allowed determination of absolute configuration of various natural products in this family.

The Narasimhan synthesis (chart 25) takes advantage of the pronounced tendency of 2,4-dimethoxyquinolines to lithiate at C<sub>3</sub>. This provides an efficient synthesis of these alkaloids which promises to replace the Grundon synthesis in cases where



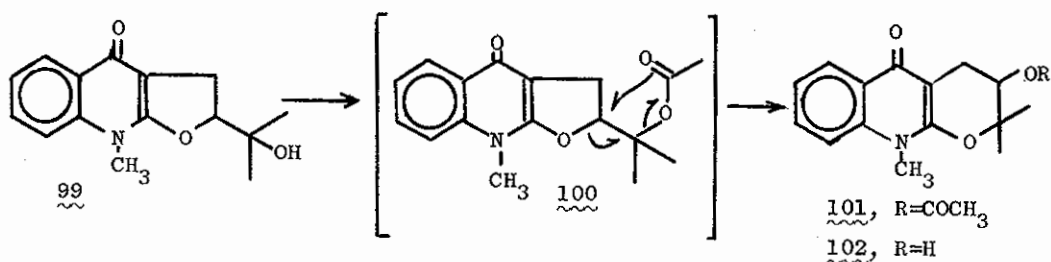


Chart 21. Rearrangement of dihydrofuroquinolones to dihydropyranoquinolones with acetic anhydride.

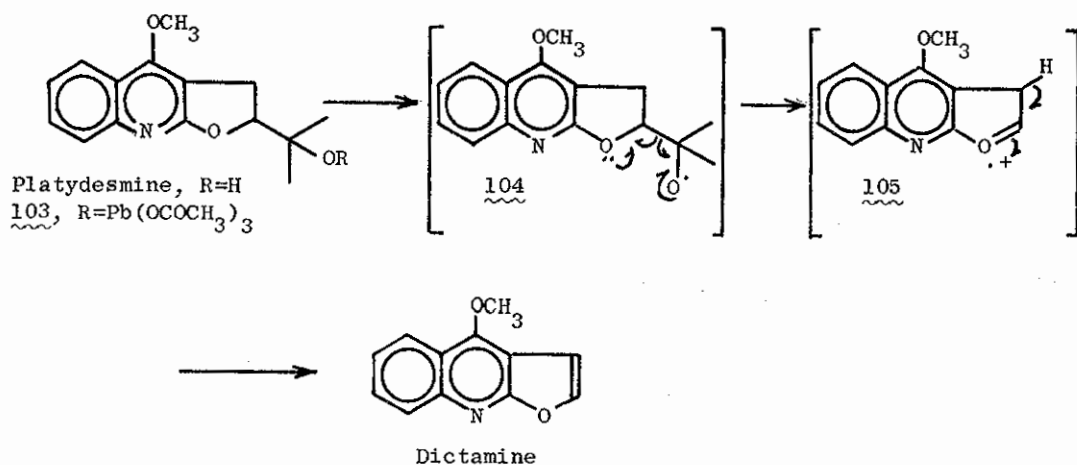


Chart 22. Conversion of dihydrofuroquinolines to furoquinolines with lead tetraacetate.

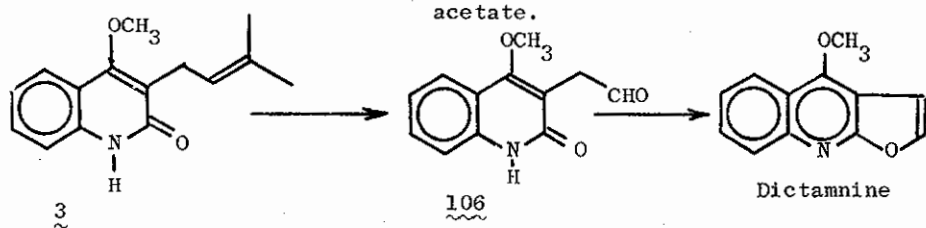


Chart 23. Oxidative conversion of 3-dimethylallylquinolones to furoquinolines.

the requisite dimethoxyquinolines are readily accessible.<sup>44,76-79</sup> Two syntheses of dictamnine are given in chart 25. Aniline is converted to the 2,4-dioxyquinolines with malonate and

[chart 25]

the dichloro derivative is prepared by treatment with  $\text{POCl}_3$ . Sodium methoxide leads to nucleophilic aromatic substitution and formation of 111. Lithiation gives 112 which can react with ethylene oxide to form 115. Selective ether cleavage followed by cyclization with polyphosphoric acid leads to dihydrodictamnine. Bromination with NBS followed by dehydrohalogenation with triethylamine gives dictamnine. Alternately lithio derivative 112 is formylated to give 114 by reaction with *N*-formyl-*N*-methylaniline. A Wittig reaction leads to homologation of the aldehyde and selective hydrolysis leads to 113. Acid catalyzed cyclization leads to dictamnine. The most recent adaptations overcome poor yields at the last steps of some of the earlier published procedure so that this method now seems preferred for radioisotope syntheses.

Reaction of lithio derivative of 111 (chart 26) with 3,3-dimethylallyl bromide (to 116) followed by selective ether cleavage (to 117) prevents dialkylation of the type that plagued Venturella *et al.*<sup>41</sup> and provides an efficient entry into the dihydrofuran series.<sup>77</sup>

[chart 26]

All of the syntheses of linear tricyclics discussed to this point suffer from the same potential drawbacks. Each is dependent upon the availability of an appropriately

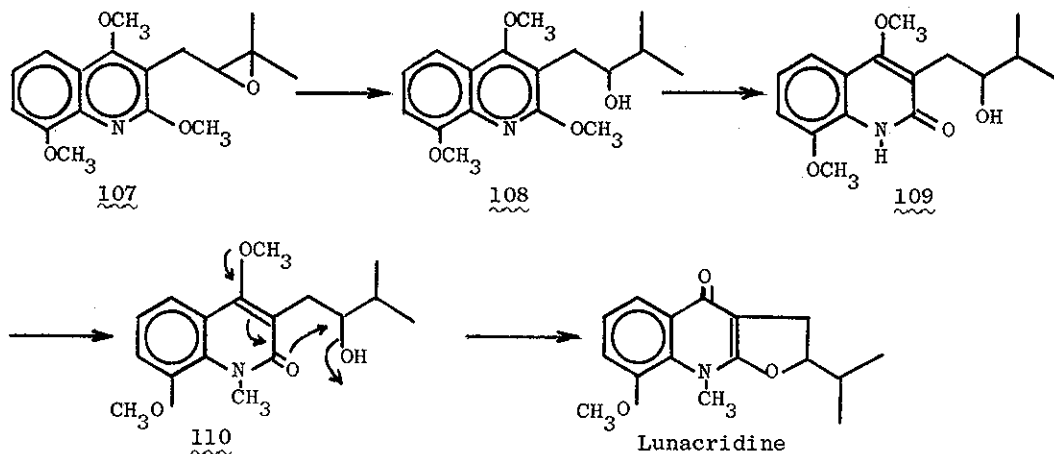


Chart 24. Reductive transformation of 3-dimethylallylquinolines to lunacridine types.

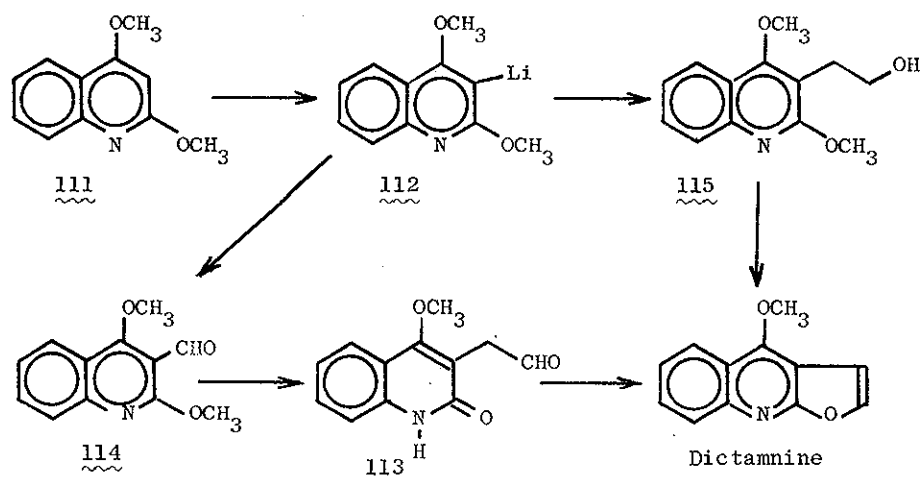


Chart 25. The Narasimhan synthesis.

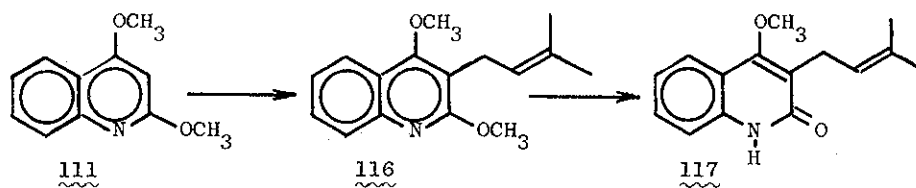


Chart 26. Modified Narasimhan synthesis.

substituted aniline derivative. That derivative must possess rotational symmetry in order to avoid isomer formation when the second ring is added, and the benzene ring must be relatively activated for the cyclization step to go in satisfactory yields. It must not, however, be too activated or substitution there in subsequent steps will take precedence over the pyridine ring. The syntheses to be discussed in this subsection are based upon anthranillic acid derivatives so that both of the above defects are potentially overcome.

The Kuwayama synthesis (chart 27) is based upon the Viscontini  $\beta$ -keto ester synthesis. For example, 2-nitro-5-methoxybenzoyl chloride (118) is condensed with cyclic  $\beta$ -keto-ester 119 with magnesium ethoxide as basic catalyst to produce 120.<sup>80</sup> Reaction with diazomethane produces the enol ether 122 and catalytic reduction of the nitro group to the aniline is succeeded by ring closure to 121. Halogenation-dehydrohalogenation then completes the synthesis of pteleine. It

[chart 27]

frequently happens that the intermediate tricarbonyl compound, such as 123, is isolated.<sup>80</sup> These products can be converted to the desired 124 by cleavage with dilute hydroalcoholic ammonia solution. The reduction step must also be carefully controlled, or hydrogenolysis to less immediately useful products (125) can result.

Numerous applications have been made of this useful process for the synthesis of furoquinoline alkaloids.<sup>81,82</sup>

Those with more complex side-chains are best made by other methods.

The Haynes synthesis (chart 28) is now primarily of historical interest although it has potential utility, not yet developed, for specific substances.<sup>83</sup> In this application

[chart 28]

methyl 4-methoxyanthranillate is acylated with succinic anhydride to give 126. Esterification with diazomethane is followed by Dieckmann-type cyclization with sodium dispersion to give 127 and its undesired isomer 131. Ether formation with diazomethane ensures regiospecificity after reduction with  $\text{LiAlH}_4$  (to 128) and cyclization to 129 with polyphosphoric acid or  $\text{POCl}_3$  treatment followed by silver oxide. Adjustment to the correct oxidation level by halogenation-dehydrohalogenation produces the desired 130.

The most recently published method is the Mitscher synthesis (chart 29).<sup>48</sup> In this case the appropriately substituted isatoic anhydride (132), readily available either from an anthranilic acid or from indoles via isatins, is reacted with the anion of the appropriately substituted malonic ester. Attack occurs preferentially at the ester-like carbonyl rather than the carbamate and expulsion of  $\text{CO}_2$  leads to intermediate 133. The negatively charged nitrogen then attacks either of the ester carbonyls to liberate  $\beta$ -tricarboxyl compound 135. Alkylation with 3,3-dimethylallyl bromide occurs on carbon (134). Dialkylation is, of course,

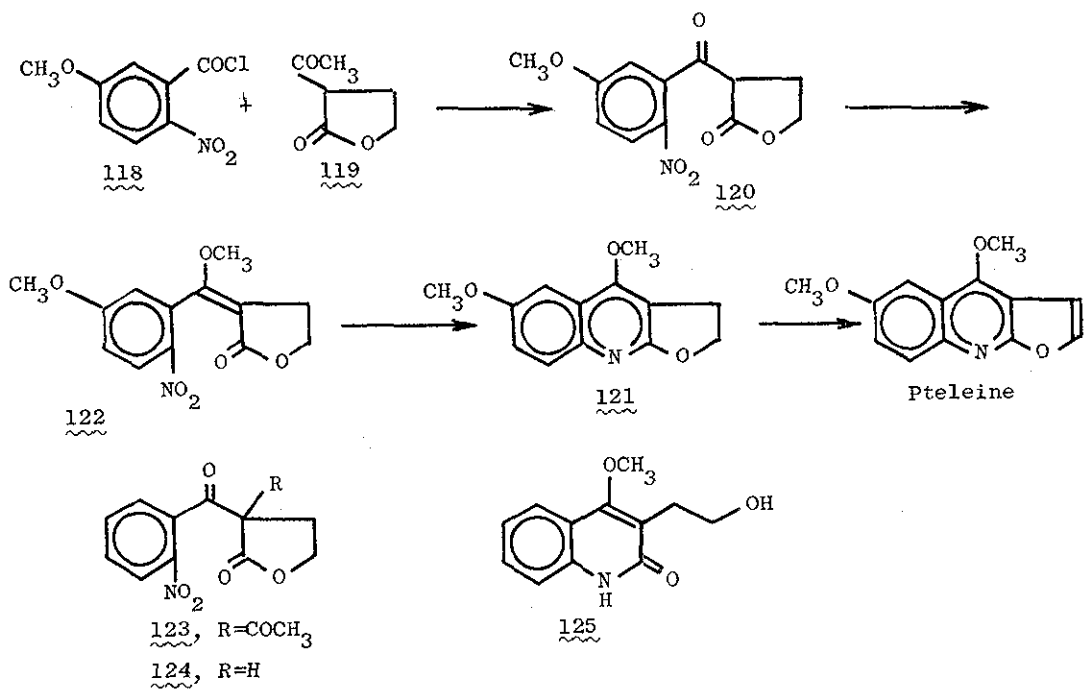


Chart 27. The Kuwayama synthesis.

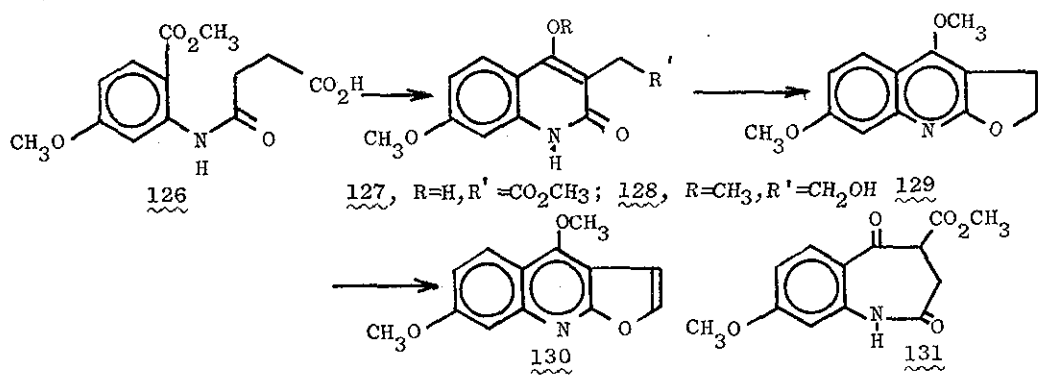


Chart 28. The Haynes synthesis.

## [chart 29]

not possible. The no longer needed carboethoxy group is selectively cleaved by strong heating with copper (II) acetate in hexamethylphosphorous triamide (136). Several alternate and more traditional conditions for saponification of the ester function resulted in cleavage of the undesired carbonyl instead.

IV. Synthesis of Dihydrofuranquinoline Bases of the Ifflaiamine Group

The alkaloids in this subgroup are biogenetically considered to be the result of Claisen rearrangement (chart 2), and their synthesis follows this pattern also. Among the alkylation products of 2 is found 22% of the O-alkylether (137).<sup>36,84</sup> Heating at 130-140° for 5 hours gave a series of Claisen rearrangement products. Presumably an electrocyclic process like that illustrated in formula 137 leads

## [chart 30]

first to intermediate 138 which, after enolization to 139, would undergo a second electrocyclic process to cyclopropane 140. Scission of one or the other of the cyclopropane bonds followed by prototropic shifts would lead to the isolated products 141, 142 and 143. Unfortunately, none of these products is the desired one. When longer heating times were used, the product distribution altered as would be expected for a reaction in which several products flow reversibly through a common intermediate. This established a preference for angular products, but no iffliamnine.

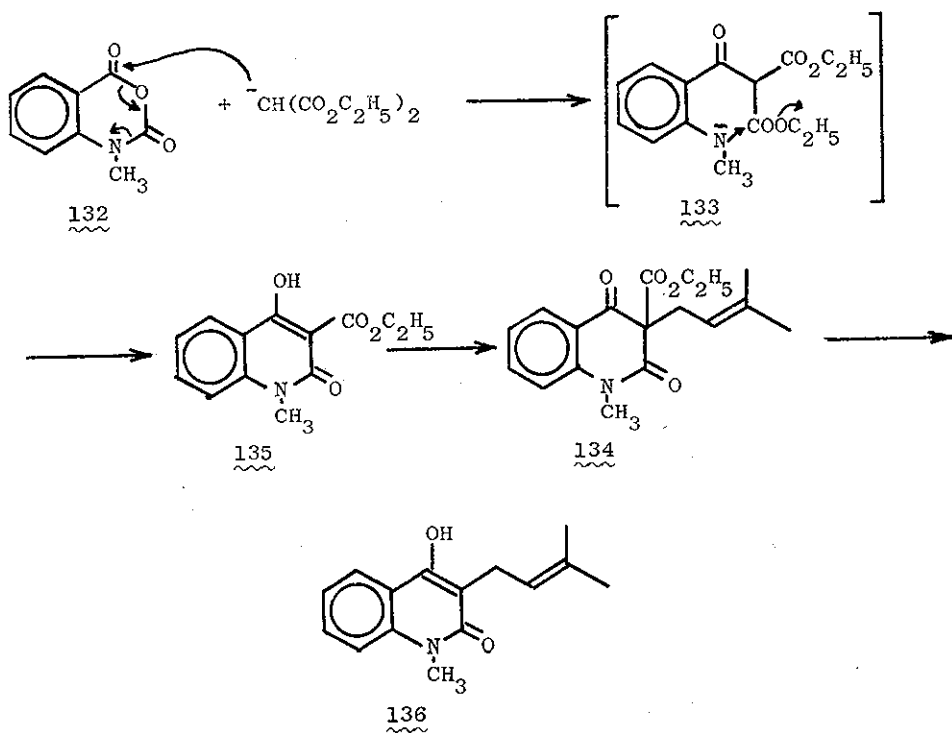


Chart 29. The Mitscher synthesis.



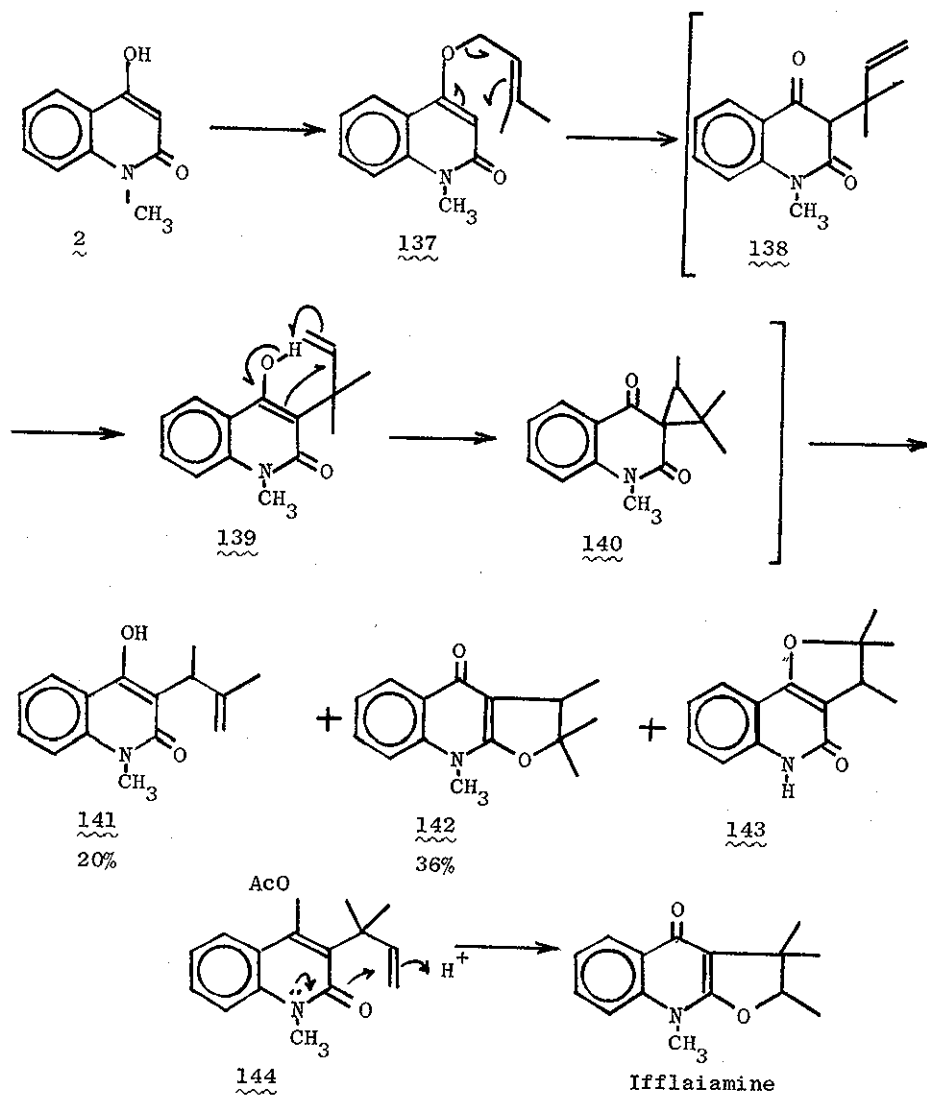


Chart 30. Synthesis of ifflaiamine by Claisen rearrangement.

It was intelligently reasoned that participation of the 4-OH group should be suppressed in order to alter the reaction course away from "abnormal" products via 139. When the rearrangement was carried out in the presence of N-methyl-piperidine and acetic anhydride, a quantitative yield of simple cyclization product 144 was obtained. Acid hydrolysis removed the acetyl ester and led to a concomitant acid catalyzed cyclization to the desired ifflaiamine.

#### V. Conclusion

As the result of intense investigation, predominantly in the last decade, a variety of useful syntheses of various types of 2,4-dioxyquinoline alkaloids have been developed so that most uncomplicated substances can now be prepared readily. Intense activity can now be expected to concentrate on the synthesis of the more complicated members and on resolving the remaining uncertainties in the biosynthesis of these widespread alkaloids.

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