2,3-POLYMETHYLENEQUINOLINES AND RELATED COMPOUNDS (REVIEW)*

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The methods for the synthesis of and the chemical properties and biological activity of 2,3-polymethylenequinolines and related β-quinindines are reviewed.

With respect to their properties, 2,3-polymethylenequinolines differ considerably from the related three-ring acridine system but are similar to quinaldines. At the same time, the presence of a cycloalkene ring affects the properties of the quinoline ring condensed with it or the functional substituents in it. Thus 2,3-dimethylene- and 2,3-trimethylenequinolines have a planar cycloalkene ring with considerable strain, and this affects the basicity and aromatic character of the quinoline fragment. In 2,3-tetra- and 2,3-pentamethylenequinolines, which are free of angular strain, the methylene groups in the 2 and 3 positions hinder reactions with the participation of adjacent substituents (esterification of the corresponding acids and nucleophilic substitution of the halogen in the 4 position).

The theoretical significance of these structures is also due to the fact that unsaturated compounds of the 2,3-trimethylenequinoline series — 1H- and 4H-β-quinindines — are the nitrogen analogs of azulenes.

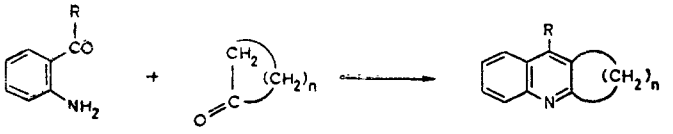
2,3-Polymethylenequinolines are also important in a practical respect as physiologically active compounds.

The names corresponding to the IUPAC nomenclature rules are used for most 2,3-polymethylenequinolines, but the names β-quinindanes [1] or 2,3-dihydro-β-quinindines [2] have become deeply-rooted for 2,3-trimethylenequinolines.

Synthesis of 2,3-Polymethylenequinolines

Most of the methods for the synthesis of structures of this sort consist in building on a pyridine ring by means of well-known reactions in the chemistry of quinolines.

For example, 2,3-polymethylenequinolines are formed by condensation of o-aminobenzaldehyde or o-amino ketones with cyclic ketones — cyclobutanone [3, 4], cyclopentanone [5-8], cyclohexanone [6, 8, 9] or its derivative [10, 11], suberone [5], and alicyclic diketones [9, 12, 13] — in aqueous alcoholic alkali or — better — under acid-catalysis conditions [14].



The method has limited application for the synthesis of 4-unsubstituted 2,3-polymethylenequinolines because of the low accessibility of o-aminobenzaldehyde and its instability. A variant of the synthesis based on anils of o-aminobenzaldehyde and its derivatives is known [15].

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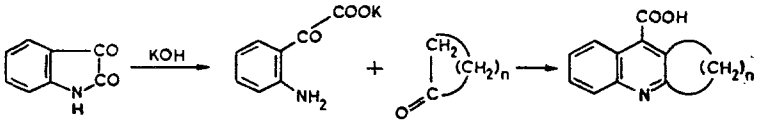
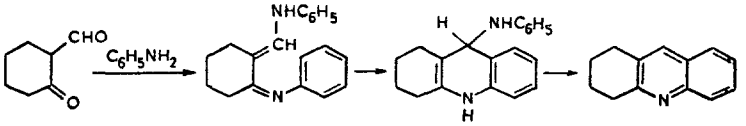
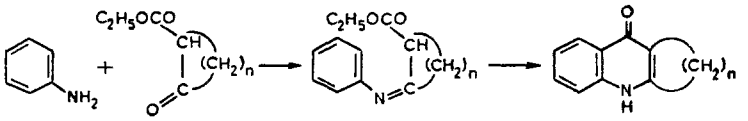
2,3-Polymethylenequinoline-4-carboxylic acids are obtained in good yields by the Pfitzinger reaction by heating a solution of isatin or its derivatives in aqueous alcoholic alkali with cyclic ketones [3-5, 16, 17].



1,2,3,4-Tetrahydroacridines are formed in ~60% yields by reaction of formylcyclohexanones with aromatic amines in alcohol solutions in the presence of excess arylamine hydrochloride and anhydrous zinc chloride [18-21].



2,3-Polymethylene-4-quinolones have been synthesized by the Conrad–Limpach method from aromatic amines and esters of cyclopentanone-2- [22-25], cyclohexanone- [26-29], and cycloheptanone-2-carboxylic [30] acids.



Reaction of the starting materials at room temperature in the presence of a few drops of HCl gives the intermediate anils [24, 31], which are cyclized at 255°C without a solvent [26, 32] or at 250-280° in a liquid paraffin [27] or diphenyl ether [23].

Heating anthranilic acid or its derivatives with cycloalkanones has been used for the synthesis of 1,2,3,4-tetrahydro-9-acridones [16, 23, 33, 34], 2,3-pentamethylene-4-quinolones [35], and 2,3-hexamethylene-4-quinolones [36, 37].

The intermediates in this reaction are cycloalkylideneanthranilic acids, which have been isolated in a number of cases [33, 35]. At the same time, the intermediate — 3-spirocyclohexane-1-oxo-2,3-dihyrobenz[d]-1,3-oxazine [38] — has been isolated in the condensation of anthranilic acid with cyclohexanone in diphenyl ether (120-220°).

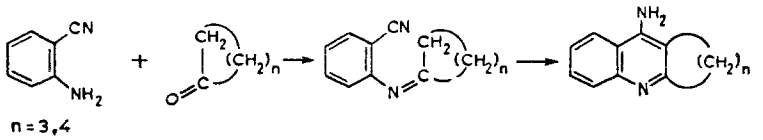
Decarboxylation was observed in the condensation of 4-methoxy- [23] and 5-nitroanthranilic [16] acids with cyclohexanone. N-Methylanthranilic acid gives 10-methyl-1,2,3,4-tetrahydroacridone when it is heated (220°) with cyclohexanone for 3 h [39]. It is assumed that the reaction proceeds through a step involving the formation of the corresponding enamine [40].

3-Cyclopentylidene-β-quinindan-9-one was obtained instead of the expected product in an attempt to synthesize β-quinindan-9-one from anthranilic acid and cyclopentanone [41, 42].

Until recently, nucleophilic substitution of the halogen atom in 4-chloro-2,3-polymethylenequinolines by an amino group was used for the synthesis of 4-amino-2,3-polymethylenequinolines. This synthesis is fraught with difficulty because of the low lability of the chlorine atom. The reaction is carried out by heating an alcohol solution of the starting materials in a sealed tube at 220-240° in the presence of copper [22, 43]; the products are obtained in ~50-60% yields. The reaction does not take place in solution in boiling phenol [22, 43], whereas in p-cresol [44] the amino derivatives obtained contain considerable amounts of cresoxy derivatives. A variant of the synthesis of 4-amino-2,3-polymethylenequinolines by heating 4-chloro-2,3-polymethylenequinolines with urea in phenol at 180-190° with subsequent saponification of the intermediate 4-carbamido derivative has been proposed [45].

The synthesis of 9-amino-1,2,3,4-tetrahydroacridine by reduction of 9-nitro-1,2,3,4-tetrahydroacridine N-oxide has been described [46].

A method for the preparation of 4-amino-2,3-polymethylenequinolines by heating anthranilonitrile with cyclopentanone [47] or cyclohexanone [48] in the presence of anhydrous zinc chloride is interesting. The yields in this case reach 85%.



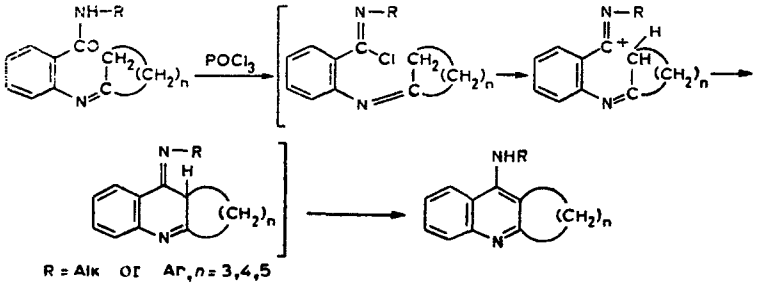
n = 3,4

9-Amino-β-quinindanes are obtained by cyclization of (2-arylamino)cyano-1-cyclopentenes in the presence of aluminum chloride [49].

N-Substituted 4-amino-2,3-polymethylenequinolines are synthesized by condensation of 4-chloro-2,3-polymethylenequinolines with amines at 170-200° [22, 28, 34, 50]. Although the possibility of this sort of condensation in phenol has been disputed, a number of investigators [51-59] have shown that 4-alkylamino-4-dialkylamino-, and 4-arylamino-2,3-polymethylenequinolines can be obtained in this manner. This synthesis is simpler to carry out, but the formation of admixed phenoxy derivatives is observed in most cases.

9-Anilino-β-quinindane and 9-anilino-1,2,3,4-tetrahydroacridines are obtained from the dianilides of adipic and pimelic acids by cyclization by means of phosphorus pentachloride [60]. 9-Anilino-1,2,3,4-tetrahydroacridine is formed by heating N,N-diphenylthiourea with cyclohexanone [61].

A method for the synthesis of 4-alkylamino- and 4-arylamino-2,3-polymethylenequinolines by cyclization of substituted amides of N-cycloaklylideneanthranilic acids by means of phosphorus oxychloride was recently proposed [55, 59, 62-68].

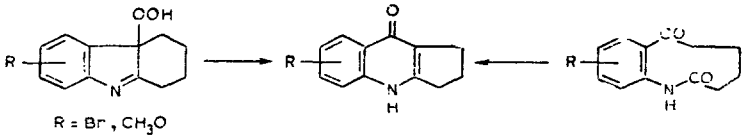


R = Alk or Ar, n = 3,4,5

The synthesis of β-quinindanes by cyclization of 3-(α,β-dibromoethyl)-4-chloroquinaldines by heating with 50% sulfuric acid is interesting [69].

R = H, CH_3O

The side products in the Fischer synthesis of 1,2,3,4-tetrahydrocarbazoles — 1,2,3,4-tetrahydrocarbazole hydroperoxide and δ-(2-aminobenzoyl)valerolactam — are converted to β-quinindan-9-one [70, 71] by the action of alkali.



R = Br, CH_3O

Chemical Properties of 2,3-Polymethylenequinolines

Reactions at the Nitrogen Atom. 2,3-Polymethylenequinolines have basic character. They form salts with hydrochloric and picric acids [18, 72]. 4-Amino-2,3-polymethylenequinolines form hydrochlorides only with one equivalent of acid. The heteroring nitrogen atom rather than the amino group is protonated, as attested to by the bathochromic shift of the UV spectrum during salt formation [65].

The pK_a values of 2,3-dimethylene-, 2,3-trimethylene-, and 2,3-tetramethylenequinolines are 4.55, 5.45, and 6.41, respectively, whereas the pK_a value of 2,3-dimethylquinoline is 5.99 [3]. The considerable decrease in the basicity of 2,3-dimethylquinoline is associated

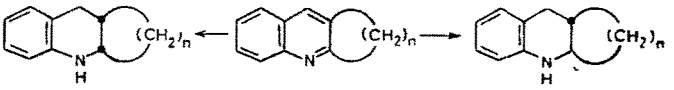
with angular strain in this condensed system. When amino groups are introduced into the 4 position of 2,3-polymethylenequinolines the basicity increases sharply due to the inclusion of the amino group in conjugation with the ring-nitrogen atom [58, 59]. The basicities of 6-substituted 4-butylamino- and 4-morpholine-2,3-polymethylenequinolines [58, 59] are found to be a linear function of the σ-substituted constants for quinoline [73].

β-Quinindane [5, 74, 75] and 1,2,3,4-tetrahydroacridine [16] methiodides and N-phenacylquinindanium bromide [76] have been obtained. The latter is converted to β-quinindane phenacylide by treatment with sodium carbonate solution.

2,3-Polymethylenequinolines are oxidized by hydrogen peroxide or peracids to the corresponding N-oxides [4, 77-80].

Substitution Reactions in the Quinoline Ring. 1,2,3,4-Tetrahydroacridine is sulfonated at 110° to the monosulfo derivative with partial formation of the disulfonic acid and undergoes nitration to give two mononitro derivatives (the positions of the substituents were not established) [16]. Bromination of 2,3-tetramethyl-4-quinolones [81, 82] and 2,3-pentamethylene-4-quinolone [35] gives their 6-bromo and 6,8-dibromo derivatives; nitration gives the 6- and 8-nitro derivatives [28, 35, 51]. Nitration of β-quinindane gives 5-nitro- and 8-nitro-β-quinindanes [83]. Nitration of β-quinindane N-oxide gives 5-, 8-, and 9-nitro-β-quinindane N-oxides in a ratio of 1:2:2 [47].

Reduction. 2,3-Polymethylenequinolines are reduced with tin and hydrochloric acid to give a mixture of cis- and trans-1,2,3,4-tetrahydro-2,3-polymethylenequinolines [84-87].

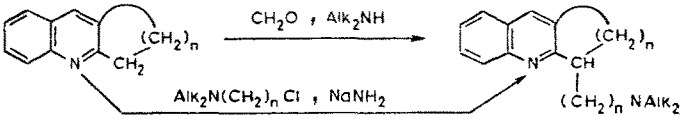


The 1,2,3,4-tetrahydro-2,3-trimethylenequinoline isomers were separated by crystallization of the benzoyl derivatives, after which the bases were obtained in a ratio of 1:3 [84]. The higher solubility of the hydrochloride [88] or of the sulfate [85] of the cis isomer in water was used to separate cis- and trans-asym-octahydroacridines. 1,2,3,4-Tetrahydroacridine is reduced to asym-octahydroacridine by means of formic acid in the presence of sodium formate [88]; the yield of cis-trans isomers (in a ratio of 1:3) was 70%. The isomeric cis- and trans-asym-octahydroacridines were separated into their optical antipodes [89, 90].

Hydrogenation of β-quinindane and 1,2,3,4-tetrahydroacridine over nickel gives mixtures of substances with hydrogenated pyridine and benzene rings [91]. Hydrogenation of 1,2,3,4-tetrahydroacridines over palladium or platinum on carbon in methanol [78, 92] or over copper chromite [93] gives asym-octahydroacridines.

1,2,3,4-Tetrahydro-9-acridone is reduced by sodium in alcohol to asym-octahydroacridine [7].

Reactions of the Polymethylene Chain. As in the case of quinaldine, the α-methylene group in 2,3-polymethylenequinolines contains labile hydrogen atoms and displays increased reactivity. Thus 1,2,3,4-tetrahydroacridine is oxidized by SeO_2 to 4-keto-1,2,3,4-tetrahydroacridine [94]. Refluxing β-quinindane with formalin gives 3-hydroxymethyl- and 3,3-di(hydroxymethyl)-β-quinindane [76]. When tetrahydroacridine is heated with paraformaldehyde in dioxane it is converted to 4,4-di(hydroxymethyl)tetrahydroacridine [95]. Like quinaldine [96], β-quinindane and 1,2,3,4-tetrahydroacridine undergo the Mannich reaction under mild conditions to give dialkylaminomethyl derivatives [76, 97].



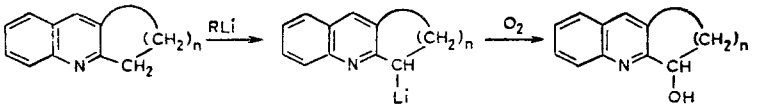
These same amines were obtained by alkylation with (dialkylamino)alkyl chlorides in the presence of sodium amide [97, 98].

The condensation of β-quinindane and 1,2,3,4-tetrahydroacridine with diethyl oxalate under the conditions of the Claisen reaction gives 3-ethoxalyl-β-quinindane and 4-ethoxalyl-1,2,3,4-tetrahydroacridine, respectively [99].

2,3-Tri- and 2,3-tetramethylenequinoline methiodides condense with p-dimethylaminobenzaldehyde in the presence of piperidine [74] or in refluxing acetic anhydride [75].

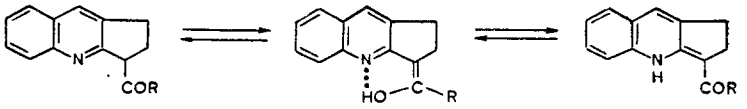
2,3-Trimethylenequinoline [100] and 2,3-trimethylene- and 2,3-tetramethylenequinoline-4-carboxylic acid [101] and their amides [102] also undergo condensation with aldehydes at the α-methylene group to give benzylidene derivatives.

2,3-Tri- and 2,3-tetramethylenequinolines react with phenyllithium to give lithium derivatives, which react with oxygen to give the corresponding alcohols [1, 103, 104].



The reaction of 3-lithio-β-quinindane with cyanogen bromide at −15° gives 3-bromo-β-quinindane in 60% yield [1]. 3-Lithio-β-quinindane reacts with esters at −15° to give a mixture of 3-acyl-β-quinindanes, di(β-quinindan-3-yl)carbinols, and (primarily), 3,3,-diacyl-β-quinindanes. At −40° the chief products are 3-acyl-β-quinindanes [1].

It has been shown by means of the IR, UV, and PMR spectra that 3-acyl-β-quinindanes exist in solution in the form of a mixture of three tautomers with predominance of the enamine form [105]. They have an enamine structure in the crystalline state.



In solution, 3-acyl-β-quinindanes are oxidized spontaneously to β-quinindan-3-ones and the corresponding acids [105].

4-Lithio-1,2,3,4-tetrahydroacridine reacts with alkyl halides to give 4-alkyltetrahydroacridines [106] and with benzonitrile or benzoyl chloride to give 4-benzoyl-1,2,3,4-tetrahydroacridine [107].

4-Lithio-1,2,3,4-tetrahydroacridine reacts with aromatic aldehydes or ketones to give (1,2,3,4-tetrahydro-4-acridyl)carbinols [108, 109]. It forms 4-oximino-1,2,3,4-tetrahydroacridine with isoamyl nitrite (at −20°) [95].

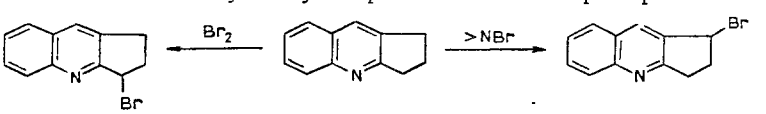
sym-Octahydroacridine reacts with aromatic aldehydes in acetic anhydride to give mono- and dibenzylidene derivatives [110, 111]. The reaction proceeds less efficiently in acetic acid and does not take place at all in the presence of zinc chloride.

The corresponding carbinols are obtained in the reaction of 4-lithio-sym-octahydroacridines with aldehydes or ketones [112].

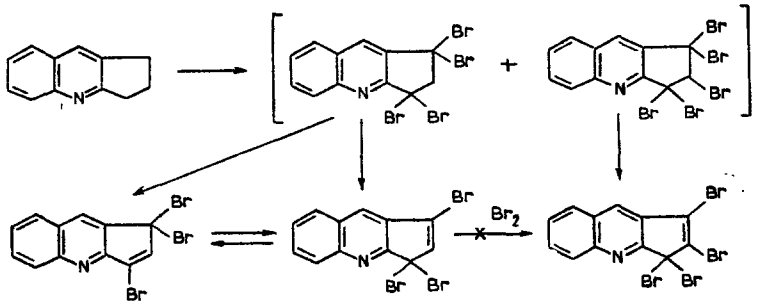
1,1,2,3,3-Pentachloro-β-quinindane is formed when β-quinindane is heated to 120-130° with excess phosphorus pentachloride in phosphorus oxychloride [113]. Under similar conditions, 1,2,3,4-tetrahydroacridine is chlorinated to give the 3,4,4-trichloro derivative.

Chlorination of β-quinindan-9-one and 1,2,3,4-tetrahydro-9-acridone gives 3,3,9-trichloro-β-quinindane and 4,4,9-trichloro-1,2,3,4-tetrahydroacridine, respectively. Under these conditions, β-quinindane-9-carboxylic acid and 1,2,3,4-tetrahydroacridine-9-carboxylic acid give 3,3-dichloro-β-quinindane-9-carbonyl and 4,4-dichloro-1,2,3,4-tetrahydroacridine-9-carbonyl chloride.

Bromination of β-quinindane with bromine (1 mole) in glacial acetic acid containing anhydrous sodium acetate gives 3-bromoquinindane [104]. If the bromination is carried out with N-bromosuccinimide (NBS) in carbon tetrachloride, 1-bromo-β-quinindane is obtained [104]. Both bromides are converted to hydroxy derivatives upon hydrolysis. 3-Bromo-β-quinindane can be obtained from 3-hydroxy-β-quinindane and phosphorus tribromide [114].



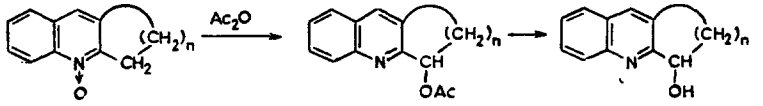
1,2,3,3-Tetrabromo-3H-β-quinindine and a mixture of 1,1,3-tribromo-1H- and 1,3,3-tribromo-3H-β-quinindines are obtained by bromination of β-quinindane with excess bromine [115].



Polybromo-β-quinindines are very sensitive to alkali and sodium carbonate solutions but are stable to the action of acids in the cold. 1,2-Dibromo-3H-β-quinindine is formed when solutions of the tribromides in concentrated sulfuric acid are heated. They are hydrolyzed to 1-bromo-3H-β-quinindin-3-one with an aqueous acetone solution of silver nitrate.

β-Quinindane-9-carboxylic acid is brominated to give an equimolar mixture of 1,3,3-tribromo- and 1,2,3,3-tetrabromo-3H-β-quinindine-9-carboxylic acids [116].

Reactions of 2,3-Polymethylenequinoline N-Oxides. Like their simpler analogs [117], 2,3-polymethylenquinoline N-oxides are rearranged to acetoxy derivatives, which are hydrolyzed to hydroxy-2,3-polymethylenequinolines, when they are refluxed with acetic anhydride [78, 79, 114, 118].



sym-Octahydroacridine N-oxide undergoes a similar transformation [80, 118-120].

4-Oximino-1,2,3,4-tetrahydroacridine is formed in the reaction of 1,2,3,4-tetrahydroacridine N-oxide with isoamyl nitrite in the presence of sodium amide [95].

Nitration of sym-octahydroacridine N-oxide gives 9-nitro-sym-octahydroacridine N-oxide [121, 122]. Reaction of the latter with phosphorus trichloride gives primarily 9-nitro-sym-octahydroacridine with traces of the 9-chloro derivative. 9-Bromo-sym-octahydroacridine N-oxide is formed in the reaction with acetyl bromide. The reaction with acetyl chloride is complicated by the formation of 9-chloro-4-acetoxyl-sym-octahydroacridine along with 9-chloro-sym-octahydroacridine N-oxide. The reactions of 9-chloro-sym-octahydroacridine N-oxide with thionyl chloride, acetic anhydride, and monoethanolamine have been studied [123].

Other Reactions. Except for the 2,3-dimethylenederivative, 2,3-polymethylenequinoline-4-carboxylic acids are readily decarboxylated to give 2,3-polymethylenequinolines [6, 16, 124]. This reaction is a better method for the synthesis of 4-unsubstituted 2,3-polymethylenequinolines. The carboxyl group in 2,3-polymethylenequinoline-4-carboxylic acid is inert and, except for β-quinindane-9-carboxylic acid, is not esterified under the usual conditions. Esters of 1,2,3,4-tetrahydroacridine-9-carboxylic acid were obtained from the silver salt of the acid and alkyl halides [16] or by the action of dimethyl sulfate on the sodium salt of the acid in alcohol [78].

Substituted amides and hydrazides of 2,3-polymethylenequinoline-4-carboxylic acids were synthesized from the chlorides of the appropriate acids and amines (arylhydrazines) and also by means of dimagnesylamines and the methyl esters of these acids [102, 125, 126].

On heating with phosphorus oxychloride, 2,3-polymethylene-4-quinolones are converted to 4-chloro-2,3-polymethylenequinoline in good yields [22, 34, 42, 51].

4-Chloro-2,3-polymethylenequinolines react with sodium methoxide to give 4-methoxy derivatives. A study of the kinetics of this reaction showed that the chlorine atom in these compounds, because of the inductive and steric effects of the polymethylene chain, is less labile by a factor of 6-60 than the chlorine atom in 4-chloroquinolines [127].

1,2,3,4-Tetrahydro-10-methyl-9-acridone is reduced by means of lithium aluminum hydride in tetrahydrofuran (THF) to 10-methylhexahydroacridan-9-ol [128]. The reaction of 1,2,3,4-tetrahydro-10-methyl-9-acridone with a Grignard reagent was also described in a patent [128].

4-(Dialkylaminoalkoxy)- or 4-(dialkylaminoalkylthio)-2,3-pentamethylenequinolines, respectively, were obtained by heating 2,3-pentamethylene-4-quinolone or 2,3-pentamethylenethio-4-quinolone with dialkylaminoethyl chloride in the presence of sodium hydride [129].

9-Methyl-1,2,3,4-tetrahydroacridine was isolated instead of hexahydroiminostilbene in an attempt to expand the ring in 9-hydroxymethyl-asym-octahydroacridine [130]. Ermolaeva and co-workers [130] assumed that disruption of the aromatic character of one of the rings prevents expansion of the nitrogen-containing ring.

1,2-Dihydro-4H-β-Quinindines

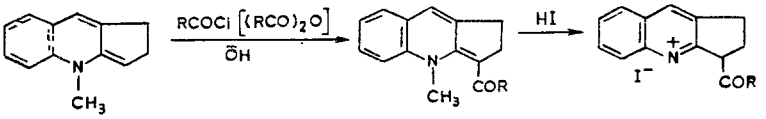
The reaction of methiodides of β-quinindane and its derivatives with alkali is accompanied by splitting out of a proton from the 3 position to give 4-methyl-1,2-dihydro-4H-β-quinindines [7, 131, 132].

This compound is very unstable and was not isolated in the free form. It readily undergoes oxidation, polymerization, and electrophilic substitution and addition reactions. The reason for this, according to Kholodov and co-workers [133], is the increased electron density in the 3 position because of "expulsion" of one of the seven 2p electrons from the pyridine ring in order to realize an aromatic sextet.

Although this assumption is justified to a certain extent, one should nevertheless recall that a similar phenomenon is also observed in enamines [40] — compounds that are inclined to undergo similar reactions — in which striving to retain an aromatic sextet is clearly absent.

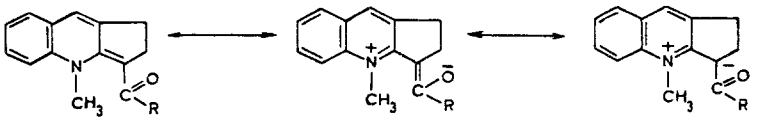
4-Methyl-1,2-dihydro-4H-β-quinindines with substituents that prevent localization of the electron density in the 3 position are stable [7].

4-Methyl-1,2-dihydro-4H-β-quinindine is acylated in the 3 position by the action of various acylating agents [131-134].



In connection with the instability of 4-methyl-1,2-dihydro-4H-β-quinindine, β-quinindane methiodide is normally used; the methiodide is treated with alkali, and the liberated base is extracted with ether and subjected to reaction with acid chlorides in the presence of aqueous alkali.

3-Acyl-4-methyl-1,2-dihydro-4H-β-quinindines are stable crystalline substances. Their stability is explained by stabilization due to resonance [133].

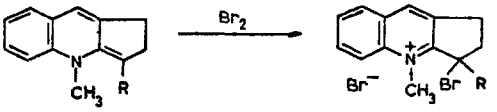


This distribution of the electron density in the acyl derivatives is confirmed by their IR spectra, in which the frequency of the carbonyl group is reduced to 1500-1520 cm^{-1}, whereas the carbonyl group in 3-acyl-β-quinindane methiodides absorbs at 1690 cm^{-1}.

Upon acidification with hydriodic acid, 3-acyl-4-methyl-1,2-dihydro-4H-β-quinindines are protonated in the 3 position and are converted to 3-acyl-4-methyl-β-quinindane methiodides, and the protonation is accompanied by decolorization of the solutions [131-133]. The addition of a proton to the 3 position was confirmed by the UV spectra, which are identical to the spectra of β-quinindane methiodides but differ from the spectra of 3-acyl-1,2-dihydro-4H-β-quinindines [133].

3-Aroyl-4-methyl-1,2-dihydro-4H-β-quinindines are acylated at the oxygen atom of the carbonyl group by the action of acyl chlorides [135].

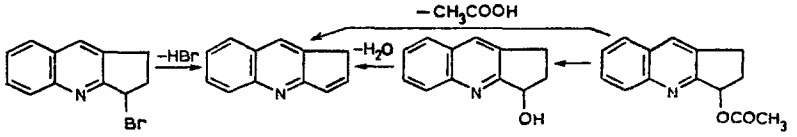
4-Methyl-1,2-dihydro-4H-β-quinindines add bromine and form the hydrobromides of 3-bromo-4-methyl-β-quininindanium and its derivatives [136, 137].



The reaction of 3-acyl-3-bromo-4-methyl-β-quinindanium bromide with pyridine dibromide gives 1-bromo-3-acyl-4-methyl-4H-β-quinindines [138].

β-Quinindines

The synthesis of β-quinindine by two different methods was recently described.

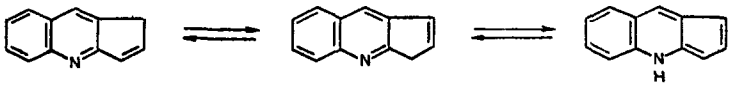


3- Bromo-β-quinindane is smoothly converted to β-quinindine by heating on a boiling-water bath in dimethylformamide (DMFA) in the presence of triethylamine [114]. When DMFA is replaced by acetonitrile or chloroform the reaction is accompanied by the formation of 2-(β-quinindan-2-yl)-1H-β-quinindine. The latter was also obtained as the primary product of the dehydration of 3-hydroxy-β-quinindane with concentrated sulfuric or polyphosphoric acids.

β-Quinindine was obtained from 3-hydroxy- and 3-acetoxy-β-quinindanes in 50-60% yields by treatment of them with concentrated sulfuric acid [104].

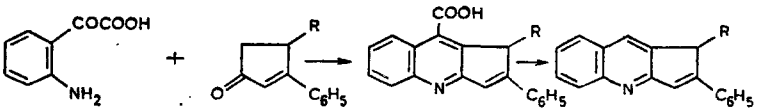
β-Quinindine is vacuum distilled as a purple oil that solidifies on cooling to give a colorless substance with mp 59-61°; it gives a picrate and forms complexes with chloroplatinic and picrolonic acids and 1,3,5-trinitrobenzene. It decolorizes a solution of bromine in benzene and a solution of potassium permanganate; it dimerizes on heating and even on standing.

The absorption maximum (333 nm) in the UV spectrum of β-quinindine in ethanol is shifted by 10 nm to the red region as compared with the spectrum of β-quinindane, and this confirms lengthening of the conjugation chain. A solution of β-quinindine in benzene has a broad band centered at 507 nm [104]. The PMR spectrum of β-quinindine shows that it exists as two isomers — 1H- and 3H-β-quinindines [104, 114]. At the same time, the presence of a maximum at 507 nm in its UV spectrum, like the maximum of azulenes, shows that 4H-β-quinindine is present in small amounts (~0.1%).



A lithium salt [104], a solution of which in benzene has a long-wave maximum at 530 nm that is very close to the maximum of 5,6-benzazulene [139], is formed in the reaction of β-quinindine with butyl- or phenyllithium.

Substituted β-quinindines are more stable than β-quinindine itself, and they can be obtained by the Pfitzinger reaction from isatin and substituted Δ^2-cyclopentenones with subsequent decarboxylation of the intermediate β-quinindine-9-carboxylic acids [100].

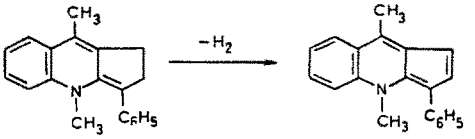


As pointed out above, the spectral properties of 4H-β-quinindine are similar to those of azulenes. An examination of its electronic structure makes it possible to conclude that this compound and compounds similar to it are actually heterocyclic analogs of 5,6-benzazulenes. The role of the —CH=CH— group, which in azulenes supplies the electron pair for the provision of aromatic character, is played by the nitrogen atom in 4H-β-quinindines. The possibility of the existence of these compounds, which was first demonstrated in [7, 140, 141], is determined by the obligatory presence, in place of a hydrogen atom, of substituents attached to the nitrogen atom, which prevents isomerization of them to the more stable 1H- and 3H-β-quinindines. These compounds have been called azalenes or pseudoazulenes.

Methods similar to those previously used for the synthesis of azulenes are used to synthesize them.

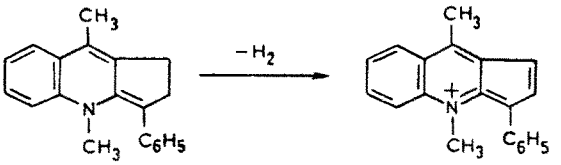
β-Quinindane methiodide reacts with chloranil (2 moles) to give 1,3-bis(3,5,6-trichloro-1,4-benzo-2-quinoyl)-4-methyl-4H-β-quinindine [142].

3-Phenyl-4,9-dimethyl-1,2-dihydro-4H-β-quinindine is dehydrogenated by refluxing in xylene in the presence of palladium on carbon [7].

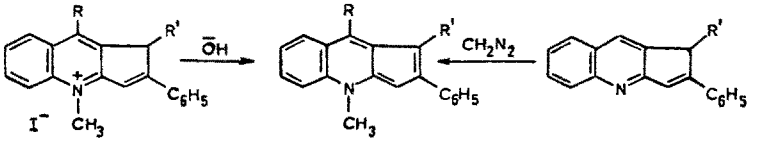


Dehydrogenation of 3-acyl-4-methyl-1,2-dihydro-4H-β-quinindines in the presence of palladium on carbon or platinum black in ethylene glycol, alcohol, or chloroform could not be realized [143]. On reaction with chloranil they give 3-acyl-1-(3,5,6-trichloro-1,4-benzo-2-quinoyl)-4-methyl-4H-β-quinindines [143].

The reaction of 3-acetoxy-β-quinindane with dimethyl sulfate and subsequent treatment of the product with concentrated sulfuric acid and 50% alkali give 4-methyl-4H-β-quinindine, which is stable only in solution in a nitrogen atmosphere at temperatures below 0°. The reaction of the latter with phenyllithium gives 4-methyl-9-phenyl-β-quinindine, which is obtained as the picrate [144].



Substituted 4-methyl-4H-β-quinindines are formed by the action of alkali on the methiodides and methylsulfonates of 1H-β-quinindines or by the action of diazomethane on the corresponding 1H-β-quinindines [100].



The properties of azalenes are similar to those of azulenes: they absorb at 574 nm (and, as a consequence of this, are colorless), have weak basic properties, give colored solutions with concentrated sulfuric acid and orthophosphoric acid, as well as with chloroplatinic, picric, and other acids, and form colored complexes with 1,3,5-trinitrobenzene.

Biological Activity of 2,3-Polymethylenequinolines

9-Amino-1,2,3,4-tetrahydroacridines display weak antibacterial activity coupled with considerable toxicity [28, 51, 128, 145, 146]. However, they have a broad spectrum of pharmacological activity (antichlorinesterase [146-148] and analeptic activity [149]) and are morphine antagonists [150-152], psychotomimetics [153], and curare antagonists [154].

9-Amino-1,2,3,4-tetrahydroacridine (tacrine) is a better agent that relatively rapidly restores the normal psychic state in mental disturbances induced by basic esters of substituted glycolic acid [155] and is a ditran antagonist [156].

1,2-Dihydro-3,4-benzacridine-9-carboxylic acid (tetraphan) [157, 158] and aminocycloheptaquinoline [159] have analeptic activity. 1,2,3,4-Tetrahydroacridone is a morphine antagonist [38].

4-Alkylamino- and 4-dialkylamino-2,3-polymethylenequinolines [54, 57-59, 65] and substituted amides and hydrazides of 2,3-polymethylenequinoline-4-carboxylic acids [102, 125, 126] inhibit the anticurare activity of diplacine and potentiate ditilin.

9-Diaklylaminoacylamino-1,2,3,4-tetrahydroacridines [160] and 1,2,3,4-tetrahydroacridine-9-carboxylic acid diethylamides [51] have strong local anesthetic action coupled with relatively low toxicity.

Some asym-octahydroacridines display antihistamine activity [92].

1,2,3,4,4a,9a-Hexahydro-9-acridanols [128], hexahydro-9-acridonones [161], octahydro-9-acridanones [162], and their salts have hypotensive action, absorb UV rays, and are used as sun-protection agents.

Isomeric cis- and trans-10-(γ-dimethylaminopropyl)-1,2,3,4,4a,9a,10-octahydroacridines affect the central nervous system giving a number of effects characteristic for imizin [88]. 4-Dialkylaminoalkyl-1,2,3,4-tetrahydroacridines have antidepressive activity [97].

α- and β-10-aminoperhydroacridines are MAO inhibitors, and the α form blocks the disintegration of serotonin in the brain and liver of rats [163].

5-Hydroxy-β-quinindanes have strong activity against typhoid bacilli (Shingella Flexneri and Salmonella typhi) [77].

4-Amino- and 4-carbamoyl-2,3-pentamethylenequinolines display analgesic, local-anesthetic, analeptic, and anticholinesterase activity [53].

4-Chloro-, 4-hydroxy-, 4-amino-, 4-mercapto-2,3-tetramethylene-, and 2,3-pentamethylenequinoline and their derivatives with respect to the functional group have antidepressive, analgesic, sedative, and ataractic activity [30] and also stimulate the activity of the central nervous system [129].

Substituted hexahydrocycloocta[b]quinolines [36, 37] have hypotensive activity [36, 37].

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