QUININDINES

VII.* ROUTES FOR THE SYNTHESIS OF β-QUININDINE

I. F. Tishchenkova, L. E. Kholodov, and V. G. Yashunskii

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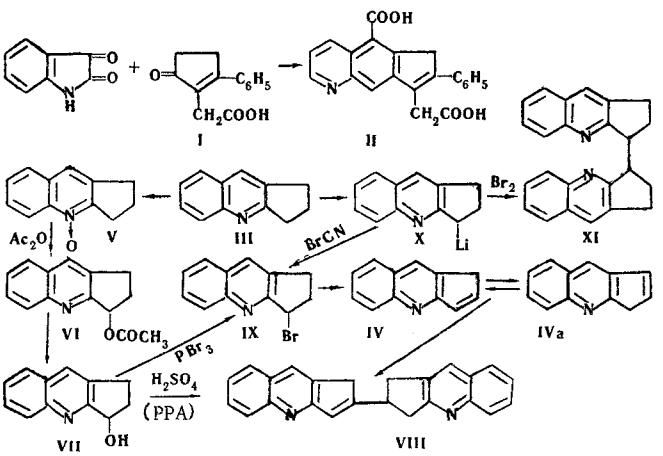
The previously unknown parent compound of the β-quinindine series, viz., unsubstituted 1H-β-quinindine, was obtained by dehydrobromination of 3-bromo-β-quinindane. The dehydration of 3-hydroxy-β-quinindane in concentrated sulfuric and polyphosphoric acids leads to a dimer—2-(2'-quinindanyl)-β-quinindine. The structures of the compounds were confirmed by the UV, IR, and PMR spectra.

Only two derivatives of 1H-β-quinindine (with phenyl substituents in the cyclopentadiene ring) are described in the literature. These compounds were obtained by the Pfitzinger reaction from phenyl-substituted cyclopentenones [2]. We have shown that quinindines with functional substituents in the five-membered ring can be obtained by this method. Thus 2-phenyl-3-carboxymethyl-1H-β-quinindine-9-carboxylic acid (II) was obtained by refluxing isatin with 3-phenyl-2-carboxymethyl-Δ^2-cyclopentenone (I) in aqueous alcoholic alkali.

In a previous communication [1] we described the first representatives of the 3H-β-quinindine system, which were obtained by bromination of β-quinindane (III). As a consequence of the high activity of the bromine atoms, the polybromo-3H-β-quinindines thus formed can serve as the starting materials for the synthesis of other compounds of this series. However, the parent compound of the series, β-quinindine (IV), cannot be obtained by this or another method since Δ^2-cyclopentenone polymerizes under the conditions of the Pfitzinger reaction, and it is extremely difficult to replace bromine by hydrogen in the polybromoquinindines without affecting the double bond:



*See [1] for communication VI.

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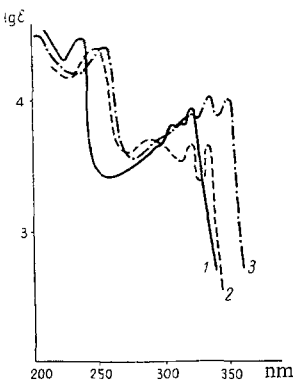


Fig. 1. UV spectra (in alcohol): 1) β-quinindane (III); 2) β-quinindine (IV); 3) 3-methylene-β-quinindane (XII).

Dehydrogenation of β-quinindane (III) is also unlikely since it is well known that pyrindane (6,7-dihydro-5H-1-pyrindine) is not converted to 5H-pyrindine even under severe dehydrogenation conditions [3].

We have attempted to obtain β-quinindine (IV) in analogy with the synthesis of 5H-pyrindine [3,4]: the latter was obtained by dehydration of 7-hydroxypyrindane.

Rearrangement of β-quinindane N-oxide (V), obtained by heating β-quinindane (III) with acetic acid and hydrogen peroxide, under the influence of acetic anhydride leads to 3-acetoxy-β-quinindane (VI). Saponification of VI in an alkaline medium gives 3-hydroxy-β-quinindane (VII). It turned out that dehydration of VII in concentrated sulfuric acid and in polyphosphoric acid (PPA) gives the same crystalline, high-melting substance, which is the dimer (VIII) of β-quinindine (IV) rather than IV itself.

We therefore decided to obtain IV by dehydrobromination of 3-bromo-quinindane (IX). An attempt to carry out this synthesis was previously undertaken. A dark oil was formed by the bromination of β-quinindane (III) with N-bromosuccinimide; treatment of this oil with alkali resulted in the decomposition and polymerization of the product [2].

3-Bromo-β-quinindane (IX) was synthesized by us in five steps from β-quinindane (III) through 3-hydroxy-β-quinindane (VII). The overall yield of IX was ~20% based on III. An attempt was therefore made to obtain IX starting from III via its 3-lithio derivative (X). A bromine-free product with empirical formula $C_{24}H_2ON_2$ is formed by the action of bromine on X. Its UV spectrum is similar to that of III, but the absorption intensity is doubled. The 3-(3'-β-quinindanyl)-β-quinindane structure (XI) was assigned to this compound on the basis of these data. At −15° X reacts with cyanogen bromide to give 3-bromo-β-quinindane (IX) in the form of a colorless, crystalline substance with a sharp melting point. The yield of IX was 60%.

IX was dehydrobrominated by heating with triethylamine with and without a solvent. Judging from the results of thin-layer chromatography, IX remains virtually unchanged on refluxing with triethylamine for 6 h, and a small amount of IV is formed. When the reaction is carried out in acetonitrile or benzene in the presence of triethylamine, dimer VIII is detected along with starting IX in the reaction mixture. IX is smoothly converted to IV (a mobile oil with an odor similar to that of III) only when it is heated in dimethylformamide for 30 min on a boiling-water bath in the presence of triethylamine. It decolorizes a solution of bromine in benzene and potassium permanganate solution. It reacts with bromine to give a product with R_f 0.80 (chloroform, activity II Al_2O_3); bromine apparently adds to the double bond. The oil could not be crystallized, and it was not possible to distill it since it is converted to dimer VIII on heating or simply on standing. IV gives a picrate which was only washed with chloroform since recrystallization of it also leads to dimerization.

The purity of IV and its picrate was established by means of thin-layer chromatography on aluminum oxide in chloroform. In the case of the picrate, picric acid remained at the start, while base IV gave a sharply defined spot with R_f 0.60 (R_f of dimer VIII was 0.30; chloroform, activity II Al_2O_3).

Monomer IV is still less stable than the corresponding pyrindine, which has definite stability in strongly acid media [4] and can be vacuum-distilled under nitrogen. IV dimerizes in an acidic medium.* IV is also rapidly converted to dimer VIII on heating without a solvent.

IV and its picrate were characterized by their UV and PMR spectra. A shift of ~10 nm (as compared with the bands in the spectrum of III) of all of the bands in the visible region is observed in the UV spectrum of IV (Fig. 1). This shift is particularly clearly noticeable in the long-wave portion of the spectrum where an intense band appears at 333 nm, while the longest-wave maximum in the spectrum of III appears at 319 nm. This bathochromic shift confirms the formation of a new double bond, which leads to lengthening of the conjugation chain. The UV spectrum of the picrate of β-quinindine is in fact the sum of the spectra of IV and picric acid: the UV spectrum of the picrate of IV, obtained relative to a solution of picric acid, coincides with the spectrum of IV with respect to the wavelengths and the intensities of the maxima.

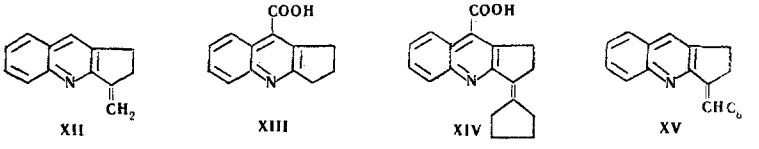
Although IV gives a single spot on the chromatogram, this substance, as would be expected, is, judging from the PMR spectra, a mixture of isomeric 1H- and 3H-β-quinindines (IV and IVa), similar to

*It was recently shown that 5H-1-pyrindine methiodide also dimerizes readily [5].

pyrindines [6, 7] and unsymmetrically substituted indenes [8]. The PMR spectrum of the picrate of β-quinindine was obtained in deuterated dimethyl sulfoxide. In this spectrum in the region of the absorption of aliphatic protons one can observe two groups of signals of about equal intensity, and these signals constitute a total of two proton units. The first signal (δ 3.80 ppm) apparently corresponds to the methylene group in the 1 position in IV, while the second signal (δ 3.95 ppm) corresponds to the methylene group in the 3 position of IVa. The aromatic-proton region contains a singlet (δ 8.44 ppm) with an intensity of two proton units, which is ascribed to the protons of picric acid. In addition, there are also signals centered at ~8.9 ppm, which are the superimposition of two doublets from the C_5 protons of the two isomers (IV and IVa). The aromatic protons and the protons on the double bond of both isomers give a complex multiplet with an overall intensity of six proton units at 7.6-8.3 ppm. The absorption of protons on a double bond at such a weak field has already been noted for pyrindines [9]; it is also known that the proton on the double bond in indenes [10] absorbs at ~1 ppm weaker field as compared with the similarly substituted styrenes. The spectrum of IV, obtained in CCl_4, is very close to that described above, but, as would be expected, for this solvent all of the signals are shifted to stronger field. The spectrum contains a doublet at 7.85 ppm from the C_5 proton, a multiplet at 6.8-7.6 ppm from the aromatic protons and the protons on the double bond, and two groups of signals at 3.1 ppm (C_1 in IV) and 3.4 ppm (C_3 in IVa).

It was shown by means of the UV and PMR spectra that the dimer is 2-(2'quinindanyl)-β-quinindine (VIII). Since the two conjugated systems in this compound do not interact, the UV spectrum of dimer VIII is very similar to the curve obtained by summation of the UV spectra of III and IV. The spectrum of VIII contains bands at 239, 306, and 312 nm, characteristic for III, and at 250 and 333 nm, characteristic for IV, as well as a band at 319 nm, also observed in the spectra of III and IV. The PMR spectrum of dimer VIII consists of a complex multiplet from the ten aromatic protons at 7.3-8.2 ppm, a singlet at 6.69 ppm with an intensity of one proton unit, which should be ascribed to the single proton on a double bond, a group of signals from the methylene protons (3.3-3.7 ppm), and a multiplet of one proton unit from the methine proton (4.05 ppm).

From a comparison of the UV spectra of III, IV, and 3-methylene-β-quinindane (XII) (obtained in [11]), it is apparent (Fig. 1) that a shift of the bands to the long-wave region relative to III is observed for IV and XII. However, the magnitude of this shift depends on the position of the double bond: for example, a shift of 14 nm is observed for IV, while the shift is 31 nm for XII. The interaction of quinoline with the endocyclic double bond (in IV) is less than that with the exocyclic double bond (in XII).



XII XIII XIV XV

A similar phenomenon is observed for substituted β-quinindines. The long-wave band itself (at 319 nm) in the spectrum of β-quinindane-9-carboxylic acid (XIII) [12] is shifted to the long-wave region by 26 nm in the case of 2-phenyl-3-carboxymethyl-1H-β-quinindine-9-carboxylic acid (II), while the shifts are 40 and 58 nm, respectively, for 3-cyclopentadiene-β-quinindane-9-carboxylic acid (XIV) [12] and 3-benzylidene-β-quinindane (XV).*

EXPERIMENTAL

2-Phenyl-3-carboxymethyl-β-quinindine-9-carboxylic Acid (II). A solution of 2.65 g (0.018 mole) of isatin in 15 ml of 30% potassium hydroxide and 2.5 g (0.012 mole) of 3-phenyl-2-carboxymethyl-Δ^2-cyclopentenone (I) [13, 14] in 30 ml of alcohol was refluxed for 7 h. The solvent was then evaporated, the residue was treated with dilute acetic acid until the pH was 5, and the resulting precipitate was filtered to give 3.0 g (72.5%) of II with mp 263-264° (dec., from 80% aqueous dimethylformamide). Found %: C 73.38; H 4.49; N 4.26. $C_{21}H_{15}NO_4$. Calc. %: C 73.04; H 4.34; N 4.06. UV spectrum in 0.1 N NaOH, λ_{max}, nm (log ε): 223 (4.41), 280 (4.36), 345 (4.35).

β-Quinindane N-Oxide (V). A mixture of 4.42 g (0.026 mole) of β-quinindane (III) [15] in 16 ml of glacial acetic acid and 2.6 ml of 30% hydrogen peroxide was heated at 70° for 3 h, another 2.6 ml of 30% hydro-

*The spectra of the carboxylic acids were obtained in alkali; in the case of XIII and XIV it was shown that the spectra do not change substantially on ionization of the acids.

gen peroxide was added, and the mixture was heated for 16 h. The solvent was vacuum-evaporated to half the initial volume, and the residue was treated with sodium sulfite solution until the reaction mixture no longer gave a positive test for peroxide with potassium iodide solution. After evaporation of the solvent, the residue was triturated with saturated potassium carbonate solution until a slightly alkaline medium was obtained, and the mixture was extracted with chloroform. The extract was dried and evaporated to dryness, and the residue was triturated with petroleum ether to give 4.0 g (83%) of V with mp 114-115° (dec., from ethyl acetate). Found %: C 77.32; H 5.92; N 7.61. $C_{12}H_{11}NO$. Calc. %: C 77.80; H 5.95; N 7.56. UV spectrum in alcohol, λ_{max}, nm (log ε): 217 (4.14), 241 (4.78), 300 (3.76), 318 (3.95), 330 (3.86), R_S 0.27.

The following conditions were used for the chromatography: a) activity II aluminum oxide treated with acetic acid (2.5 wt. %), benzene; b) activity II aluminum oxide, chloroform. The chromatograms were developed with iodine, and the reference spot was the starting III [R_f 0.5 (a), $R_f \sim 0.8$ (b)] (the variants in the conditions for chromatography are given in parentheses).

3-Acetoxy-β-quinindane (VI). V [0.74 g (0.004 mole)] and two drops of water were added to 4 ml (0.04 mole) of acetic anhydride, and the reaction mass was allowed to stand at room temperature for 1 h and was then slowly heated to 95° and heated for 2.5 h on a boiling-water bath. The excess acetic anhydride was vacuum-evaporated, and the residue was purified by chromatography on a column filled with aluminum oxide with elution by benzene. Removal of the solvent by distillation yielded 0.7 g (77%) of VI with mp 104-105° (from alcohol) and R_S 0.80 (a). Found %: C 73.85; H 5.72; N 6.39. $C_{14}H_{13}NO_2$. Calc. %: C 74.01; H 5.72; N 6.16.

3-Hydroxy-β-quinindane (VII). A mixture of 1.07 g (0.0047 mole) of VI, 0.28 g (0.007 mole) of sodium hydroxide, and 2.5 ml of water was heated under argon on a boiling-water bath for 40 min. The precipitate was filtered to give 0.65 g (75%) of VII with mp 124-125° (from 66% alcohol) and R_f 0.13 (a). Found %: C 78.08; H 6.00; N 7.67. $C_{12}H_{10}NO$. Calc. %: C 77.80; H 5.93; N 7.55. ν_{OH} 3220 cm^{-1}. UV spectrum in alcohol, λ_{max}, nm (log ε): 235 (4.52), 238 (4.50), 280 (3.56), 294 (3.60), 300 (3.60), 307 (3.71), 313 (3.64), 320 (3.82).

2-(2'-Quinindanyl)-β-quinindane (VIII). A) A mixture of 1.75 g (0.0094 mole) of VII and 1.75 ml of sulfuric acid was heated under argon at 130° for 2 h. Water was then added, the mixture was neutralized with 10% sodium hydroxide (up to pH 8), and the product was extracted with ether. Evaporation of the dry ether extract yielded 0.68 g (43%) of VIII with mp 192-192.5° (from alcohol) and R_S 0.75 (a). Found %: C 85.80; H 5.79; N 7.87. $C_{24}H_{18}N_2$. Calc. %: C 86.23; H 5.39; N 8.38. UV spectrum in alcohol, λ_{max}, nm (log ε): 239 (4.73), 252 (4.62), 306 (4.12), 312 (4.07), 319 (4.26), 333 (4.07).

B) VII [1.12 g (0.0062 mole)] was heated at 80° for 1 h with polyphosphoric acid prepared by the addition of 12 g of phosphorus pentoxide to 8 ml of phosphoric acid. Ice water was then added with cooling, and the mixture was neutralized with 10% sodium hydroxide (to pH 8) and extracted with ether. Evaporation of the dry ether extract yielded a substance which, from the melting-point analysis, UV spectrum, and the results of thin-layer chromatography, was identical to the compound obtained via method (A).

3-(3'-β-Quinindanyl)-β-quinindane (XI). The lithium derivative (X) of β-quinindane [16], obtained in ether from 3.38 g (0.02 mole) of IV and phenyllithium, was added under argon to a solution of 1.2 ml (0.02 mole) of bromine in 20 ml of absolute benzene cooled to −50°. The mixture was held at this temperature for 15 min and at room temperature for 2 h. Water was added, and the precipitate was filtered to give 1.3 g (38.6%) of XI with mp 208-209° (dec., from alcohol) and R_S 0.38 (b). Found %: C 84.88; H 5.97; N 8.39. $C_{24}H_{20}N_2$. Calc. %: C 85.70; H 5.95; N 8.33. UV spectrum in alcohol, λ_{max}, nm (log ε): 240 (4.76), 280 (3.87), 295 (3.88), 308 (4.05), 314 (4.01), 322 (4.22).

3-Bromo-β-quinindane (IX). A) III [6.76 g (0.04 mole)] was added under argon to 48 ml of a 0.9 N ether solution of phenyllithium. After 1.5 h this mixture was added to a solution of 5.4 g (0.05 mole) of cyanogen bromide in 160 ml of absolute ether cooled to −8 to −14°. The mixture was held at this temperature with stirring for 2 h and acidified with 10% hydrochloric acid to pH 7.0. The dried ether extract was vacuum-evaporated, and the residue was triturated with absolute ether to give 3.38 g (60.6%, based on converted III) of IX with mp 126.5-127° (dec., from alcohol) and R_S 0.88 (b). Found %: C 58.40; H 3.96; Br 32.28. $C_{12}H_{10}NBr$. Calc. %: C 58.07; H 4.03; Br 32.26.

B) A solution of 0.12 ml (0.00125 mole) of phosphorus tribromide in 1 ml of chloroform was added with cooling and stirring to a solution of 0.3 g (0.0016 mole) of VII in 2 ml of chloroform. After 1.5 h the

reaction mass was poured into cold water, and the mixture was treated with a saturated solution of sodium carbonate (to pH 8) and extracted with chloroform. The chloroform extract was passed through a column filled with aluminum oxide, and the solution was evaporated to give 0.16 g (42.1%) of IX with mp 126-126.5° (dec., from alcohol), which was identical to the compound obtained via method (A).

β-Quinindine (IV). A solution of 2.4 g (0.01 mole) of 3-bromoquinindane (IX) in 15 ml of dimethylformamide was heated with 7.2 ml (0.052 mole) of triethylamine and several crystals of hydroquinone for 20 min. After cooling, 50 ml of water was added, and the mixture was neutralized to pH 7 with 10% hydrochloric acid and extracted with benzene. The benzene extract was evaporated to give IV in the form of an oily liquid with R_s 0.76 (b). UV spectrum in alcohol, λ_{max}, nm (log ε): 230 (4.18), 250 (4.41), 289 (3.71), 320 (3.67), 333 (4.18).

An alcohol solution of picric acid was added to an alcohol solution of the oil to give (after washing with chloroform) 1.5 g (38%) of a picrate with mp 177-181° (dec.). Found %: N 13.72. $C_{18}H_{12}N_4O_7$. Calc. %: N 14.14.

3-Benzylidene-β-quinindane (XIV). A mixture of 6 g (0.035 mole) of III and 10 g (0.094 mole) of benzaldehyde was heated at 150° for 2 h and at 180-200° for 1.5 h with azeotropic distillation of the water formed. The excess benzaldehyde was vacuum-distilled, and the residue was triturated with alcohol to give 6 g (76.4%) of XIV with mp 136-136.5° (from alcohol) (mp 119-120° [2]). UV spectrum in alcohol, λ_{max}, nm (log ε): 220 (4.51), 285 (4.44), 360 (4.43), 376 (4.40).

The IR, UV, and PMR spectra were obtained with the same spectrometers as in [17]. The authors thank N. P. Kostyuchenko for obtaining the PMR spectra.

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