QUININDINES

III. AMINOMETHYLATION AND HYDROXYMETHYLATION OF β-QUININDANE AT THE 3 POSITION

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The Mannich reaction and hydroxymethylation of β-quinindane at the 3 position were studied. The dialkylaminomethyl derivatives readily split out dialkylamine to form 3-methylene-β-quinindane, the structure of which was proved by the IR, UV, and PMR spectra. The dipole moments and pK values of the compounds were measured. No tetracyclic compounds are formed; the reaction ceases at the step involving formation of N-phenacylido-β-quinindane.

The chemical properties of the tricyclic β-quinindane system (I) or of 2,3-dihydro-1H-β-quinindane, which was obtained in 1910 [1], have been only slightly investigated. Quaternary derivatives have been obtained [1,2], 3-benzylidene-β-quinindane has been synthesized by condensation with benzaldehyde [3], the N-oxide has been prepared [4], and the nitration of I in the benzene ring has been investigated [5]. This study is devoted to an investigation of several reactions of β-quinindane at the active methylene group in the 3 position.

We carried out the Mannich reaction (with diethylamine and formaldehyde) under the conditions previously used for quinaldine [6] – by refluxing with a large excess of reagents. However, while the reaction in the case of quinaldine was carried out for 18 h, in the case of β-quinindane (I), starting compound I was almost completely absent after 5 min in the reaction mass, according to thin-layer chromatography. In addition to the expected hydrochloride of Mannich base II, compound III, with empirical formula $C_{13}H_{11}N$, was also formed, to which the 2-methylene-β-quinindane structure (III) was assigned on the basis of the UV, IR, and PMR spectra.

A pronounced bathochromic shift of all of the bands (by 20-30 nm), as compared with the position of the bands in the spectrum of the starting β-quinindane, is observed in the UV spectrum of III; this indicates lengthening of the conjugation chain in III. The IR spectrum of III contains bands which confirm the presence of a methylene group, in addition to bands at 1618, 1570, 1500, and 1470 cm^{-1}, which are characteristic for an aromatic system of bonds and the valence vibration bands of the aromatic C–H bonds (ν_{CH} 3080 cm^{-1}): a band which corresponds to the out-of-plane deformational vibration of the terminal methylene group (ν_{CH} 908 cm^{-1}), the overtone of these vibrations (1802 cm^{-1}), the valence vibration of the exocyclic double bond ($\nu_{C=C}$ 1650 cm^{-1}), and the valence vibrations of the C–H bonds in the $\rangle C{=}CH_2$ group (ν_{CH} 3100 cm^{-1}).

The PMR spectrum of 3-methylene-β-quinindane (III) in CCl_4 consists of signals from the aromatic protons (δ_5 7.95 ppm, doublet; δ_9 7.66 ppm, singlet; protons attached at C_6, C_7, and C_8 7.2-7.6 ppm, multiplet), protons on the $\rangle C{=}CH_2$ group (δ_{10} 6.23 ppm and $\delta_{10'}$ 5.17 ppm, $I_{10-10'}$ 3 Hz), and protons of the two methylene groups at C_1 and C_2 (poorly resolved, almost symmetrical multiplet from 2.8 to 3.1 ppm). One's attention is directed to the large difference between the signals of the two terminal protons ($\Delta\delta$ = 1.06 ppm). Such a large difference can be explained by the fact that the deshielding effect (magnetic anisotropy) of the nitrogen atom and of the quinoline ring are added together, during which the effect for the cis proton

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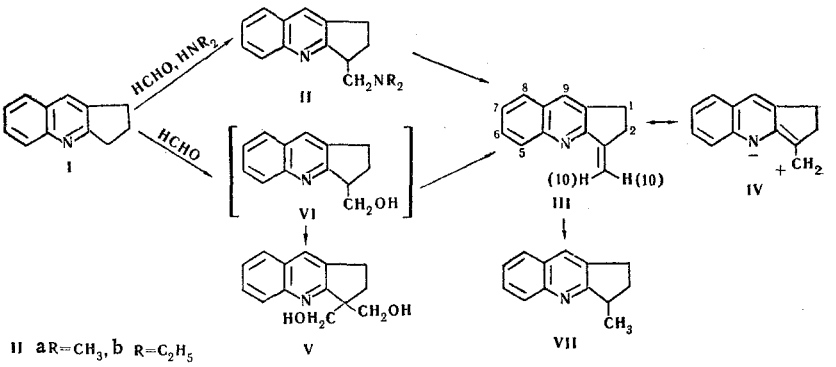
(10), as usual, is stronger than that for the trans proton (10'). This explanation is confirmed by the position of these signals in the PMR spectrum of a solution of III in trifluoroacetic acid – here, only the effect of the aromatic ring remains due to protonation of nitrogen, and the difference in the signals of the 10 and 10' protons decreases: $\Delta\delta$ = 0.47 ppm (δ_{10} 6.60 ppm and $\delta_{10'}$ 6.13 ppm), although both signals are shifted to weak field.

In trifluoroacetic acid the group of partially superimposed bands, centered at 3.44 ppm with an intensity of four proton units and a base width of 45 Hz, corresponds to the methylene protons at C_1 and C_2. This confirms the previous assignment [7] of the broad signal at 3.16 ppm (35 Hz at the base) of the same intensity in the spectrum of 3-cyclopentylidene-β-quinindine-9-carboxylic acid to the absorption of the analogous protons at C_1 and C_2.

In order to study the interaction of the quinoline system with the exocyclic double bond in III, we measured the dipole moment (μ 2.19 D, benzene) and the basicity constant (pK_a 3.74, 50% alcohol) of III. Comparison with the same parameters for starting I (μ 2.06 D, benzene, and pK_a 4.57, 50% alcohol) indicates that the interaction is primarily due to the inductive effect. The contribution of saturated structure IV is small since the change in the dipole moment on passing from I to III is small ($\Delta\mu$ 0.13 D), and the basicity decreases appreciably (ΔpK_a 0.83). A similar phenomenon can be observed in the pyridine series: 2-vinylpyridine has pK_a 4.98 [9], which is in completely satisfactory agreement with the pK_a of 4.96 calculated for this compound from the equation $pK_a = 5.48 - 10.3\sigma_I$ [10], assuming only the inductive effect of the α-substituent.* On the other hand, it is interesting to note that the $CH_2=CH$ group in 4-vinylpyridine is an electron donor – introduction of this group increases the basicity from pK_a 5.17 to pK_a 5.62 [12], which attests to the significant contribution of the dipolar saturated structure.

The formation of 3-methylene-β-quinindane (III) can be explained in two ways: III is obtained either as a result of thermal decomposition of the hydrochloride of Mannich base II or as a result of reaction of I with formaldehyde. We have shown that methylene derivative III is not formed by refluxing I with formalin, and that 3,3-dihydroxymethyl-β-quinindane (V) was isolated. The pK_a of V in 50% alcohol is 4.17. In addition, another substance, apparently 3-hydroxymethyl-β-quinindane (VI), is also obtained. The action on this compound (without isolation) of acetic anhydride in the presence of concentrated sulfuric acid gave III. Compound III was also obtained by refluxing a concentrated aqueous solution of 3-diethylaminomethyl-β-quinindane hydrochloride.

To increase the yields of the aminomethyl derivatives (II), the Mannich reaction was carried out under the milder conditions recently proposed [13] for quinaldine: 60°, pH 7.5 for equimolecular amounts of the reagent; under these conditions, only very little of methylene derivative III is formed.



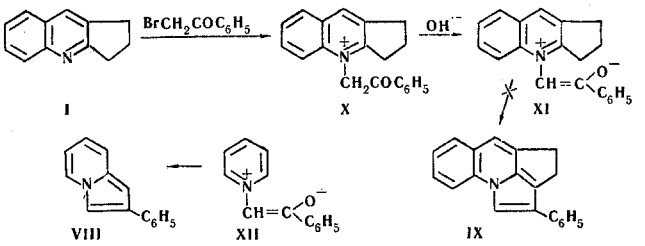
II a R=CH_3, b R=C_2H_5

3-Methyl-β-quinindane (VII), purified as the hydrochloride, is formed from 3-methylene-β-quinindane (III) by hydrogenation over a Raney-nickel catalyst at atmospheric pressure and room temperature.

Quaternary salt X (ν_{CO} 1698 cm^{-1}) was obtained by reaction of β-quinindane with bromoacetophenone and was characterized by means of the UV and IR spectra; unstable yield XI, the structure of which was demonstrated by analysis and the IR spectrum (–CH=C–O group: 1590, 1565 cm^{-1}), was isolated by heating X with sodium bicarbonate solution. For comparison, bands at 1572, 1545, and 1520 cm^{-1} are ob-

*The inductive constant σ_I is +0.05 for the $CH_2=CH$ group from data on the reactivity of aromatic compounds [11].

served for this group in ylid XII [15]. With chloranil, ylid XI gives a stable blue color characteristic for such "enol-betaines" [15]. While ylids of the XI type are cyclized usually immediately or after a short heating period during the synthesis of indolicine systems to form a second pyrrole ring (XII→ VIII) [14], in our case no cyclization occurs.



The reason for this apparently lies in the very large ring strain in the IX system. This explanation is confirmed by means of framework molecular models*: models of I and VIII are readily assembled, but the distortion of the valence angles in IX is so great that it is not even possible to construct a model of this molecule. Moreover, according to [16], not one condensed system in which there are three rings with two five-membered and one six-membered ring has been synthesized: there would be one common carbon atom with sp^2 hybridization (there are reports of unsuccessful attempts to synthesize such systems [17]).

EXPERIMENTAL

Mannich Reaction of β-Quinindane with Diethylamine. A mixture of 22.5 g (0.2 mole) of diethylamine hydrochloride, 17.5 ml of 33% formalin, and 14 g (0.085 mole) of β-quinindane [1, 7] was refluxed for 3 min until the compounds had completely dissolved and turbidity appeared. After cooling, the reaction mass was poured into 100 ml of water, and the mixture was filtered to give 5.3 g of 3-methylene-β-quinindane (III) with mp 99-100° (from hexane). Found %: C 85.75; H 5.91; N 7.67. $C_{13}H_{11}N$. Calculated %: C 86.14; H 6.12; N 7.74. R_f 0.80 (benzene).† The product was soluble in all organic solvents; UV spectrum in alcohol, λ_{max}, nm (log ε): 256 (4.42); 320 (3.88); 335 (4.03); 350 (4.03).

The aqueous mother liquor was made alkaline to pH 9, extracted with ether, and the ether extract was dried over magnesium sulfate. The ether was removed in vacuo, and the oily residue was dissolved in acetone. A freshly prepared sulfuric-acid solution in acetone was added to pH 1. The solution was decanted from the resulting oil, and the oil was washed with acetone (by decantation), triturated with alcohol, and filtered to give 8.5 g of 3-(diethylaminomethyl)-β-quinindane bisulfate (IIb). It decomposed without melting; it was purified by reprecipitation with acetone from a methanol–acetonitrile mixture. Found %: C 46.00; H 6.03; S 14.12. $C_{17}H_{22}N_2 \cdot 2H_2SO_4$. Calculated %: C 45.30; H 5.82; S 14.23.

Hydrochloride of 3-(Dimethylaminomethyl)-β-quinindane (IIa). A solution of 2.46 g (0.03 mole) of dimethylamine hydrochloride and six drops of triethylamine in 3 ml of 50% aqueous alcohol were added in 30 min with stirring to a mixture of 5.1 g (0.03 mole) of β-quinindane [1,7], 2.73 g (0.03 mole) of 33% formalin, 4 ml of alcohol, and 3 drops of triethylamine (pH of the mixture 7.5) at 60°. The reaction mass was stirred for 3.5 h at 58-60°. The mixture was then evaporated to dryness in vacuo, the residue was triturated with ether, and the precipitate was filtered. After recrystallization from alcohol, 2.9 g of 3-(dimethylaminomethyl)-β-quinindane hydrochloride with mp 156-157° (decomp.) was obtained. Found %: C 68.74; H 7.49; Cl 13.30. $C_{15}H_{18}N_2 \cdot HCl$. Calculated %: C 68.58; H 7.29; Cl 13.49. UV spectrum of base IIa in alcohol, λ_{max}, nm (log ε): 235(4.53); 238 (4.53); 288 (3.57); 294 (3.61); 300 (3.62); 306 (3.74); 314 (3.68); 320 (3.87).

Reaction of β-Quinindane (I) with Formaldehyde. A mixture of 2.8 g of β-quinindane and 2.8 g of 33% formalin was refluxed for 30 min; after cooling, the mixture was extracted with dichloroethane. Two spots with R_f 0.25 and 0.60 (chloroform) appeared on a chromatogram of the extract. The extract was dried, the solvent was removed in vacuo, the residue was triturated with benzene, and 0.6 g of 3,3-dihydroxymethyl-β-quinindane (V) with mp 129-130° (from alcohol) was filtered. Found %: C 73.14; H 6.60; N 6.23. $C_{14}H_{16}NO_2$.

*Framework Molecular Models (USA).

† In all cases, chromatography was carried out in a thin layer of activity-II aluminum oxide; development was accomplished with iodine vapors, and the solvents are indicated in parentheses.

Calculated %: C 73.03; H 6.99; N 6.08. Compound V was soluble in chloroform and methanol, insoluble in benzene and water, and had R_f 0.25 (chloroform) and 0.10 (benzene). The benzene filtrate [practically only one spot with R_f 0.25 (benzene) appeared on the chromatogram] was concentrated in vacuo, 1.5 ml of acetic anhydride and one drop of concentrated H_2SO_4 were added, and the mixture was allowed to stand for 1 day; 10 ml of alcohol was then added, and the mixture was evaporated to dryness in vacuo. One spot with R_f 0.80 (benzene) appeared on the chromatogram of the residue. 3-Methylene-β-quinindane (III) with mp 97-99°, which was identical to an authentic sample of III, was obtained after recrystallization of this residue from hexane.

Hydrochloride of 3-Methyl-β-quinindane (VII). Compound III [1.0 g (0.0055 mole)] was hydrogenated in 20 ml of absolute alcohol over a Raney-nickel catalyst at room temperature. After 6 h, 130 ml of hydrogen (758 nm, 19°, 0.0053 mole) had been absorbed. After removal of the catalyst, the alcohol was removed by vacuum distillation, the residual mobile oil was dissolved in absolute ether, and an excess of an ether solution of hydrogen chloride was added with cooling. The solution was poured off from the precipitate, and the precipitate was triturated with acetone, filtered, and reprecipitated from alcohol with ether to give 0.65 g of VII hydrochloride with mp 164-166° (decomp.). Found %: Cl 16.36. $C_{13}H_{13}N \cdot HCl$. Calculated %: Cl 16.17. UV spectrum of the base (in alcohol), λ_{max}, nm (log ε): 235 (4.00); 238 (4.04); 251 (3.04); 288, shoulder (3.3); 294 (3.37); 300 (3.38); 306 (3.43); 312 (3.37); 319 (3.37).

N-Phenacyl-β-quinindanium Bromide (X). A mixture of 1.69 g (0.01 mole) of β-quinindane [1,7] and 1.99 g (0.01 mole) of ω-bromoacetophenone in 2.5 ml of absolute alcohol was heated to 60°. The alcohol was removed in vacuo, and the residue was triturated with acetone to give 2.6 g of X with mp 228-230° (decomp., from butanol). Found %: C 65.41; H 4.83; Br 21.80. $C_{20}H_{18}BrNO$. Calculated %: C 65.22; H 4.92; Br 21.69. UV spectrum (in alcohol), λ_{max}, nm (log ε): 244, shoulder (4.58); 248 (4.61); 257, shoulder (4.23); 322, shoulder (3.46); 329 (3.49).

N-Phenacylido-β-quinindane (XI). A solution of 0.8 g of sodium bicarbonate in 5 ml of hot water was added to a solution of 1.20 g of X in 8 ml of hot water, the mixture was heated for 15 min at 70°, and the resulting precipitate of ylid XI was filtered to give 0.8 g of a product with mp 147-148° (decomp., from dimethylformamide). Found %: C 83.18; H 5.95; N 5.28. $C_{20}H_{17}NO$. Calculated %: C 83.58; H 5.96; N 4.87. The product was soluble in dichloroethane and chloroform, and insoluble in acetone, ether, and benzene.

The dipole moments and the pK_a values were determined at 20°. The pK_a values were determined by potentiometric titration. The authors thank I. V. Persianov for the measurements.

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