ELECTROPHILIC ADDITION OF HALOGENS TO THE ENAMINE GROUPING OF 1,2-DIHYDRO-4H-β-QUININDINES

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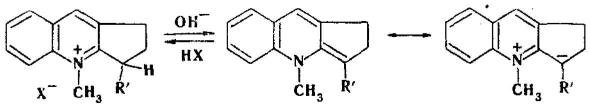
Electrophilic addition of halogens to 1,2-dihydro-4H-β-quinindines gives quaternary salts of 3-halo-β-quinindanes, from which the corresponding isothiocyanates and nitro and iodo derivatives are readily obtained by substitution of the halogen. The structures of the compounds were confirmed by the IR, UV, and PMR spectra.

We have previously shown that electrophilic substitution of the hydrogen atom in the 3 position occurs readily because of the excess electron density on the $C_{(3)}$ atom in the 4-methyl-1,2-dihydro-4H-β-quinindine molecule (I), i.e., because of the large contribution of limiting structure III. In particular, this method was used to obtain 3-acyl-substituted compounds (II) [1] in which the contribution of limiting structure IV is also quite large. Spectral methods have been used [2] to show that protonation of II, as in the case of other enamines, proceeds primarily at the $C_{(3)}$ atom to give quaternary salt VI.



V, VI I, II III, IV

I, III, V R'=H; II, IV, VI R'=COR

In the present study we have carried out the electrophilic addition of halogens to the enamine grouping of 4-methyl-1,2-dihydro-4H-β-quinindine (I) and its 3-substituted derivatives (II). Compound I, which was obtained by treatment of β-quinindane methiodide (V, X = I) with aqueous alkali, was extracted with benzene and, without isolation, subjected to the action of bromine. In this case, a crystalline colorless substance precipitated. On the basis of the results of analysis and the spectra, the 3-bromo-β-quinindane methobromide structure (VII) was assigned to it. It is formed as a result of electrophilic addition of bromine to I rather than by substitution of a hydrogen in I, since in the latter case the liberated hydrogen bromide should have converted a part (about half) of I to β-quinindane methobromide (V, X = Br). However, there is practically no V in the reaction products – the formation of 3-benzoyl-1,2-dihydro-4-methyl-4H-β-quinindiene (IIa) by the action of alkali and benzoyl chloride on the products of this reaction was not noted even by means of thin-layer chromatography (TLC).

A similar reaction to give quaternary salts of 3-bromo-3-substituted β-quinindanes (VIII) also occurs in the case of the action of bromine on 3-substituted 4-methyl-1,2-dihydro-4H-β-quinindines (II). Here the formation of VIII can only be the result of electrophilic addition of bromine. Orange or light-brown crystalline compounds with empirical formulas $C_{20}H_{17}Br_4NO$ or $C_{20}H_{17}I_4NO$, respectively, are formed when a benzene solution of bromine or iodine is added rapidly to a benzene solution of 3-benzoyl-4-methyl-1,2-dihydro-4H-β-quinindine (IIa). The UV spectrum of the first substance is similar to the UV spectrum of the methobromide (VIIIa), while the PMR spectrum of the compound with four bromine atoms is practically the same as the PMR spectrum of VIIIa, i.e., only one bromine atom is in the β-quinindane ring in the orange compound. Consequently, the remaining three atoms are contained in the anion (Br_3^-). On the basis

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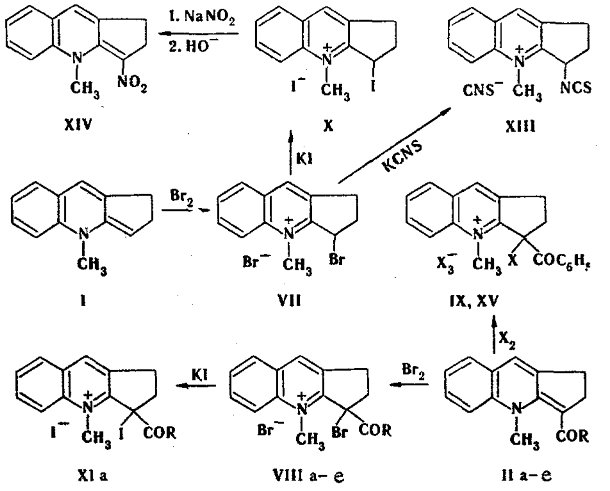
of these data, the 3-benzoyl-3-bromo (or, respectively, 3-iodo)-β-quinindane methoperbromide or methoperiodide structure (IX and XV) can be assigned to the compounds obtained.

It was found that the bromine in the 3 position of VII and VIIIa is very labile. On attempts to replace the ionic bromine by iodine, both the ionic and covalently bonded bromine are replaced immediately to give X and XIa. However, in the case of 3-N-phenylcarbamoyl-3-bromo-β-quinindane methobromide (VIIIe) under similar conditions, only the ionic bromine is replaced to give the methiodide (XII).

Using this high reactivity of the halogen in the 3 position, we carried out other nucleophilic substitution reactions. When aqueous solutions of 3-bromo-β-quinindane methobromide (VII) and potassium thiocyanate are mixed, the quaternary salt – 3-isothiocyanato-β-quinindane methothiocyanate (XIII) – precipitated, while 3-nitro-4-methyl-1,2-dihydro-4H-β-quinindine (XIV) was obtained (after treatment with alkali) by the action of sodium nitrite in aqueous alcohol on X at 50°.

The structures of the compounds were confirmed by the IR, UV, and PMR spectra. The UV spectra of the quaternary salts (VII, IX, XV, VIIIa-e, and XIII) are very similar to one another and to the spectrum of β-quinindane methiodide (V, X = I) because of the absecne of conjugation of the substituent in the 3 position with the basic chromophore – the quinolinium ring. Two maxima at 244-250 and 329-337 nm are characteristic for these compounds, while there is very intense absorption in the visible region (455-480 nm [1]) for the starting 1,2-dihydro-4H-β-quinindines, for example, the 3-acyl-substituted compounds (IIa-e). In contrast to the corresponding starting 1,2-dihydro derivatives, in which the carbonyl frequency is very strongly shifted to the low-frequency region (ν_{CO} 1500-1525 cm^{-1}) [2], a ν_{CO} carbonyl band is observed at 1658-1680 cm^{-1} in the IR spectra of 3-aroyl-substituted methobromides (VIIIa-d). An amide carbonyl band is observed at 1670 cm^{-1} in the IR spectrum of 3-bromo-3-N-phenylcarbamoyl-β-quinindane methobromide (VIIIe), while ν_{CO} is at 1620 cm^{-1} in the spectrum of the starting amide (IIe).



II, VIII a R = C_6H_5; b R = p-$CH_3C_6H_4$; c R = m-ClC_6H_4; d R = p-$CH_3OC_6H_4$;
e R = NHC_6H_5; IX X = Br; XV X = I

Bands characteristic for the CNS^- anion at 2160 cm^{-1} (vs) and for isothiocyanates at 2060 (s) and 1980 (m) cm^{-1} are noted in the IR spectrum of methothiocyanate XIII; a ν_{C-Br} band at 524 cm^{-1} is observed for the bromide (VII), while a ν_{C-I} band at 497 cm^{-1} is observed for the iodide (X).

Signals from aromatic protons at 7.8-8.92 ppm, a singlet from an N-methyl group (δ 4.51 ppm), a multiplet centered at 3.55 ppm from the protons of the methylene group attached to $C_{(1)}$, a markedly split multiplet from the protons of the $C_{(2)}$ methylene group at 2.63-3.4 ppm, and a quartet from the $C_{(3)}$ methylidyne proton (6.04 ppm) are observed in the PMR spectrum of 3-benzoyl-4-methyl-1,2-dihydro-4H-β-quinindine (IIa) in CF_3COOH. The signal of a methylidyne proton is absent in the PMR spectrum of 3-bromo-3-benzoyl-β-quinindane methobromide (VIIIa) in trifluoroacetic acid, while the signals of the methylene protons attached to $C_{(1)}$ and $C_{(2)}$ are multiplets centered at 3.74 and 3.51 ppm, respectively; δ_{NCH_3} 4.48 ppm (singlet). The shape of the PMR spectra in the aromatic proton region for IIa and VIIIa is almost completely coincident. As already stated, the PMR spectrum of 3-bromo-3-benzoyl-β-quinindane methoperbromide (IXa) is practically the same as that of the spectrum of the methobromide (VIIIa): multiplets centered at 3.74 and 3.49 ppm [protons attached to $C_{(1)}$ and $C_{(2)}$, respectively], signals from five aromatic protons at 7.53-8.5 ppm, and a singlet of an N-methyl group at 4.48 ppm.

TABLE 1. 3-Bromo-3-aroyl-β-quinindane Methobromides (VIIIa-d)

Comp.	mp, °C (decomp.)	Empirical formula	Found, %				Calculated, %				λ_{max}, nm (lg ε)	ν_{CO}, cm⁻¹	Yield, %
			C	H	Br	N	C	H	Br	N			
VIIIa	156—157	$C_{20}H_{17}Br_2NO$	55,6	3,9	35,5	—	55,7	3,8	35,7	—	249 (4,49), 355 (4,06)	1667	67
VIII b	115—118	$C_{21}H_{19}Br_2NO$	54,2	4,1	34,5	3,4	54,7	4,1	34,6	3,0	250 (4,52), 337 (4,52)	1663	66
VIII c	126—127	$C_{20}H_{16}Br_2ClNO$	49,9	3,4	Br+Cl 40,5	3,0	49,9	3,4	Br+Cl 40,5	2,9	247 (4,48), 334 (4,05)	1680	75
VIII d	190—193	$C_{21}H_{19}Br_2NO_2$	52,8	4,2	33,4	2,9	52,8	4,0	33,5	2,9	245 (4,45), 333 (4,13)	1658	66

EXPERIMENTAL

3-Bromo-β-quinindane Methobromide (VII). Benzene (12 ml) was added to a suspension of 1.24 g (4 mmole) of β-quinindane methiodide (V, X = I) [3] in 10 ml of water, after which 5 ml of 10% sodium hydroxide solution was added with stirring under argon. After 10 min, the benzene solution was separated and cooled, and a solution of 0.22 ml (4 mmole) of bromine in 5 ml of benzene was added slowly. The resulting oil was triturated with acetone, and the solid was removed by filtration to give 0.95 g (69%) of VII with mp 132-133.5° (decomp., from acetonitrile). UV spectrum, λ_{max}, nm (log ε): 248 (4.42), 334 (4.01). Found,%: Br 46.8; N 4.1. $C_{13}H_{13}Br_2N$. Calculated,%: Br 46.6; N 4.1.

3-Bromo-3-aroyl-β-quinindane Methobromides (VIIIa-d, Table 1). A solution of an equimolecular amount of bromine in benzene was added with cooling to a benzene solution of 3-aroyl-4-methyl-1,2-dihydro-4H-β-quinindine (IIa-d). After 2 h, the precipitated VIIIa-d was removed by filtration and recrystallized from alcohol.

3-Bromo-3-N-phenylcarbamoyl-β-quinindane Methobromide (VIIIe). A solution of 0.1 ml (2 mmole) of bromine in 5 ml of benzene was added with cooling to a suspension of 0.6 g (2 mmole) of 3-N-phenylcarbamoyl-4-methyl-1,2-dihydro-4H-β-quinindine (IIe). After 30 min, the precipitate was removed by filtration to give 0.85 g (95%) of VIIIe with mp 180° (decomp., from alcohol). UV spectrum, λ_{max}, nm (log ε): 248 (4.55), 334 (4.05). IR spectrum: ν_{CO} 1670 cm⁻¹. Found,%: C 51.8; H 4.1; Br 34.7; N 6.2. $C_{26}H_{23}Br_2N_2O$. Calculated,%: C 52.0; H 3.9; Br 34.6; N 6.1.

3-Bromo-3-benzoyl-β-quinindane Methoperbromide (IX). A solution of 0.2 ml (4 mmole) of bromine in 10 ml of benzene was added to a solution of 1.14 g (4 mmole) of 3-benzoyl-4-methyl-1,2-dihydro-4H-β-quinindine (IIa) in 90 ml of benzene. After 10 min, the precipitate was removed by filtration and washed with benzene to give 0.9 g (38%) of IX with mp 130.5-132.5° [from acetonitrile–water (1 : 1)]. UV spectrum, λ_{max}, nm (logε): 250 (4.44), 334 (4.00). Found, %: C 39.5; H 2.4; Br 53.1. $C_{20}H_{17}Br_4NO$. Calculated,%: C 39.8; H 2.5; Br 52.8.

3-Iodo-3-benzoyl-β-quinindane Methoperiodide (XV). A solution of 1 g (3.95 mmole) of iodine in 10 ml of alcohol was added with cooling to a suspension of 1.18 g (4.1 mmole) of IIa in 50 ml of alcohol. After 30 min, the precipitate was removed by filtration to give 1.44 g (44%) of XV with mp 75.5-77.5° (decomp.). Found,%: I 62.8; N 1.9. $C_{20}H_{17}I_4NO$. Calculated,%: I 63.4; N 1.8.

3-Iodo-β-quinindane Methiodide (X). A total of 0.5 ml of a saturated aqueous solution of potassium iodide was added to a concentrated aqueous solution of 0.2 g (0.6 mmole) of VII. The resulting precipitate was removed by filtration to give 0.15 g (41.2%) of X with mp 121-122° (decomp., from water). Found,%: I 56.0; H_2O 3.8. $C_{13}H_{13}I_2N \cdot H_2O$.* Calculated,%: I 55.7; H_2O 4.0.

3-Iodo-3-benzoyl-β-quinindane Methiodide (XIa). A 2-ml sample of a saturated aqueous solution of potassium iodide was added to a solution of 0.45 g (1 mmole) of 3-bromo-3-benzoyl-β-quinindane methobromide (VIIIa) in 40 ml of water. The resulting precipitate was removed by filtration to give 0.37 g (68%) of XIa with mp 80-82° (decomp.). Found,%: I 46.8; N 2.5. $C_{20}H_{17}I_2NO$. Calculated,%: I 46.9; N 2.6.

3-Bromo-3-N-phenylcarbamoyl-β-quinindance Methiodide (XII). A saturated aqueous solution of 0.33 g (2 mmole) of potassium iodide was added to a solution of 0.46 g (1 mmole) of VIIIe in 2 ml of water. The precipitate was

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* The compound loses water of crystallization on vacuum drying (at 15 mm and 75°) over phosphorus pentoxide.

removed by filtration to give 0.4 g (78%) of XII with mp 124-128° (decomp., softens at 99°, from water). UV spectrum, λ_{max}, nm (log ε): 244 (4.56), 329 (3.92). Found,%: C 46.6; H 3.5; I 25.4; N 5.2. $C_{20}H_{18}BrIN_2O$. Calculated,%: C 47.2; H 3.6; I 25.1; N 5.5.

3-Isothiocyanate-β-quinindane Methothiocyanate (XIII). A solution of 0.35 g (0.365 mmole) of potassium thiocyanate in 2 ml of water was added to a solution of 0.5 g (0.146 mmole) of VII in 20 ml of water. After 1 h, the precipitated XIII (0.27 g) was removed by filtration to give a product with mp 124-125° (decomp., from alcohol). UV spectrum, λ_{max}, nm (log ε): 250 (4.31), 334 (4.01). Found,%: C 60.1; H 4.5; S 21.0. $C_{15}H_{13}N_3S_2$. Calculated,%: C 60.2; H 4.3; S 21.4.

3-Nitro-4-methyl-1,2-dihydro-4H-β-quinindine (XIV). A solution of 0.07 g (0.1 mmole) of sodium nitrite was added to a heated (to 50°) solution of 0.22 g (0.05 mmole) of X in 10 ml of 80% aqueous alcohol, and the mixture was allowed to stand at 50° for 2 h, after which 20 ml of benzene and 0.2 ml of 10% sodium hydroxide solution were added. The dried benzene solution was vacuum evaporated to give 0.11 g of XIV with mp 144° (from alcohol). Found,%: C 68.3; H 5.3; N 12.1. $C_{13}H_{12}N_2O_2$. Calculated,%: C 68.8; H 5.3; N 12.3.

The IR spectra of suspensions in mineral oil were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions were recorded with a Hitachi recording spectrophotometer. The PMR spectra of solutions in deuterochloroform were recorded with a JNM-4H spectrometer with an operating frequency of 100 MHz with hexamethyldisiloxane as the internal standard; the chemical shifts are indicated relative to tetramethylsilane.

LITERATURE CITED

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