REACTION OF BENZO[b]QUINUCLIDINE WITH ELECTROPHILIC REAGENTS

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Bromination of benzo[b]quinuclidine yields its perbromide and a molecular complex with bromine, while nitration and chlorosulfonation form 7-nitro- and 7-chlorosulfobenzo[b]-quinuclidines. The results of electrophilic substitution attest to the absence in benzo[b]-quinuclidine of a mesomeric interaction between the free electron pair of nitrogen and the π electrons of the benzene ring.

It is well known that N,N-dialkylanilines, 1,2,3,4-tetrahydroquinolines, and indolines, owing to conjugation between the free electron pair of nitrogen and the π electrons of the aromatic system, readily undergo electrophilic substitution to form chiefly para-substituted (with respect to the amino group) derivatives.

In contrast to these compounds, the free p electrons of nitrogen and the π-electron system of the benzene ring in benzo[b]quinuclidine (I) are orthogonal, which excludes the possibility of resonance interaction. The absence of a $p-\pi$ mesomeric effect in I is reflected in its pK_a, the value of which is considerably higher than, for example, for N,N-diethylaniline (7.79 and 6.56, respectively). Compound I does not enter into azo coupling with p-nitrophenyldiazonium chloride [1,2].

We have studied several electrophilic substitution reactions of I (bromination, nitration, and chlorosulfonation), the results of which are also intimately associated with the absence of a $p-\pi$-electron interaction in benzo[b]quinuclidine.

Only perbromide II and a molecular complex of I with bromine (III) were obtained by bromination of I in various solvents (acetic acid and chloroform) at 0, 20, and 60° in the presence of catalysts (iron filings or a mixture of iron filings and iodine) and in the absence of catalysts. The bromination of benzo[b]quinuclidine methobromide (VII) also resulted in a molecular complex of the latter with bromine (VIII).

Perbromide II loses bromine on heating in water, chlorobenzene, and even on standing in air and is converted to benzo[b]quinuclidine hydrobromide. The formation from II of a compound brominated in the aromatic ring was not observed in a single case; this sort of process is extremely readily accomplished in a number of perbromides of aromatic amines. Molecular complex III, which under the influence of aqueous alkali is converted to I, is formed on treatment of II with aqueous sodium carbonate. Perbromide II was obtained from III and hydrobromic acid. In contrast to II, which reacts with acetone even at room temperature, III is debrominated by acetone only on heating and does not lose bromine on standing in air.

In contrast to bromination, nitration and chlorosulfonation of I lead to the formation of electrophilic substitution products. Thus, treatment of I with a nitrating mixture at -4 to $-7°$ gives mononitrobenzo[b]-quinuclidine, while treatment of I with chlorosulfonic acid initially at 0° and then at 50° gives benzo[b]quinuclidine sulfonyl chloride. Sulfamido and N,N-dimethylsulfamido derivatives are obtained from the latter by the action of ammonia or dimethylamine.

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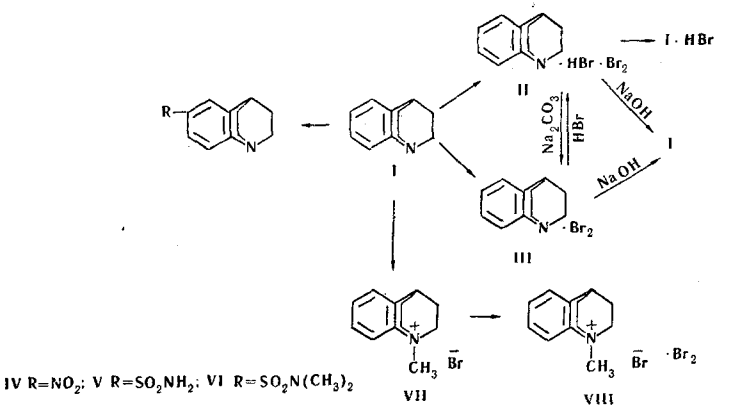
TABLE 1. Characteristics of the PMR Spectra of 7-Substituted Benzo[b]quinuclidines*

No.	Compound	Solvent	δ, ppm				J, Hz			
			H_4	H_5	H_6	H_8	4,8	5,6	5,8	6,8
1	IV	$CDCl_3$	3,21	7,30	8,09	7,96	0,7	8,1	0,4	2,1
2	IV	CD_3OD—D_2O (10 : 1)		7,45	8,12	7,92				
3	IV · H+	$CDCl_3$—CF_3COOH (20 : 1)		7,70	8,44	8,49				
4	IV · CH_3I	CD_3OD—D_2O (10 : 1)		7,85	8,50	8,53				
5	VI	CH_2Cl_2		7,38	7,64	7,50	0,6	8	(~0,5)	2
6	VI	CD_3OD—D_2O (10 : 1)		7,52	7,70	7,51				
7	VI · H+	CH_2Cl_2—CF_3COOH (20 : 1)		7,63	7,88	8,06				
8	VI · CH_3I	CD_3OD—D_2O (10 : 1)		7,84	8,01	7,98				

*The PMR spectra were obtained with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz with tetramethylsilane (Nos. 1, 3, 5, and 7) and tert-butanol (Nos. 2, 4, 6, and 8) (δ = 1.2 ppm) as the internal standard.



The structure of the synthesized compounds as 7-substituted benzo[b]quinuclidines was proved from the dipole moments and PMR spectroscopy. The dipole moment (in benzene) of nitrobenzo[b]quinuclidine (μ = 5.23 ± 0.01 D), benzo[b]quinuclidine (μ = 1.50 ± 0.01 D), and quinuclidine (μ = 1.39 ± 0.02 D) were determined.

Vector addition of the dipole moments of quinuclidine and p-nitrotoluene (μ = 4.39 D) [3] in benzene solution gives 5.23 D, which agrees satisfactorily with the experimental data and rigorously determines orientation of the nitro group in the 7-position. The dipole moments for 5-, 6-, and 8-nitrobenzo[b]quinuclidines should have been 2.4, 3.8, and 5.6 D, respectively, on the basis of vector addition.

Analysis of the PMR spectra confirms the formation of 7-substituted benzo[b]quinuclidines (see Table 1).

The large values of the spin-spin interaction constants for IV and VI attest to a 1,2,4-trisubstituted benzene ring, which excludes a 5- and 8-orientation for the products of electrophilic substitution of I.

The problem of the 6- and 7-position of the substituents was solved as follows. For bicyclic aromatic compounds, for example 1,7-naphthyridine [4], the spin-spin interaction constants of the protons in the 5- and 8-positions lie at 0.5 Hz. The same splitting also occurs in substituted benzo[b]quinuclidines, which indicates the presence of a proton in the 8-position. This proton also interacts with the H_6 meta proton (J = 2.2 Hz), and additional splitting of the signal with a long-range spin-spin interaction constant of 0.6-0.7 Hz is observed. The double resonance method established that splittings with constants of 0.6-0.7 Hz arise due to interaction of the H_4 and H_8 protons. A shift of the aromatic signals to weak field is observed during protonation and quaternization of IV and VI, and the maximum weak-field shift, as compared with the others (by ~0.2 ppm), is characteristic for the signal of the H_8 proton. This is explained by the fact that the H_8 proton, which is in the ortho position with respect to the protonation or quaternization center and with respect to the electronegative substituent in the 7-position, experiences a strong deshielding effect of two

groups. In the case of 6-substituted benzo[b]quinuclidines the H_8 proton signal in the protonated and quaternized forms would be found under the deshielding effect of only one electronegative group, which would cause its shift to weak field by about the same value as in the remaining aromatic protons. The assignment to H_8 of the signal which experiences the maximum weak-field shift on passing from benzo[b]quinuclidine bases to derivatives with a positively charged atom and the determination by the double resonance method of the nature of all of the spin-spin splitting constants of this signal made it possible to arrive at the independent conclusion that IV, V, and VI are 7-substituted benzo[b]quinuclidines.

EXPERIMENTAL

Benzo[b]quinuclidine (I). A mixture of 3 g (17.3 mmole) of 3-ketobenzo[b]quinuclidine [5], 30 ml of glycerine, 6 g of potassium hydroxide, and 6 ml of hydrazine hydrate was heated for 5 h at 165-170° (bath temperature). The reaction product was then distilled from the reaction mass with water, and the distillate was extracted with benzene. Drying of the extract and removal of the solvent by distillation yielded 2.2 g (80%) of I with mp 68-69° (from petroleum ether) [1]. Found %: C 83.2; H 8.0; N 8.9. $C_{11}H_{13}N$. Calculated %: C 83.0; H 8.2; N 8.8. The hydrobromide was obtained as colorless crystals with mp 267-269° (from alcohol). Found %: Br 32.9. $C_{11}H_{13}N \cdot HBr$. Calculated %: Br 33.3. The methbromide was obtained as colorless crystals with mp 231-232°. Found %: Br 32.7; N 5.7. $C_{12}H_{16}BrN$. Calculated %: Br 33.0; N 5.8.

Reaction of Benzo[b]quinuclidine with Bromine. A. A solution of 4 g (25 mmole) of bromine in 40 ml of acetic acid was added in the course of 4 h at 20° to a solution of 4 g (25 mmole) of I in 40 ml of glacial acetic acid. Yellow crystals began to precipitate about 2 h after the start of the addition of bromine. The precipitate was filtered and washed with acetic acid and ether to give 5 g (62%) of III as light-yellow crystals which were quite soluble in benzene and methanol, slightly soluble in ethanol, acetone, and ethyl acetate, and insoluble in water. The substance was vacuum sublimated (15 mm, bath temperature 120-130°) to give a product with mp 152-153°. Found %: C 41.6; H 4.3; Br 50.4; N 4.3. $C_{11}H_{13}N \cdot Br_2$. Calculated %: C 41.4; H 4.1; Br 50.1; N 4.4.

A total of 0.8 g (8%) of bright-orange crystals of perbromide II with mp 89-90° (from ether) precipitated from the mother liquor on standing. Found %: Br 60.6. $C_{11}H_{13}N \cdot Br_2 \cdot HBr$. Calculated %: Br 60.0.

The solution remaining after removal of II was evaporated, and the crystalline residue was washed with acetone to give 0.85 g (13%) of benzo[b]quinuclidine hydrobromide with mp 267-269° (from alcohol).

B. A solution of 1.6 g (10 mmole) of bromine in 16 ml of chloroform was added to a solution of 1.6 g (10 mmole) of I in 9 ml of dry chloroform at 20° in the course of 3 h. The precipitated crystals were filtered and washed with chloroform to give 0.85 g (27%) of III with mp 152-153°. The chloroform solution remaining after removal of III was evaporated, and the residue was recrystallized from alcohol to give 1.2 g (50%) of the hydrobromide of I with mp 267-269°.

C. Bromine [4.8 g (30 mmole)] was added at 0° in the course of 1 h to a solution of 3.2 g (20 mmole) of I in 7 ml of glacial acetic acid and 1 ml of concentrated sulfuric acid. The mixture was held for another hour under the same conditions and then heated for 2 h at 60° and allowed to stand for 20 h at room temperature. The dark-red solution was poured over ice, and the resulting orange precipitate was filtered and washed with water, squeezed thoroughly, and dissolved in 20 ml of ether. On standing, 1.8 g (22.5%) of II with mp 88-90° precipitated from the ether solution. The acidic mother liquor was saturated with sodium carbonate and extracted with benzene to give 1.5 g of I.

Reaction of Benzo[b]quinuclidine Methobromide with Bromine. A solution of 2 g (8 mmole) of VII in 15 ml of glacial acetic acid was treated at 20° with a solution of 1.32 g (8 mmole) of bromine in 13 ml of acetic acid. The resulting precipitate was filtered and washed with acetic acid and ether to give 3 g (92%) of VIII as yellow crystals with mp 137-138°. Found %: C 34.5; H 3.6; Br 58.1. $C_{12}H_{16}BrN \cdot Br_2$. Calculated %: C 34.8; H 3.9; Br 57.7.

Transformations of II and III under the Influence of Various Reagents. A. Compound II (0.5 g) was dissolved in 5 ml of acetone, the solution decolorized rapidly, and colorless crystals of the hydrobromide of I with mp 267-269° precipitated.

B. A mixture of 0.5 g of III and 10 ml of acetone was refluxed for 4 h. A colorless precipitate of the hydrobromide of I precipitated gradually to give 0.35 g (93%) of a product with mp 267-269°.

C. A mixture of 0.8 g of II and 10 ml of chlorobenzene was refluxed for 5 h to give 0.4 g (83%) of I · HBr with mp 267-269°.

D. A mixture of 0.5 g of II and 10 ml of water was refluxed for 2 h. Bromine was evolved in the process and the aqueous solution became colorless. Removal of the water by distillation yielded 0.24 g (80%) of I·HBr.

E. Compound II (0.5 g) was shaken with 10 ml of 15% aqueous sodium carbonate to give 0.35 g (75%) of III with mp 153-155°.

F. A solution of 0.3 g of III in 20 ml of benzene was shaken with 10 ml of 20% aqueous sodium hydroxide. The benzene solution was separated, the solvent was removed by distillation, and the residue was vacuum sublimated to give 0.13 g (87%) of I with mp 68-69°.

G. A solution of 0.2 g of III in benzene was acidified with hydrobromic acid. A total of 0.2 g (80%) of orange crystals of perbromide II with mp 89-90° precipitated.

H. Compound VIII (0.5 g) was dissolved in 5 ml of acetone. After several minutes the solution decolorized and 0.23 g (77%) of colorless crystals of VII precipitated.

7-Nitrobenzo[b]quinuclidine (IV). A nitrating mixture (1.6 ml of nitric acid with sp. gr. 1.5 and 36 ml of concentrated sulfuric acid) was added gradually to a solution of 3 g (19 mmole) of I in 25 ml of concentrated sulfuric acid while maintaining the temperature of the reaction mass at −7 to −4°. The mixture was stirred at the same temperature for another hour and poured over ice. The mixture was neutralized with sodium carbonate and extracted with benzene to give 3.4 g (89%) of IV as pale-green crystals which were quite soluble in chloroform, benzene, and methanol, slightly soluble in ethanol, and insoluble in water and had mp 117-118° (from ethyl acetate). Found %: C 64.6; H 6.0; N 13.6. $C_{11}H_{12}N_2O_2$. Calculated %: C 64.7; H 5.9; N 13.7. The methiodide had mp 234-235° (decomp.). Found %: I 36.7; N 8.5. $C_{12}H_{15}IN_2O_2$. Calculated %: I 36.7; N 8.1.

7-Sulfamidobenzo[b]quinuclidine (V). Compound I [3.2 g (20 mmole)] was added at 0° to 10 ml of chlorosulfonic acid. The resulting solution was heated for 2 h at 50°, poured over ice, filtered, and the acidic solution was added with cooling to 50 ml of 25% ammonium hydroxide. The mixture was held for 2 h at 0°, and the precipitate was filtered, washed with water, and dried to give 2.7 g (56%) of V with mp 236-238° (from methanol) as colorless crystals which were slightly soluble in chloroform, methanol, and methylene chloride and insoluble in water. Found %: C 55.7; H 5.8; N 11.6; S 13.3. $C_{11}H_{14}N_2O_2S$. Calculated %: C 55.4; H 5.9; N 11.8; S 13.5. The hydrochloride was obtained as colorless crystals with mp 274-275° (decomp.). Found %: Cl 12.8; N 10.0; S 11.6. $C_{11}H_{14}N_2O_2S \cdot HCl$. Calculated %: Cl 12.9; N 10.2; S 11.6.

7-(N,N'-Dimethylsulfamido)benzo[b]quinuclidine (VI). An aqueous solution of 7-(chlorosulfo)benzo[b]-quinuclidine, obtained by the method described above from 2 g of I and 7 ml of chlorosulfonic acid, was poured into 30 ml of a 25% aqueous solution of dimethylamine. After 20 h the precipitated crystals were filtered and washed with water and ether (0.4 g of I was isolated from the ether solution) to give 0.8 g (30%) of VI as colorless plates which were soluble in acetone, chloroform, ethanol, and methanol, insoluble in ether and water, and had mp 148-150° (from ethyl acetate). Found %: C 58.9; H 7.0; N 10.2; S 12.1. $C_{13}H_{18}N_2O_2S$. Calculated %: C 58.6; H 6.8; N 10.5; S 12.0. The methiodide had mp 184-185°. Found %: I 31.4; N 6.8. $C_{14}H_{21}N_2O_2S$. Calculated %: I 31.1; N 6.9.

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