

STEREOCHEMISTRY OF BENZO[b]QUINUCLIDINES
 I. ESTABLISHMENT OF THE CONFIGURATIONS OF 3- AND 2,3-
 SUBSTITUTED BENZO[b]QUINUCLIDINES BY PMR SPECTROSCOPY

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The PMR spectra of several 3- and 2,3-substituted benzo[b]quinuclidines were studied. It is shown that the following can be used to establish the configurations of this series of compounds: the differences in the chemical shifts of the protons of the quinuclidine ring in the syn and anti orientations relative to the benzene ring, the shift in the signals of the protons of the alkyl groups of a substituent relative to the signals of the same protons in the analogous quinuclidine derivative, and the stereospecificity of the long-range, spin-spin interaction constants of the protons of the quinuclidine ring.

PMR spectroscopy has often been used to determine the structures of quinuclidine derivatives [1-5]. In this paper we examine the application of this method to the study of the stereochemistry of compounds of the benzo[b]quinuclidine [6,7] and quinuclidine [5,8-10] series that contain similar substituents.*



I, VIII R = R' = H; II, IX_s α R = H, R' = OH; III, X_s α R = H, R' = OCOCH₃; IV, XI_s R = H, R' = NH₂; V, XII R = H, R' = -O;
 VI, XIII_s α R = COOC₂H₅, R' = -O; VII, XIV_s R = COOC₂H₅,
 R' = OH (*cis*)

The peculiarities of the PMR spectra of benzo[b]quinuclidines are determined by the presence in their molecules of a benzene ring, which is characterized by great anisotropy of the magnetic susceptibility. The presence of this group leads to simplification of the spectrum due to the difference in the chemical shifts of the geminal protons of the quinuclidine ring in the syn or anti orientation relative to the benzene ring. A qualitative evaluation of the effect of the anisotropy of the magnetic susceptibility of the benzene ring on the chemical shift of these protons makes it possible to assign the signals at relatively weaker field for VIII to the protons in the anti orientation relative to the benzene ring (Table 1).

For an assignment of this sort, which is also confirmed by a study of the long-range, spin-spin interaction constants (see below), we compared the measured and calculated (from the tables of Johnson and Bovey [11]) values of the change in the chemical shifts of the α and β protons in VIII relative to I (Table 2). The calculation was carried out using the geometrical parameters of benzo[b]quinuclidine obtained by a study of the Dreiding molecular models.

It follows from Table 2 that there is correlation between the calculated value and experimental value for unsubstituted benzo[b]quinuclidine in the case of the β protons. However, the measured value

*Here and elsewhere, the letters s or a after the compound number correspond to the isomer with the syn or anti orientation of the substituent relative to the benzene ring.

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TABLE 1. Chemical Shifts of the Protons of the Quinuclidine Ring in Benzo[b]quinuclidine Derivatives

Compound	Chemical shifts δ , ppm										
	2s*	2a*	3s	3a	4	7s	7a	8s	8a	CH ₃	CH ₂
VIII	2,69	3,18	1,53	1,84	3,08	3,69	3,18	1,53	1,84		
IX _s †	2,97	4,02	—	4,57	3,57	3,13	3,58	1,93	2,11		
IX _a †	3,60	3,33	4,20	—	3,55	3,30	3,80	1,68	2,59		
X _s	2,52	3,54	—	5,07	3,29	2,61	3,03	1,55	2,02	1,86	
X _a	3,18	2,84	4,75	—	3,34	2,75	3,26	1,41	2,23	2,09	
XI _s †	3,37	4,25	—	4,35	—	—	—	—	—	—	—
XII	3,19	3,43	—	—	3,68	2,92	3,25	2,01	2,30		
XIII _s	—	4,23	—	—	3,79	2,95	3,33	2,1	2,4	1,06	4,06
XIII _a	3,90	—	—	—	3,76	2,8	3,8	—	—	1,28	4,33
XIV _s	—	4,04	—	4,47	3,36	2,66	3,20	1,5	2,0	1,22	4,11

*The s and a indices correspond to syn or anti orientations of the proton relative to the benzene ring.

† See Experimental.

TABLE 2. Calculated and Measured Changes in the Chemical Shifts of the Protons of the Quinuclidine Ring in VIII Relative to I*

	β_a	β_s	$\Delta\beta$	α_a	α_s	$\Delta\alpha$	γ
Calculation	0,22	-0,03	0,25	0,24	0,01	0,23	0,73
Experiment	0,33	0,02	0,31	0,34	-0,15	0,49	1,36

*The δ values are given in parts per million. $\beta_a = \delta_{H-\beta\text{-anti}}(\text{VIII}) - \delta_{H-\beta}(\text{I})$, etc.; $\Delta\beta = \beta_a - \beta_s$, etc.

$$\Delta\alpha = \alpha_a - \alpha_s = \delta_{H-\alpha\text{-anti}}(\text{VIII}) - \delta_{H-\alpha\text{-syn}}(\text{VIII})$$

proved to be twice the calculated value as a consequence of a shift in the signal of the α -syn proton to strong field as compared with the calculated value and with the corresponding value for the β -syn proton. This deviation may be associated with the disparity between the geometry of the model and that of the real benzo[b]quinuclidine molecule, in which the α -syn protons are apparently drawn in toward the benzene ring.

The introduction of substituents into the quinuclidine ring causes the greatest changes in the chemical shifts of the protons in the gem, cis, and trans positions relative to the substituent. A comparison of the chemical shifts of these protons in substituted and unsubstituted quinuclidines makes it possible to find increments D_g , D_c , and D_t for the gem, cis, and trans effects of the substituents (Table 3).

The increments found were used for a semiempirical calculation of the chemical shifts of the protons in the 3- and 2,3-substituted benzo[b]quinuclidines and to establish the configurations of these compounds. In the calculation it was assumed that the chemical shift of each of the protons attached to the C_2 or C_3 atoms is equal to the sum of three values: 1) the chemical shift of the corresponding proton in the unsubstituted quinuclidine [$\delta_{H-\alpha}(\text{I})$ or $\delta_{H-\beta}(\text{I})$]; 2) the increment that characterizes the substituent effect (D_c , D_t , or D_g); 3) the experimental increment for the α or β proton that reflects their syn or anti orientation relative to the benzene ring (α_s , α_a , β_s , or β_a). The values obtained are compared with the measured shifts in Table 4.

It follows from Table 4 that the deviation between the calculated and experimental value is substantially less than the difference in the shifts of the identically oriented (relative to the substituent) protons in the two isomers. The assignment of the configurations of pairs of diastereomers of IX and X indicated in Table 4 is therefore the only one that satisfies the values of the chemical shifts. In the case of 3-amino-benzo[b]quinuclidine (XI), the data presented in Table 4 indicate a syn orientation of the amino group relative to the benzene ring.

TABLE 3. Chemical Shifts of the Protons of the C₍₂₎ - C₍₃₎ - C₍₄₎ Fragment and Increments of the Effects of Substituents in Quinuclidine Derivatives*

Compound	δ_{H_g}	$\delta_{H_c}; \delta_{H_t}$	δ_{H_g}	δ_{H_4}	δ_R	D_C	D_t	D_g
I		2,84	1,51	1,72				
I†		3,27	1,87	2,11				
II† 3-OH		3,01; 3,54	4,24	2,16		-0,26	0,27	2,37
III 3-OCOCH ₃		2,62; 3,23	4,76	1,96	2,05	-0,22	0,39	3,25
IV† 3-NH ₂		3,43; 3,82	3,95	2,48		0,16	0,55	2,08
V 3=O		3,27		2,42				
VI 3=O								
2-COOC ₂ H ₅	3,98			2,41	1,21; 4,13			1,14‡
VII 3-OH								
2-COOC ₂ H ₅	3,54		4,12	2,04	1,33; 4,27			

* The shifts (δ) are given in parts per million; $D_C = \delta_{H_2C} - \delta_{H_2(I)}$, etc.

† See Experimental.

‡ This is the overall effect of COOC₂H₅ substituents in the 2-position and of C=O substituents in the 3-position

TABLE 4. Measured and Calculated Chemical Shifts of the Protons of the N₍₁₎ - C₍₂₎ - C₍₃₎ - C₍₄₎ Fragment of Substituted Benzo[b]quinuclidines*

Compound	H _{2-syn}		H _{2-anti}		H _{3-syn}		H _{3-anti}	
	calc.	exp.	calc.	exp.	calc.	exp.	calc.	exp.
IX s	2,86	2,97	3,88	4,02			4,57	4,57
IX a†	3,35	3,33	3,39	3,60	4,26	4,20		
X s	2,47	2,52	3,57	3,54			5,09	5,07
X a	3,08	3,18	2,96	2,84	4,78	4,75		
XI s†	3,28	3,37	4,16	4,25			4,28	4,35
XI a†	3,67		3,77		3,97			
XIII s	3,83	3,90						
XIII a			4,32	4,23				

* The shifts are given in parts per million.

† See Experimental.

TABLE 5. Long-Range SSIC (⁴J_{H_{2-S}-H_{7-S}} and ⁴J_{H_{3-S}-H_{8-S}}) in Benzo[b]quinuclidine Derivatives

	IXs	IXa	Xs	Xa	XIIIa
⁴ J _{H_{2-S}-H_{7-S}} , Hz	2,7	2,5	2,5	2,3	2,2
⁴ J _{H_{3-S}-H_{8-S}} , Hz	(2,7)*	(8,8)*	(3,3)*	(7,9)*	

* The vicinal ³J_{H_{2-S}-H₃} SSIC are indicated in parentheses in Hertz units.

The application of this method to disubstituted benzo[b]quinuclidines XIII and XIV demonstrates that the COOC₂H₅ group in isomers XIII and XIV are in the syn orientation relative to the benzene ring. The OH group in XIV is also in the same orientation.

The conformity of the calculated (from increments) and measured values of the δ protons of the quinuclidine ring in Xs and Xa attests to an additive effect of the OCOCH₃ group and the benzene ring on the chemical shifts; this is possible only for a sufficiently weak interaction of these groupings. It hence follows that the difference in the shifts of the methyl protons of the OCOCH₃ group in Xs, Xa and III is determined

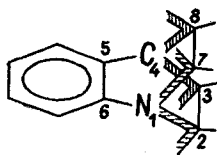


Fig. 1. Stereospecificity of the 4J SSIC of the protons of the quinuclidine ring of benzo[b]-quinuclidine.

as well as in VII and XIVs (Tables 1 and 3). Thus a comparison of the chemical shifts of the alkyl groups of a substituent is an independent method of determining the configuration of substituted benzo[b]quinuclidines.

The stereospecificity of the long-range (through four σ bonds) spin-spin interaction constants (SSIC) of the protons in the various fragments of the quinuclidine ring can also be used to solve this problem. According to the literature data with respect to the PMR spectra of alicyclic compounds, the maximum long-range SSIC were observed for trans-trans orientation of the interacting protons (all of the bonds lie in a single plane and correspond to trans orientation of the atoms) [12, 13]. This sort of "double zig-zag" or "M-path of interaction" geometry in the examined benzo[b]quinuclidine derivatives is also realized for the H_{2-s} and H_{7-s} α -protons and the H_{3-s} and H_{8-s} β -protons (Fig. 1).

A study of the PMR spectra of the benzo[b]quinuclidine derivatives demonstrated that the 4J constants of protons that interact via an M path reach 2.7 Hz and considerably exceed the remaining long-range constants, which do not exceed 0.7 Hz.

The absence of this sort of interaction is therefore readily detected from the character of the multiplicity of the signal of the proton in the gem-position relative to the substituent and serves as a proof of the substitution of the corresponding syn proton of the quinuclidine ring of benzo[b]quinuclidine in IXs, Xs, XI, XIII, and XIVs. The configuration of a compound can also be similarly established from the character of the multiplicity of the other protons of the $N_{(1)} - C_{(2)} - C_{(3)} - C_{(4)}$ fragment (see Table 5). In so doing, it is necessary to take the inequality $J_{H_2-H_3}(\text{cis}) > J_{H_2-H_3}(\text{trans})$ into account in addition to the expressions $^4J_{H_{2-s}-H_{7-s}} \gg J_{H_{2-a}-H_{7-s}}$, $^4J_{H_{2-s}-H_{7a}}$, and $^4J_{H_{2-a}-H_{7-a}}$.

EXPERIMENTAL

The PMR spectra were obtained with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz. The compounds that are marked with asterisks in the tables were studied as hydrochlorides in D_2O solutions; the internal standard under these conditions was dioxane (δ 3.70 ppm). Deuteriochloroform was used as the solvent for the remaining compounds with tetramethylsilane as the internal standard.

Diastereomeric 3-Hydroxybenzo[b]quinuclidines (IXs and IXa). A. A solution of 11.6 g (6.7 mmole) of 2-hydroxybenzo[b]quinuclidine (XII) in 67 ml of isopropyl alcohol was added rapidly to a suspension of 6.9 g (300 mmole) of sodium in 150 ml of anhydrous toluene. The mixture was refluxed for 5 h, cooled, and 50 ml of water and hydrochloric acid were added until the mixture gave an acid reaction to Congo Red. The aqueous layer was separated, made alkaline with potassium carbonate, and extracted with ether and chloroform. The ether solution yielded a mixture of IXs and IXa, while the chloroform extract gave primarily IXs, which was free of IXa after recrystallization from ethyl acetate. The overall yield of IX was 10.6 g (91.2%), and IXs melted at 169-170°. Alcohol IXa was isolated by the method described below.

B. Sodium borohydride [2 g (52 mmole)] was added in very small portions to a solution of 2 g (11.5 mmole) of XII in 70 ml of methanol. The mixture was held at 20° for 20 h, refluxed for 5 h, and vacuum evaporated. The residue was mixed with 15 ml of water, and the mixture was made alkaline with potassium carbonate and extracted with ether and chloroform to give 1.8 g (90%) of IXs and IXa.

The ratio of the diastereomeric alcohols (IXs and IXa) obtained by the different methods of reduction of the ketone (XII) was determined by gas-liquid chromatography (GLC). According to GLC (20% E-301 adsorbent, gas flow rate 6-7 liters/h, column temperature 185°), the ratio of IXs and IXa was as follows: 70:30 for reduction by sodium in ethanol; 40:60 for reduction by sodium in isopropyl alcohol; 62.8:37.2 for reduction by sodium borohydride; 68:32 for catalytic reduction over platinum in acetic acid.

3-(p-Nitrobenzoyloxy)benzo[b]quinuclidine (XVa). A solution of 4 g (22.8 mmole) of a mixture of IXs and IXa (40 : 60) and 4.3 g (25 mmole) of p-nitrobenzoyl chloride in 90 ml of chloroform was held at 20° for 50 h and refluxed for 5 h. The chloroform was removed in vacuo, and the residue was triturated with acetone to give 5.8 g (70.5%) of a mixture of esters XVs and XVa, which was refluxed with 150 ml of anhydrous ethanol. The undissolved crystals were filtered and washed with ether to give 1.6 g (19.5%) of the hydrochloride of XVa with mp 268–270°. Found %: C 60.0; H 4.9; Cl 10.1; N 8.0. $C_{18}H_{16}N_2O_4 \cdot HCl$. Calculated %: C 60.0; H 4.7; Cl 9.8; N 7.8.

3-Acetoxybenzo[b]quinuclidine (Xa). A 6 g (34 mmole) sample of a mixture of IXs and IXa (obtained by reduction of XII with sodium in isopropyl alcohol) and 30 ml of acetic anhydride were heated at 100° for 2 h to give 6 g (81%) of a mixture of Xs and Xa with bp 120–124° (0.8 mm). After standing at 3–5° for 50 h, the crystals that formed were filtered and washed with a small amount of petroleum ether to give 1.7 g of Xa with mp 38–40°. The hydrochloride had mp 125–126° (from ethyl acetate). Found %: C 61.4; H 6.4; Cl 13.9; N 5.5. $C_{13}H_{15}NO_2 \cdot HCl$. Calculated %: C 61.7; H 6.4; Cl 14.0; N 5.5.

3-Hydroxybenzo[b]quinuclidine (IXa). A mixture of 1.4 g (3.9 mmole) of XVa and 15 ml of 17% HCl was refluxed for 8 h. The precipitated p-nitrobenzoic acid was extracted with ether, and the hydrochloric acid solution was vacuum evaporated. The residue was made alkaline with 50% KOH and extracted with chloroform to give 0.4 g (68%) of IXa with mp 160–161°. Chromatography on paper with a butanol–water–acetic acid system (4 : 5 : 1) gave R_f 0.68. Alcohol IXs had R_f 0.54 under the same conditions. Found %: C 75.2; H 7.1; N 8.1. $C_{11}H_{13}NO$. Calculated %: C 75.4; H 7.5; N 8.0.

B. A mixture of 1.7 g (7.8 mmole) of Xa and 20 ml of 17% HCl was refluxed for 4 h. The subsequent workup was similar to that described above to give 1.22 g (87.5%) of Xa with mp 160–161°.

C. A 0.8 g sample of a mixture of IXs and IXa was chromatographed with a 60 × 2.5 cm column filled with 100 g of activity II aluminum oxide. The column was washed with 200 ml of petroleum ether, and IXa was then eluted with 75 ml of petroleum ether–ether (3 : 2). The eluate yielded 0.1 g of IXa with mp 160–161°.

2-Ethoxycarbonyl-3-hydroxybenzo[b]quinuclidine (XIII). A 65 g (0.22 mole) sample of 1-ethoxycarbonyl-methyl-4-ethoxycarbonyl-1,2,3,4-tetrahydroquinoline was cyclized in the presence of potassium ethoxide [obtained from 27 g (0.7 mole) of potassium and 42 ml of ethanol] in 180 ml of anhydrous toluene [6]. The reaction mixture was refluxed for 6 h and cooled. The toluene was decanted from the caramel-like mass, which was cooled and treated with 41.5 g (0.7 mole) of acetic acid (as a 10% aqueous solution). Anhydrous potassium carbonate [48.8 g (0.35 mole)] was added gradually to the resulting solution, and the mixture was extracted with chloroform. The chloroform solution was dried with magnesium sulfate, and evaporated, and the residue was vacuum distilled to give 16.8 g (30.7%) of XIII as a viscous, colorless liquid that was quite soluble in organic solvents and had bp 140–141° (0.6 mm). Found %: C 68.5; H 6.1; N 5.7. $C_{14}H_{15}NO_3$. Calculated %: C 68.8; H 6.2; N 5.9.

cis-2-Ethoxycarbonyl-3-hydroxybenzo[b]quinuclidine (XIVs). A solution of 0.95 g (4 mmole) of XIII in 20 ml of anhydrous ethanol and 0.1 g of platinum oxide was shaken with hydrogen. After one equivalent of hydrogen had been absorbed, the platinum was filtered, the alcohol was removed by vacuum distillation, and the residue was triturated with ether to give 0.9 g (93.6%) of XIVs as colorless crystals with mp 133–135°. Found %: C 67.9; H 7.1; N 5.8. $C_{14}H_{17}NO_3$. Calculated %: C 68.0; H 6.9; N 5.7.

LITERATURE CITED

1. M. V. Rubtsov, L. N. Yakhontov, and L. I. Mastafanova, *Zh. Obshch. Khim.*, **33**, 1180 (1963).
2. G. V. Binst, J. C. Nouls, J. Stokoe, C. Danheux, and R. H. Martin, *Bull. Soc. Chim. Belg.*, **74**, 506 (1965).
3. L. N. Yakhontov, L. I. Mastafanova, K. F. Turchin, Yu. N. Sheinker, and M. V. Rubtsov, *Dokl. Akad. Nauk SSSR*, **168**, 1085 (1966).
4. E. E. Mikhlina, V. Ya. Vorob'eva, K. F. Turchin, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin.*, 1083 (1968).
5. K. F. Turchin, E. E. Mikhlina, V. Ya. Vorob'eva, A. D. Yanina, Yu. N. Sheinker, and L. N. Yakhontov, *Dokl. Akad. Nauk SSSR*, **192**, 823 (1970).
6. A. D. Yanina, E. E. Mikhlina, K. A. Zaitseva, M. D. Mashkovskii, and L. N. Yakhontov, *Khim.-Farmats. Zh.*, No. 8, 7 (1969).
7. E. E. Mikhlina, A. D. Yanina, L. N. Yakhontov, K. A. Zaitseva, L. F. Roshchina, and M. D. Mashkovskii, *Khim.-Farmats. Zh.* (in press).

8. E. E. Mikhlina and M. V. Rubtsov, *Zh. Obshch. Khim.*, 30, 163 (1960).
9. E. E. Mikhlina, V. Ya. Vorob'eva, and M. V. Rubtsov, *Khim. Geterotsikl. Soedin.*, 243 (1966).
10. L. N. Yakhontov and M. V. Rubtsov, *Zh. Obshch. Khim.*, 29, 2343 (1959).
11. C. E. Johnson and F. A. J. Bovey, *J. Chem. Phys.*, 29, 1012 (1958).
12. N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* (1964).
13. V. F. Bystrov and A. U. Stepanyants, *J. Mol. Spectr.*, 21, 241 (1966).