STEREOCHEMISTRY OF BENZO[b]QUINUCLIDINES

III.* SYNTHESIS AND CONFIGURATION OF 3-HYDROXY-3-ALKYL(ARALKYL, ARYL)BENZO[b]QUINUCLIDINES

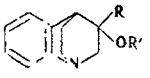
E. E. Mikhlina, K. F. Turchin, A. D. Yanina, Yu. N. Sheinker, and L. N. Yakhontov

UDC 547.834.4.07:541'632:543.422.25

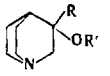
The stereochemistry of the reaction of 3-hydroxybenzo[b]quinuclidine with organometallic compounds was studied. It was observed that 3-aryl-3-hydroxybenzo[b]quinuclidines are readily converted to 3-arylquinolines on heating with acetic anhydride.

In our preceding communications [1, 2] we have described some regularities with regard to the stereospecificity of the reduction of the carbonyl group and the cyanohydrin synthesis in the 3-oxobenzo[b]quinuclidine series.

The reaction of 3-oxobenzo[b]quinuclidine with organolithium and organomagnesium compounds gave 3-hydroxy-3-alkyl(aralkyl, aryl)benzo[b]quinuclidines (I, III, V, and VII), in which I and III are formed as a mixture of syn and anti isomers with predominance of the anti form, while V and VII are obtained practically entirely in the form of individual anti isomers. The observed stereospecificity of the reaction of lithium and halomagnesium derivatives with 3-oxobenzo[b]quinuclidine is possibly determined by the fact that the indicated reagents form, with the phenyl portion of the molecule, unstable donor–acceptor complexes [3] that hinder the approach of the organometallic compounds to the reaction center on the phenyl ring side. As a result, RLi or RMgBr attack the carbonyl group primarily or exclusively from the sterically more hindered position – on the side of the bridge fragment of the molecule – and this leads to the formation of the anti isomers.



I–VIII



IX–XIV

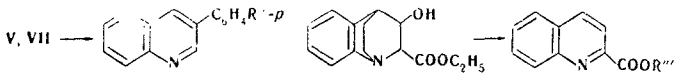
I, IX R=CH_3, R′=H; II R=CH_3, R′=$COCH_3$; III, X R=$C_6H_5CH_2$, R′=H; IV, XI R=$C_6H_5CH_2$, R′=$COCH_3$; V, XII R=C_6H_5, R′=H; VI R=C_6H_5, R′=$COCH_3$; VII, XIII R=*p*-$CH_3C_6H_4$, R′=H; VIII, XIV R=*p*-$CH_3C_6H_4$, R′=$COCH_3$.

In a study of the properties of 3-substituted 3-hydroxybenzo[b]quinuclidines it was observed that compounds that contain aryl substituents (Va and VIIa)† are readily aromatized on heating with acetic anhydride. The process is accompanied by dehydration and ejection of the ethylene bridge from the quinuclidine portion of the molecule; this leads to 3-arylquinolines (XV, XVI). Similarly, when 2-carbethoxy-3-hydroxybenzo[b]quinuclidine (XIX) is refluxed with acetic anhydride it is converted to 2-carbethoxyquinoline (XVII). It should be noted that 3-hydroxy-3-arylquinuclidines and cis- and trans-2-carbethoxy-3-hydroxyquinuclidines under similar conditions form either the corresponding acetoxy derivatives or substituted Δ^2-dehydroquinuclidines [4].

*See [2] for communication II.

†The letter s (or a) after the number of the compound indicates syn (or anti) orientation of the substituent (R) relative to the benzene ring of benzo[b]quinuclidine.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 839–843, June, 1973. Original article submitted June 19, 1972.



XV, XVI XIX XVII, XVIII

XV $R''=H$; XVI $R''=CH_3$; XVII $R'''=C_2H_5$; XVIII $R'''=H$

The described transformations are apparently associated with the considerable gain in energy on passing from the benzo[b]quinuclidine system to the aromatic quinoline system.

The configurations of I-VIII and the structures of quinoline derivatives XV-XVII were determined by means of the PMR spectra. Quinuclidine derivatives IX-XIV were used as model compounds.

The establishment of the configuration was based on the shift, under the influence of the anisotropy of the magnetic susceptibility of the benzene ring, of the signals of the protons of the identical substituents of diastereomeric benzo[b]quinuclidines to strong or weak field with respect to the signals of the analogous quinuclidine derivatives. The effect of the magnetic anisotropy of the benzene ring on the chemical shifts of the protons of the CH_3 and $CH_2C_6H_5$ groups was calculated from the table of Johnson and Bovey [5] for the syn and anti configurations of I-IV. The calculation was made for the staggered conformation relative to the $C_{(3)}-C_{sub}$ bond [6]. It was assumed that for III and IV, as well as for I and II, the three staggered conformations are equally probable.

The results of the calculations, which are presented in Table 1, show that the anisotropic effect leads to a shift to strong field of the signal of the protons of the substituent in the syn orientation relative to the ring and to weak field when the orientation is anti. Thus the following relationship should be satisfied for the chemical shifts of the substituent protons*:

(A) δ^{syn}benzo[b]quinuclidine < δquinuclidine < δ^{anti}benzo[b]quinuclidine.

An analysis of the data in Table 1 indicates the good agreement between the calculated and experimental changes in the chemical shifts of the protons of the substituents in diastereomeric I-II relative to the corresponding quinuclidine derivatives. In the case of III and IV the discrepancies are appreciably greater; this is apparently explained by the different concentrations of the three possible conformers relative to the $C_{(3)}-C_{sub}$ bond.

The determination of the configurations of the diastereomeric 3-acetoxy-3-methyl(benzyl)benzo[b]-quinuclidines (II, IV) made it possible to detect the character of the effect of the benzene ring on the chemical shifts of the protons of the methyl group of substituent $OCOCH_3$ in these compounds. According to the data in Table 2, in which the chemical shifts of the protons of I-XIV are presented, expression (A) turns out to be valid also for the signals of the protons of substituent $OCOCH_3$. We have previously shown the validity of expression (A) for the signals of the protons of the methyl and ethyl groups of substituents $OCOCH_3$, $COOCH_3$, and $COOC_2H_5$ in the case of monosubstituted benzo[b]quinuclidines [2]. Thus expression (A) has proved to be quite universal, and this has made it possible to use it for establishing the configurations of 3-acetoxy-3-phenyl(p-tolyl)benzo[b]quinuclidines (VI, VIII). These acetates and the corresponding alcohols (V and VII) were obtained as one diastereomer. A comparison of the chemical shifts of the pro-

*Calculations made within the dipole approximation for a number of angles of rotation about the $C_{(3)}-C_{sub}$ bond have shown that relationship (A) is valid for any conformation relative to this bond.

TABLE 1. Change in the Chemical Shifts of the Protons of the Alkyl Groups of Substituents in Benzo[b]quinuclidine Derivatives I-IV Relative to the Corresponding Quinuclidine Derivatives IX-XI

$\Delta\delta$	Calc.	Exptl.			
		I-CH_3*	II-CH_3	III-$CH_2C_6H_5$	IV-$CH_2C_6H_5$†
anti‡	0,15	0,19		0,26	0,21 0,12
syn‡	−0,32	−0,25		−0,37	−0,51 −0,48
$\delta_{anti} - \delta_{syn}$	0,47	0,44	0,56	0,63	0,72 0,60

*Protons for which the data are presented are given in boldface.

†The protons of the $CH_2C_6H_5$ group are nonequivalent.

‡For I, for example, $\Delta\delta_S$ is determined as δ_{CH_3} (I) − δ_{CH_3} (IX).

TABLE 2. Chemical Shifts of the Protons of I-XIV (δ, ppm)

Compound	2s	2a	4	7s	7a	8s	8a	$OCOCH_3$	Other groups
Ia	2,73	3,05	2,99	~2,6	~3,0	~1,6	~2,0	—	1,47 (3-CH_3)
Is	~2,7	3,11	2,95	~2,7	3,28	1,37	~2,7	—	1,03 (3-CH_3)
IIa	3,07	3,07	3,76	~2,7	~3,05	~1,65	~2,05	1,68	1,78 (3-CH_3)
IIs	2,76	3,39	3,57	2,68	3,18	1,37	2,21	2,09	1,22 (3-CH_3)
IIIa	2,73	3,10	2,91					—	3,05 (3-$CH_2C_6H_5$)
IIIs	2,74	3,09	2,96	2,71	3,26	1,28	2,39	—	2,42 (3-$CH_2C_6H_5$)
IVa	3,09	3,32	3,59	2,76	3,10	~1,60	2,25	1,61	3,42 3,70 (3-$CH'H''C_6H_5$)
IVs	2,98	3,43	3,57					2,06	2,70 3,10 (3-$CH'H''C_6H_5$)
Va	2,93	3,84	3,29	~2,65	3,10	~1,45	~1,70	—	
VIa	3,24	4,07	3,73	~2,65	~3,20	1,60		1,64	
VIIa	2,93	3,82	3,29					—	2,38 (p-CH_3=C_6H_4=)
VIIIa	3,23	4,03	3,77	~2,70	~3,20			1,64	2,35 (p-$CH_3C_6H_4$=)
	C_2H'	C_2H''							
IX	~2,7	~2,7						—	1,28 (3-CH_3)
X	2,75	2,94	1,65					—	2,79 (3-$CH_2C_6H_5$)
XI	3,21	3,09						2,00	3,21 3,58 (3-$CH'H''C_6H_5$)
XII	2,81	3,24						—	
XIII	2,76	3,16						—	2,34 (3-p-$CH_3C_6H_4$=)
XIV	3,28	3,65	2,54					1,97	2,33 (3-p-$CH_3C_6H_4$=)

TABLE 3. PMR Spectra of Quinolines

Compound	$\delta_{2\text{-H}}$	$\delta_{3\text{-H}}$	$\delta_{4\text{-H}}$	J_{24}	J_{34}	$\delta_{5\text{-H}-8\text{-H}}$	δ_{R_2}	δ_{R_3}
XV[a]	9,05	—	8,07	2,4	—	7,2—8,1		7,1—7,55 (C_6H_5)
XVI[a]	9,04	—	8,11	2,4	—	7,3—8,1		7,1—7,6 (C_6H_4); 2,40 (CH_3)
XVII[a]	—	8,00	8,25	—	8,5	7,4—8,3	1,51 (CH_3); 4,47 (CH_2)	
XVIII·HCl[b]	—	8,55	9,28	—[d]	8,4	8,0—8,6		
Quinoline[a] [8]	8,81	7,27	8,00	1,8	8,3	7,4—8,1		
Quinoline[c] [9]	9,11	8,19	9,23			8,05—8,40		

[a] In CCl_4. [b] In CD_3OD. [c] CF_3COOH. [d] In 3-substituted quinolines, J_{24} increases; for example, in 3-nitroquinoline, J_{24} = 2.7 Hz [8].

tons of the methyl groups of substituent $OCOCH_3$ in VIII and XIV indicates the shift in the signals of these protons in VIII to stronger field (Table 2); this attests to the syn orientation of the $OCOCH_3$ group in VIII. The signals of the protons of the CH_3 group of the tolyl substituent are shifted to weaker field in VIII relative to XIV; this attests to the anti orientation of this group with respect to the benzene ring and additionally confirms the configuration of VIII established above. A similar effect is observed for the same signals in VII relative to XIII.

The chemical shifts of the protons of the CH_3 group of $OCOCH_3$ coincide in VI and VIII; this indicates the same configurations of these compounds. Alcohols V and VII have the same configuration – with anti orientation of the aryl substituent. The spectra of the protons of the benzo[b]quinuclidine rings practically coincide for them.

The spectra of 3-phenyl(p-tolyl)quinolines (XV, XVI) obtained from V and VII (Table 3) contain only signals of aromatic protons and of the CH_3 group (in XVI).

The spectrum of 2-carbethoxyquinoline (XVII), obtained from 2-carbethoxy-3-hydroxybenzo[b]quinuclidine (XIX), contains, in addition to signals from the protons of the ethoxycarbonyl substituent, a group of multiplets that are affiliated with the protons of the benzene portion of the quinoline ring and, at very weak field, two doublets (a spectrum of the AB type) from the 3-H and 4-H protons ($J_{34} \simeq 8.5$ Hz). Two doublet proton signals (J = 2.4 Hz) (Table 3) are observed at weakest field. The close spectral parameters of the 2-H and 4-H protons in XV and XVI and in unsubstituted quinoline [5, 6] are in agreement with proposed structures XV and XVI. The absence of a signal at 8.5-9 ppm indicates replacement of the proton attached to $C_{(2)}$ of quinoline and is in agreement with structure XVII [5, 6].

EXPERIMENTAL

The PMR spectra of I-XVIII in $CDCl_3$ (I-XIV), CCl_4 (XV-XVII), and CD_3OD (XVIII·HCl) were obtained with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz. Tetramethylsilane was used as the internal standard.

syn- and anti-3-Methyl-3-hydroxybenzo[b]quinuclidines (Is and Ia). A solution of 8 g (46 mmole) of 3-oxobenzo[b]quinuclidine [7] in 80 ml of ether was added at 2-3° to methyllithium, obtained from 16.4 g (115 mmole) of methyl iodide and 1.62 g (0.23 g-atom) of lithium in 50 ml of ether. The mixture was refluxed for 6 h and treated with 70 ml of 25% potassium carbonate solution, after which the ether layer was separated, and the aqueous layer was extracted with ether. A total of 2.1 g (24%) of Ia with mp 156-157° (from ethyl acetate) precipitated from the ether solution. Found: C 76.2; H 7.8; N 7.2%. $C_{12}H_{15}NO$. Calculated: C 76.1; H 8.0; N 7.4%.

The ether mother liquor was evaporated, and the residue was triturated with hexane and recrystallized from ether–ethyl acetate to give 1.75 g (20%) of Is containing up to 10% Ia. The mixture had mp 145-146° (dec.). Found: C 76.4; H 8.0; N 7.3%. $C_{12}H_{15}NO$. Calculated: C 76.1; H 8.0; N 7.4%.

syn- and anti-3-Benzyl-3-hydroxybenzo[b]quinuclidines (IIIs and IIIa). A solution of 8 g (46 mmole) of 3-oxobenzo[b]quinuclidine in 100 ml of ether was added to benzylmagnesium chloride [from 14.65 g (116 mmole) of benzyl chloride and 2.81 g (0.116 g-atom) of magnesium in 55 ml of ether], and the mixture was allowed to stand for 20 h and was then treated with 10% HCl. The precipitate was separated, mixed with 25% potassium carbonate solution, and extracted with benzene. The benzene was removed by distillation, and the residue was triturated with ether–petroleum ether and recrystallized (4.8 g) from ethyl acetate to give 2.75 g (22.4%) of IIIa with mp 139-140°. Found: C 81.5; H 7.2; N 5.2%. $C_{18}H_{19}NO$. Calculated: C 81.5; H 7.2; N 5.3%. The hydrochloride had mp 232-233°. Found: Cl 11.6; N 4.9%. $C_{18}H_{19}NO \cdot HCl$. Calculated: Cl 11.8; N 4.6%.

The hydrochloric acid solution was extracted with ether, after which it was made alkaline with potassium carbonate and extracted with benzene. The benzene was removed by distillation, and the residue (4.4 g) was extracted with ether to give 3 g of a mixture of IIIs and IIIa, which was recrystallized from ether to give 0.9 g of IIIs containing 25% IIIa with mp 116-118°. Found: C 81.7; H 7.0; N 5.5%. $C_{18}H_{19}NO$. Calculated: C 81.5; H 7.2; N 5.3%.

anti-3-Phenyl-3-hydroxybenzo[b]quinuclidine (Va). A solution of 8 g (46 mmole) of 3-oxobenzo[b]-quinuclidine in 30 ml of ether was added at 5° to phenyllithium [from 10.9 g (72 mmole) of bromobenzene and 0.98 g (0.14 g-atom) of lithium in 60 ml of ether]. The mixture was allowed to stand for 20 h, after which it was refluxed for 2 h, cooled, and treated with 30 ml of water. The precipitate was removed by filtration to give 7.3 g (63%) of a product with mp 160-162° (from ethyl acetate). Found: C 81.5; H 7.1; N 5.6%. $C_{17}H_{17}NO$. Calculated: C 81.2; H 6.8; N 5.6%. The hydrochloride had mp 199-201°. Found: Cl 12.2%. $C_{17}H_{17}NO \cdot HCl$. Calculated: Cl 12.3%.

anti-3-(p-Tolyl)-3-hydroxybenzo[b]quinuclidine (VIIa). This compound was similarly obtained in 76% yield and had mp 190-191° (from ethyl acetate). Found: C 81.3; H 7.2; N 5.4%. $C_{18}H_{19}NO$. Calculated: C 81.4; H 7.2; N 5.3%.

3-(p-Tolyl)-3-hydroxyquinuclidine (XIII). This compound was obtained in 77.3% yield by the method used to obtain V and had mp 132-133°. Found: C 77.3; H 8.8; N 6.3%. $C_{14}H_{19}NO$. Calculated: C 77.4; H 8.8; N 6.5%. The hydrochloride had mp 203-204°.

syn- and anti-3-Methyl-3-acetoxybenzo[b]quinuclidines (IIs and IIa). A mixture of 3 g (16 mmole) of Ia and 10 ml of acetic anhydride was refluxed for 5 h, after which the solution was evaporated, and the residue was made alkaline with potassium carbonate and extracted with ether to give 2.2 g (60%) of IIa with mp 62-63° (from hexane). Found: C 73.0; H 7.3; N 6.1%. $C_{14}H_{17}NO_2$. Calculated· C 72.7; H 7.4; N 6.1%.

Similarly, pure IIs with mp 65-67° was obtained from a mixture containing 90% Is and 10% Ia. Found: C 72.9; H 7.2; N 6.3%. $C_{14}H_{17}NO_2$. Calculated: C 72.7; H 7.4; N 6.1%.

anti-3-Benzyl-3-acetoxybenzo[b]quinuclidine (IVa). This compound, with mp 132-133° (from ether), was obtained by the method used to prepare II. Found: C 78.4; H 6.5; N 4.8%. $C_{20}H_{21}NO_2$. Calculated: C 78.1; H 6.8; N 4.6%.

A mixture of acetoxy derivatives IVs and IVa with the same percentages of isomers and mp 92-94° was obtained from a mixture containing 75% IIIs and 25% IIIa. Found: C 78.5; H 6.6; N 4.6%. $C_{20}H_{21}NO_2$. Calculated: C 78.1; H 6.8; N 4.6%.

anti-3-(p-Tolyl)-3-acetoxybenzo[b]quinuclidine (VIII). A mixture of 2.65 g (10 mmole) of VIIa and 25 ml of acetyl chloride was refluxed for 3 h, after which the solution was worked up as in the prepara-

tion of II to give 1.2 g (39%) of a product with mp 128-130°. Found: C 78.0; H 6.5; N 4.6%. $C_{20}H_{21}NO_2$. Calculated: C 78.2; H 6.8; N 4.5%. The hydrochloride had mp 166-168°.

3-(p-Tolyl)-3-acetoxyquinuclidine (XIV). A mixture of 1.5 g (6.9 mmole) of XIII and 15 ml of acetic anhydride was refluxed for 25 h to give 1.4 g (73.2%) of a product with bp 146-148° (4 mm). Found: C 74.2; H 7.9; N 5.3%. $C_{16}H_{21}NO_2$. Calculated: C 74.1; H 8.2; N 5.4%.

3-Benzyl-3-acetoxyquinuclidine (XI). This compound with bp 144-145° (4 mm), was obtained by refluxing 3-benzyl-3-hydroxyquinuclidine with acetic anhydride for 25 h. Found: C 74.2; H 7.9; N 5.3%. $C_{16}H_{21}NO_2$. Calculated: C 74.1; H 8.2; N 5.4%.

Reaction of 3-Phenyl- (V), 3-(p-Tolyl)- (VII), and 2-Carbethoxy-3-hydroxy (XIX)benzo[b]quinuclidines with Acetic Anhydride. A. A mixture of 1.75 g (7 mmole) of Va and 17 ml of acetic anhydride was refluxed for 12 h, after which the solution was evaporated, and the residue was treated with potassium carbonate and extracted with benzene to give 0.9 g (64%) of 3-phenylquinoline (XV) with bp 149-151° (0.6 mm) and mp 51-52° [10]. Refluxing Va with acetic anhydride for 5 h gave a mixture of XV and 3-acetoxy-3-phenylbenzo-[b]quinuclidine (VI).

B. A mixture of 2.5 g (9.4 mmole) of VIIa and 25 ml of acetic anhydride was refluxed for 15 h to give 1.4 g (70%) of 3-(p-tolyl)quinoline (XVI) with mp 77-79°. Found: C 87.8; H 5.9; N 6.3%. $C_{16}H_{13}N$. Calculated: C 87.6; H 6.0; N 6.4%.

C. A mixture of 1.2 g (5 mmole) of 2-carbethoxy-3-hydroxybenzo[b]quinuclidine (XIX) [9] and 10 ml of acetic anhydride was refluxed for 5 h to give 0.75 g (74%) of 2-carbethoxyquinoline (XVII) with bp 132-133° (0.6 mm). Refluxing XVII with hydrochloric acid gave the monohydrate of the hydrochloride of quinaldinic acid (XVIII) with mp 184-185° (dec.) [11].

LITERATURE CITED

1. A. D. Yanina, K. F. Turchin, E. E. Mikhlina, L. N. Yakhontov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., 222 (1972).
2. K. F. Turchin, E. E. Mikhlina, Ya. D. Yanina, V. Ya. Vorob'eva, L. N. Yakhontov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., 981 (1971).
3. R. A. Abramovitch and C. S. Giam, Can. J. Chem., 42, 1627 (1964).
4. E. E. Mikhlina and M. V. Rubtsov, Zh. Obshch. Khim., 29, 2337 (1959).
5. C. E. Johnson and F. A. J. Bovey, J. Chem. Phys., 29, 1012 (1958).
6. E. Eliel, N. Allinger, S. Angyal, and T. Morrison, Conformational Analysis, Wiley (1965), p. 13.
7. A. D. Yanina, E. E. Mikhlina, K. A. Zaitseva, M. D. Mashkovskii, and L. N. Yakhontov, Khim.-Farmats. Zh., No. 8, 7 (1969).
8. P. J. Black and M. L. Heffernan, Austr. J. Chem., 17, 558 (1964).
9. E. Diaz and P. Joseph-Nathan, Spectrochim. Acta, 25A, 1547 (1969).
10. H. Hübner, Ber., 41, 482 (1908).
11. D. L. Hammick and A. M. Roe, J. Chem. Soc., 4545 (1952).