STEREOCHEMISTRY OF BENZO[b]QUINUCLIDINES

II.* SYNTHESIS AND CONFIGURATION OF SOME 3-MONO- AND 3,3-DISUBSTITUTED BENZO[b]QUINUCLIDINES

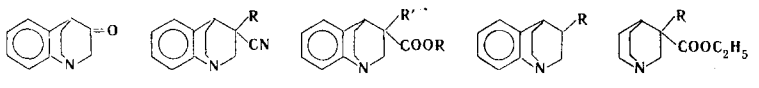
A. D. Yanina, K. F. Turchin,
E. E. Mikhlina, L. N. Yakhontov,
and Yu. N. Sheinker

UDC 547.854.4.07:541.67'63

Diastereomeric 3-carboxybenzo[b]quinuclidines were synthesized from 3-oxobenzo[b]-quinuclidine through its cyanohydrin, 3-alkoxycarbonyl-3-hydroxy(chloro)benzo[b]quinuclidines, and 3-hydroxymethylbenzo[b]quinuclidine. The configurations of the synthesized 3-mono- and 3,3-disubstituted benzo[b]quinuclidines were determined by means of the PMR spectra, and the stereospecificity of the reactions was followed.

The reduction of 3-oxobenzo[b]quinuclidine (I) under various conditions [1, 2] leads to a mixture of syn and anti isomers of 3-hydroxybenzo[b]quinuclidine. The predominant formation of the syn isomer in all cases except reduction of ketone I by sodium in isopropyl alcohol is probably due to steric factors – the freer approach to the reaction center of the catalyst (platinum) or the anion of the complex metal hydride (BH_4^-, AlH_4^-) from the phenyl ring side.

In the present paper, we examine the stereospecificity of the reaction of I with hydrogen cyanide as well as the stereochemistry of the transformations of cyanohydrin II through a number of intermediate steps to diastereomeric 3-carboxybenzo[b]quinuclidine.



I II, VIII III, IV, IX, XII–XV V–VII X, XI

II R = OH; III R = C_2H_5, R' = OH; IV R = C_2H_5, R' = Cl; V R = CH_2OH; VI R = COOH; VII R = $COOCH_3$; VIII R = Cl; IX R = C_2H_5, R' = $OCOCH_3$; X R = OH; XI R = H; XII R = H, R' = OH; XIII R = CH_3, R' = OH; XIV R = CH_3, R' = $OCOCH_3$; XV R = CH_3, R' = Cl

3-Oxobenzo[b]quinuclidine (I) was converted to a mixture of diastereomeric 3-hydroxy-3-cyano-benzo[b]quinuclidines (IIs and IIa)† in an isomer ratio of ~65 : 35 by reaction with acetone cyanohydrin. The quantitative characteristics of the reaction products indicate predominant nucleophilic attack of the CN group from the least shielded side of the molecule, i.e., from the phenyl ring side. However, since the reaction for the cyanohydrin synthesis is reversible, thermodynamic rather than kinetic factors – the lower free energy of IIs as compared with IIa – apparently are decisive in this case.

The alcoholysis of a mixture of IIs and IIa gave diastereomeric 3-hydroxy-3-ethoxycarbonylbenzo-[b]quinuclidines (IIIs and IIIa), from which the individual syn isomer (IIIs) was isolated by crystallization.

* See [2] for communication I.

† The letter s (or a) after the compound number in the text and in the tables indicates syn (or anti) orientation, relative to the benzene ring of benzo[b]quinuclidine, of the CN or COOR group in II–IV, VII–IX, XIII–XV, of the CH_2OH group in V, and of the COOH group in VI.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 222-228, February, 1972. Original article submitted March 16, 1971.

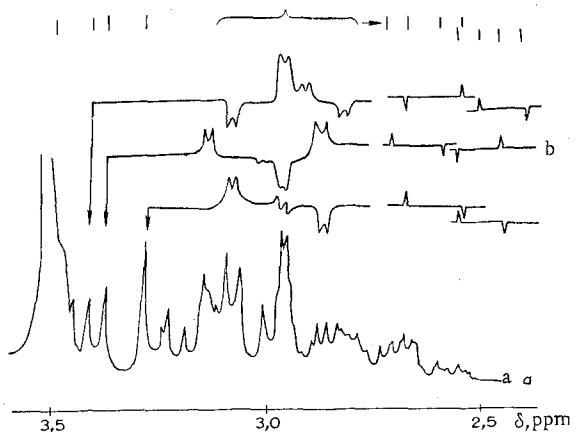


Fig. 1. Use of INDOR for the determination of the position of the spectral lines of protons of the $N-C_2HH''-C_3HR-C_4H$ link in VIIs: a) fragment of the PMR spectrum of protons of the quinuclidine ring in VIIs; b) experimental (left) and expected (right) spectra. The position of the lines of the spectrum of the $N-C_2H''-C_3H$ protons in VIIs is shown schematically above the spectrum.

Under the same conditions, syn hydroxy ester IIIs was obtained from pure syn isomer IIs. The retention of configuration on passing from II to III is associated with the fact that the alcoholysis of the CN group does not involve the asymmetric center at C_3. This is reflected in the fact that the ratio of the syn and anti isomers in the products of the alcoholysis of IIIs and IIIa is approximately the same as that in the mixture of starting hydroxynitriles IIs and IIa (68:32). Saponification of a mixture of IIIs and IIIa gave isomeric 3-hydroxy-3-carboxybenzo[b]quinuclidines XIIs and XIIa, which were converted to a mixture of syn- and anti-3-hydroxy-3-methoxycarbonylbenzo[b]quinuclidines (XIII) by esterification. Crystallization of the latter gave syn ester XIIIs. The synthesis of esters XIII through the corresponding acids is associated with the fact that the methanolysis of hydroxynitriles IIs and IIa gives lower yields (32-35%) because of the lower boiling point of methanol as compared with ethanol.

Hydroxyester IIIs forms anti-3-chloro-3-ethoxycarbonylbenzo[b]quinuclidine (IVa) on heating with thionyl chloride. Only anti isomer IVa was also isolated from the products of the reaction of IIIs and IIIa with thionyl chloride. A quantitative evaluation of the substances used in the reaction (IIIs : IIIa = 68:32) and of the substances obtained (overall yield 84% with 85% IVa) attests to the fact that syn hydroxyester IIIs reacts with thionyl chloride with inversion of configuration at C_3, while anti isomer IIIa reacts with retention of configuration. The presence of unchanged IIIa in the reaction products demonstrates that the rate of the reaction of IIIs with thionyl chloride is considerably higher than for IIIa. This is probably associated with steric factors – hindered approach of the reagent to the hydroxyl group of IIIa, which is shielded by the bridge fragment of the benzo[b]quinuclidine molecule. On the basis of these results, it can be assumed that syn hydroxy ester IIIs reacts with thionyl chloride via an Sn2 mechanism, while anti isomer IIIa reacts via a different mechanism. It should be noted that the formation of only anti-3-chloro-3-cyanobenzo-[b]quinuclidine (VIIIa) was observed in the reaction of a mixture of cyanohydrins IIs and IIa with thionyl chloride.

The reduction of anti-3-chloro-3-ethoxycarbonylbenzo[b]quinuclidine (IVa) with lithium aluminum hydride leads to a mixture of isomeric 3-hydroxymethylbenzo[b]quinuclidines (Vs and Va) in a ratio of 55:45. The partial inversion of configuration observed in this case can be explained by hydrogenolysis of the chlorine atom, not by direct nucleophilic attack of the complex metal hydride ion, which would lead to complete inversion of configuration, but by internal substitution of the chlorine atom by hydrogen in accordance with the mechanism proposed for the reduction of α-chloro esters [3].

A mixture of syn- and anti-3-carboxybenzo[b]quinuclidines (VIs and VIa), which are separated into individual syn and anti forms by crystallization, from which their methyl esters (VIIs and VIIa) were obtained, was obtained by oxidation of a mixture of alcohols Vs and Va with potassium permanganate.

The configuration and ratio of syn and anti forms during the formation of the mixture of diastereomers were determined on the basis of PMR spectroscopic data. As an example, the determination of the spectral parameters of the protons of the quinuclidine ring of VIIs in $CDCl_3$ was examined. In this spectrum, the two multiplets at strong field (δ 1.60 and 1.87 ppm), each with an intensity of one proton unit (pu), should be related to the signals of the C_8 protons. The signals of the remaining six protons (Fig. 1a) form a group of multiplets at 2.5-3.5 ppm. On the basis of the spin–spin coupling constants of the protons of the $N-C_2HH'-C_3HR-C_4$ fragment of the quinuclidine molecule in other compounds [4], it can be assumed that the lines at 3.28, 3.37, and 3.41 ppm correspond to three lines of the quartet of one of the protons attached to C_2. The expected (right-hand portion of the figure) and experimental (left-hand portion) INDOR spectra are in qualitative agreement, but a difference in the intensities and the presence of an additional splitting of the lines of the experimental spectrum are observed. The difference in the intensities is apparently associated with the strong interaction of two protons of the $N-C_2HH'-C_3HR-C_4$ fragment, which

TABLE 1. Chemical Shifts of Protons of the Quinuclidine Ring and of the Substituents in 3-Substituted Quinuclidines and Benzo[b]quinuclidines*

Compound	Chemical shifts, δ, ppm											
	syn-2-H†	anti-2-H	syn-3-H	anti-3-H	4-H	syn-7-H	anti-7-H	syn-8-H	anti-8-H	CH_2	CH_3	$COCH_3$
I	3,19	3,43	—	—	3,68	2,92	3,25	2,01	2,30			
IIs	3,45		—	—	3,62	~2,65	~3,15	1,36	~2,65			
IIa	~3,15	~3,80			3,60							
III_s	3,40	3,10	—	—	3,20	2,74	3,33	1,40	2,61	3,94	0,95	
IIIa										4,34	1,38	
IVa	3,82		—	—	4,70					4,31	1,34	
Vs	3,60	3,81	—	3,51	3,91	3,25	3,72	~1,9	2,35			
VIa	3,48	4,11	4,67	—	3,89	3,17	3,77	~1,7	2,24			
VIIs	3,04	3,37	—	2,90	3,50	2,72	3,14	1,60	1,87		3,52	
VIIa	2,89	3,58	2,61	—	3,45	2,67	3,25	1,41	1,96		3,77	
VIIIa	3,73	4,01	—	—	4,46	2,90	3,50	1,65				
IXs	3,74	3,01	—	—	3,49	2,75	3,20	1,43	2,36	3,91	0,96	2,16
IXa	2,65	4,25	—	—	3,37	2,65	3,20	1,45	1,85	4,27	1,30	1,83
	cis-2-H‡	trans-2-H	3-H		4-H	6-H, 7-H		5-H, 8-H		CH_2	CH_3	
X	3,55	2,82			1,95	2,82		1,6—2,15		4,26	1,32	
XI	3,25	3,02	2,57		2,14	2,85		1,60			3,70	

* For all compounds except II and VI, $CDCl_3$ was used as the solvent with tetramethylsilane (TMS) as the internal standard. The solvent for II was C_5H_5N with TMS as the standard. The hydrochlorides of VI were studied with D_2O as the solvent and dioxane (δ 3.70) as the standard. Compounds IIa, IIIa, and IXa were studied as mixtures with their diastereomers.

† The syn (or anti) orientation of the proton relative to the benzene ring of benzo[b]quinuclidine is indicated.

‡ The cis (or trans) orientation of the proton relative to the COOR group in the 3 position is indicated.

TABLE 2. Experimental and Calculated Chemical Shifts of 2-H and 3-H in Benzo[b]quinuclidines

Compound	Chemical shifts, δ, ppm					
	cis-2-H		trans-2-H		gem-3-H	
	exptl.	calc.	exptl.	calc.	exptl.	calc.
XI	3,25		3,02		2,57	
VIIs	3,04	3,10	3,37	3,36	2,90	2,90
VIIa	3,58	3,59	2,89	2,87	2,61	2,59

are affiliated with an ABX system rather than an AMX system. The additional splitting of the lines of the experimental INDOR spectrum is caused by vicinal interaction of 3-H with 4-H ($J_{3,4} \approx 2.7$ Hz) and long-range interaction of 2-H with 7-H ($J_{2S,7S} \approx 2.4$ Hz). The positions of all of the lines of the multiplets affiliated with the 2-H' and 3-H protons were determined by means of the INDOR method, which made it possible to find the chemical shifts and spin–spin coupling constants of these and the remaining protons (Table 1).

The spectral parameters of the protons of the quinuclidine ring in VIIa were established by a similar method and are also presented in Table 1.

The chemical shifts of the cis-2-H, trans-2-H, and gem-3-H protons, which are, respectively, in the cis, trans, and gem positions relative to the C_3 substituent, were calculated for two possible orientations (syn or anti) of the $COOCH_3$ group relative to the benzene ring of benzo[b]quinuclidine to determine the configurations of VIIs and VIIa. The calculation was performed via an additive scheme using the chemical shifts of the cis-2-H, trans-2-H, and gem-3-H protons in XI and increments $\alpha_s = -0.15$ ppm, $\alpha_a = -0.34$ ppm, $\beta_s = -0.02$ ppm, and $\beta_a = 0.33$ ppm, which were found in [2]. These increments correspond to shifts in the signals of the α-syn, α-anti-, β-syn, and β-anti protons of benzo[b]quinuclidine relative to the signals of the α and β protons of quinuclidine and reflect the orientation of these protons with respect to the benzene ring. The experimental and calculated values are compared in Table 2.

The data presented in Table 2 attest to complete agreement between the calculated and experimental chemical shifts and indicate syn orientation in VIIs and anti orientation in VIIa of the $COOCH_3$ substituent relative to the benzene ring.* The COOH groups in VIs and VIa are oriented in the same way.

The described assignment of the VIIs and VIIa configurations was also confirmed by a comparison of the chemical shifts of the CH_3 group of the $COOCH_3$ substituent in VIIs, VIIa, and XI. The signals of these protons, under the influence of the anisotropy of the magnetic susceptibility of the benzene ring of benzo-[b]quinuclidine, are shifted to stronger field in VIIs and to weaker field in VIIa as compared with XI. Similar shifts were noted previously for the CH_3 group of the $OCOCH_3$ substituent of isomeric 3-acetoxybenzo-[b]quinuclidines. The orientation of the ester group relative to the benzene ring of isomeric III was determined by the same path – comparison of the chemical shifts of the protons of the C_2H_5 groups (of the $COOC_2H_5$ substituents) in IIIs, IIIa, and X. The configurations of the two diastereomeric esters (IXs and IXa) were established on the basis of a comparison of the chemical shifts of the protons of both the methyl group of $OCOCH_3$ and of the methylene and methyl protons of the $COOC_2H_5$ groups in both compounds.

As pointed out above, only one anti form was obtained for 3-chloro-3-ethoxycarbonylbenzo[b]quinuclidine. In view of the absence of a second isomer and of the corresponding quinuclidine derivative, its structure was determined on the basis of an analysis of the chemical shifts of the protons of the C_2H_5 group of the $COOC_2H_5$ substituent in IV. These shifts practically coincide with the shift of the protons of the same groups in IIIa and IXa and differ markedly from the corresponding values in IIIs and IXs.

EXPERIMENTAL

3-Hydroxy-3-cyanobenzo[b]quinuclidines (IIs and IIa). A 4.5 g (53 mmole) sample of acetone cyanohydrin was added with stirring at 0°C to solution of 7.5 g (43 mmole) of 3-oxobenzo[b]quinuclidine (I) in 300 ml of water, and the mixture was stirred at 20° for 4 h. The resulting precipitate was removed by filtration, washed with water, and dried to give 7.3 g (90%) of a mixture of IIs and IIa (65 : 35) as colorless

* The long-range spin–spin coupling constants of the protons affiliated with different fragments of the quinuclidine ring are in agreement with the indicated assignment of the VIIs and VIIa configurations (see [2]).

crystals with mp 148-150°. Recrystallization from ethyl acetate gave IIs with mp 162-164°. Found: C 72.0; H 5.9; N 14.1%. $C_{12}H_{12}N_2O$. Calculated: C 72.1; H 6.1; N 14.0%.

anti-3-Chloro-3-cyanobenzo[b]quinuclidine (VIIIa). A mixture (3 g) of isomeric alcohols II and 15 ml of thionyl chloride was refluxed for 8 h and vacuum evaporated. The residue was made alkaline with 50% potassium carbonate solution and extracted with benzene to give 2.2 g (72%) of a mixture of isomeric chlorides VIII, from which VIIIa with mp 148-149° was isolated by crystallization from ether. Found: C 66.2; H 5.2; Cl 16.4; N 12.6%. $C_{12}H_{11}ClN$. Calculated: C 66.0; H 5.0; Cl 16.2; N 12.8%.

3-Hydroxy-3-ethoxycarbonylbenzo[b]quinuclidines (IIIs and IIIa). Dry hydrogen chloride was passed for 5 h through a refluxing solution of 25 g (0.125 mole) of a mixture of IIs and IIa in 300 ml of ethanol. The alcohol was removed by vacuum distillation, and the residue was treated with 25% potassium carbonate solution and extracted with chloroform to give 22 g (71%) of a mixture of IIIs and IIIa (68:32) with mp 70-75°. Found: C 68.0; H 6.7; N 5.9%. $C_{14}H_{17}NO_3$. Calculated: C 68.0; H 6.9; N 5.7%.

Crystallization from ether–petroleum ether (3:1) gave 9.2 g of IIIs with mp 86-88°.

3-Hydroxy-3-carboxybenzo[b]quinuclidines (XIIs and XIIa). A 21 g (85 mmole) sample of a mixture of IIIs and IIIa was refluxed for 5 h in 210 ml of 17% hydrochloric acid. The solution was vacuum evaporated, and the residue was triturated with acetone to give 20.9 g (95%) of a mixture of hydrochlorides of XIIs and XIIa with mp 227-228° (dec.). Found: C 56.2; H 5.4; Cl 13.7; N 5.4%. $C_{12}H_{13}NO_3 \cdot HCl$. Calculated: C 56.4; H 5.5; Cl 13.9; N 5.5%.

syn-3-Hydroxy-3-methoxycarbonylbenzo[b]quinuclidine (XIIIs). A 21 g (82 mmole) sample of a mixture of XIIs and XIIa, 250 ml of methanol, and 18.4 g of concentrated sulfuric acid was refluxed for 8 h. The alcohol was removed by vacuum distillation, and the residue was poured over ice. The ice mixture was made alkaline with 50% potassium carbonate solution and extracted with benzene and chloroform. The chloroform extract yielded 10 g of colorless crystals with mp 150-160°. Recrystallization from ethyl acetate gave 7.4 g (40%) of XIIIs with mp 178-179°. Found: C 67.3; H 6.6; N 6.2%. $C_{13}H_{15}NO_3$. Calculated: C 67.0; H 6.5; N 6.0%.

The benzene extract and mother liquor remaining after separation of XIIIs gave 7.8 g of a mixture of isomeric esters XIII with mp 130-133°. Three recrystallizations from ethyl acetate and ethyl acetate–hexane (3:1) gave 1.5 g of a mixture of XIIIa and XIIIs (4:1) with unalterable mp 140-142°.

syn-3-Acetoxy-3-methoxycarbonylbenzo[b]quinuclidine (XIVs). A 2 g (88 mmole) sample of XIIIs was refluxed in 10 ml of acetic anhydride for 8 h. The solution was vacuum evaporated, and the residue was treated with 25% potassium carbonate solution and extracted with ether to give 1.8 g (76%) of XIVs with mp 77-79° (from hexane). Found: C 65.8; H 6.0; N 5.2%. $C_{15}H_{17}NO_4$. Calculated: C 65.4; H 6.2; N 5.1%.

syn-3-acetoxy-3-ethoxycarbonylbenzo[b]quinuclidine (IXs). A 1.9 g sample of a mixture of IIIs and IIIa was acetylated as described above. Treatment of the viscous liquid mixture of IXs and IXa [bp 134-135° (0.6 mm)] with petroleum ether gave 1 g of IXs with mp 79-80°. Found: C 66.3; H 6.9; N 5.1%. $C_{16}H_{19}NO_4$. Calculated: C 66.4; H 6.7; N 4.8%. The mother liquor yielded 0.7 g of a mixture of IXs and IXa.

anti-3-Chloro-3-ethoxycarbonylbenzo[b]quinuclidine (IVa). A 6.9 g (28 mmole) sample of hydroxy ester III was mixed (with cooling) with 35 ml of thionyl chloride, and the mixture was then refluxed for 6 h. The excess thionyl chloride was removed by vacuum distillation, and the residue was treated with potassium carbonate and extracted with benzene to give 5 g (67%) of IVa as a viscous, oily liquid with bp 125-128° (0.3 mm). Found: C 63.4; H 6.2; Cl 13.4; N 5.4%. $C_{14}H_{16}ClNO_2$. Calculated: C 63.3; H 6.1; Cl 13.3; N 5.3%.

anti-3-Chloro-3-methoxycarbonylbenzo[b]quinuclidine (XVa). This compound [5.85 g (73%)] was similarly obtained from 7.4 g of XIIIs and had bp 145-147° (5 mm). Found: C 62.2; H 5.5; Cl 14.3; N 5.3%. $C_{13}H_{14}ClNO_2$. Calculated: C 62.1; H 5.6; Cl 14.1; N 5.6%.

3-Hydroxymethylbenzo[b]quinuclidines (Vs and Va). A 5 g sample of IVa was reduced with 3.5 g of lithium aluminum hydride in a mixture of 100 ml of ether and 160 ml of benzene. The mixture was refluxed for 7 h, 7 ml of water was added, and the aqueous mixture was extracted with benzene to give 2.8 g (74%) of a mixture of Vs and Va as a viscous liquid with bp 135-136° (0.4 mm). Found: C 75.8; H 7.8; N 7.6%. $C_{12}H_{13}NO$. Calculated: C 76.2; H 8.0; N 7.4%.

3-Carboxybenzo[b]quinuclidines (VIs and VIa). A solution of 6.73 g (42.5 mmole) of potassium permanganate in 130 ml of water was added gradually at 20° to a solution of 6 g (32 mmole) of a mixture of Vs and Va in 53 ml of 10% sulfuric acid. The manganese dioxide was removed by filtration and washed with hot water. The aqueous filtrates were evaporated, and the residue was dried and esterified by heating with 100 ml of methanol and 5 ml of concentrated sulfuric acid to give 4.15 g (60%) of a mixture of isomeric 3-methoxycarbonylbenzo[b]quinuclidines (VIIs and VIIa) with bp 116-122° (0.6 mm). Found: C 71.8; H 6.7; N 6.7%. $C_{13}H_{15}NO_2$. Calculated: C 71.9; H 7.0; N 6.4%.

A 4.15 g sample of a mixture of VIIs and VIIa and 50 ml of 17% hydrochloric acid was refluxed for 5 h and evaporated. The residue was triturated with acetone to give 3.4 g of a mixture of isomeric hydrochlorides of VIs and VIa. Two recrystallizations from ethanol gave 1 g of VIs with mp 246-247°. Found: Cl 15.0; N 5.7%. $C_{12}H_{13}NO_2 \cdot HCl$. Calculated: Cl 14.8; N 5.8%.

The mother liquor after removal of VIs yielded a mixture of the hydrochlorides of the isomeric acids, which, after three crystallizations from ethanol, gave 0.4 g of the hydrochloride of VIa with mp 228-229°. Found: Cl 15.0; N 6.0%. $C_{12}H_{13}NO_2 \cdot HCl$. Calculated: Cl 14.8; N 5.8%.

3-Methoxycarbonylbenzo[b]quinuclidines (VIIs and VIIa). These compounds were obtained by esterification of isomeric acids VIs and VIa by heating with methanolic hydrogen chloride. Compound VIIs had bp 120-122° (0.6 mm). Found: C 71.7; H 6.8; N 6.6%. Compound VIIa had bp 114-116° (0.6 mm). Found: C 71.7; H 6.8; N 6.4%. $C_{13}H_{15}NO_2$. Calculated: C 71.9; H 7.0; N 6.5%.

LITERATURE CITED

1. A. D. Yanina, E. E. Mikhlina, K. A. Zaitseva, M. D. Mashkovskii, and L. N. Yakhontov, Khim.-Farmats. Zh., No. 8, 7 (1969).
2. K. F. Turchin, E. E. Mikhlina, A. D. Yanina, V. Ya. Vorob'eva, L. N. Yakhontov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., 981 (1971).
3. E. L. Eliel and J. P. Freemen, J. Am. Chem. Soc., 74, 923 (1952).
4. E. E. Mikhlina, K. F. Turchin, V. Ya. Vorob'eva, A. I. Ermakov, R. G. Kostyanovskii, Yu. N. Sheinker, and L. N. Yakhontov, Dokl. Akad. Nauk SSSR, 195, 1347 (1970).