5. E. L. Eliel, D. Kandasamy, Yen Chen-Yu, Hargrave, J. Am. Chem. Soc., 102, No. 11, 3698 (1980).
6. O. A. Subbotin and N. M. Sergeyev, Anal. Chem., 48, 545 (1976).
7. O. A. Subbotin, N. M. Sergeev, and N. G. Nikishova, Zh. Org. Khim., 20, 1024 (1984).
8. R. W. Alder, N. C. Goode, T. Y. King, I. M. Mellor, and B. W. Miller, Chem. Comm., 173 (1976).
9. Tables of Interatomic Distances and Configuration in Molecules and Ions, L. E. Sutton (ed.), The Chemical Society, Special Publication 18, London (1968).
10. G. S. Litvinenko, A. L. Espenbetov, and Yu. T. Struchkov, Izv. Akad. Nauk Kazakh SSR, Ser. Khim., No. 5, 63 (1982).
11. E. Arte, J. Feneau-Dupont, J. P. Declerg, G. Germain, and M. Van Meersch, Cryst. Struct. Commun., 6, 773 (1977).
12. R. G. Gerr, A. I. Yanovskii, and Yu. T. Struchkov, Kristallografiya, No. 5, 1029 (1983).
13. Kägi and M. Miescher, Helv. Chem. Acta, 52, 2481 (1979).

SYNTHESIS OF STEREOISOMERIC ALKYL- AND PHENYL-SUBSTITUTED 5-CYANOPIPERIDINE-3,4-DIOLS

V. I. Tyvorskii, I. G. Tishchenko, and A. S. Kukharev

UDC 547.823.07:541.63

α-Hydroxy-β-[N-(2-cyanoethyl)amino]ketones were obtained by the reaction of methyl- and phenyl-substituted 2-acyloxiranes with 3-alkylaminopropionitriles. Treatment of the products with sodium tert-butoxide gave stereoisomeric 5e-cyanopiperidine-3,4-diols, the three-dimensional structures of which were established by means of spectral data, as well as by means of isomerization and oxidation with periodic acid.

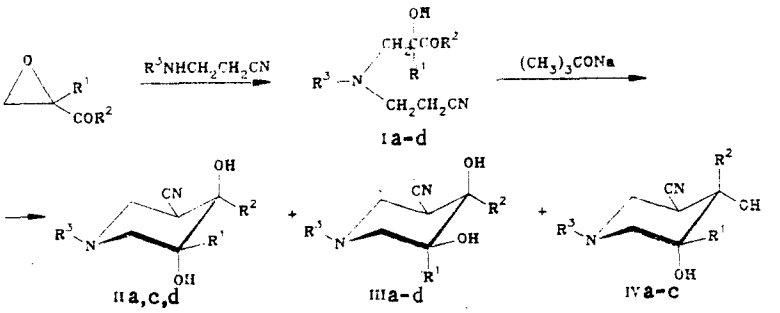
The development of new methods for the synthesis of functionally substituted piperidine-3,4-diols is of considerable interest, since some natural compounds such as the alkaloid fagomine [1], as well as substances that have antihypoxia and surface-anesthetic activity [2], belong to this group of piperidine derivatives. Alkyl- and aryl-substituted piperidine-3,4-diols are generally obtained by hydroxylation of the corresponding tetrahydropyridines [3-6], by reduction of 3-hydroxy-4-piperidones [2, 7-9], or by reaction of the latter with organometallic compounds [10]. We have previously demonstrated [11] the possibility of the synthesis of isomeric 1,3,4-trimethyl-5-cyanopiperidine-3,4-diols via intramolecular cyclization of hydroxy derivatives of β-aminoethyl ketones containing a β-cyanoethyl group attached to the nitrogen atom [12].

In the present research, we studied the reaction of a number of methyl- and phenyl-substituted 2-acyloxiranes with 3-alkylaminopropionitriles, as a result of which we obtained the corresponding α-hydroxy-β-[N-(2-cyanoethyl)amino]ketones Ia-d in 76-96% yields. We found that acyloxiranes that contain substituents in the methylene link do not undergo this transformation, in conformity with the established regioselectivity of the process. Because of their tendency to undergo isomerization in the presence of bases, unsubstituted acyloxiranes (R^1 = H) also form virtually no adducts with alkylaminopropionitriles (see scheme on following page).

The IR spectra of Ia-d contain an absorption band at 3400-3470 cm^{-1} due to a hydroxy group involved in an intramolecular hydrogen bond with the nitrogen atom of the amino group, as well as an absorption band of a nitrile group at 2240 cm^{-1}. A band of carbonyl absorption of the acetyl group of Ia, b is observed at 1710 cm^{-1}, and a band of the benzoyl group of amino ketones Ic, d is observed at 1680-1690 cm^{-1}. The PMR spectra also confirm the structure of Ia-d; in particular, a quartet of diastereotopic protons of an N–CH_2 group with

V. I. Lenin Belorussian State Univeristy, Minsk 220080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1207-1211, September, 1986. Original article submitted June 17, 1985.

 0009-3122/86/2209-0976$12.50



I—IV **a** $R^1=R^2=R^3=CH_3$; **b** $R^1=R^2=CH_3$, $R^3=C_2H_5$; **c** $R^1=R^3=CH_3$, $R^2=C_6H_5$; **d** $R^1=R^2=C_6H_5$, $R^3=CH_3$

geminal spin-spin coupling constant (SSCC) J = 13-14 Hz is present at 2.4-3.6 ppm, which indicates opening of the ring of the starting acyloxiranes by the aminopropionitrile at the unsubstituted methylene link.

In the presence of sodium tert-butoxide cyano ketones, Ia-d undergo cyclization to methyl- and phenyl-substituted 5-cyanopiperidine-3,4,-diols II-IV with the participation of the caronyl group and the cyanoethyl fragment, which, under the influence of a base, generates a carbanion, as we established in [11] and Unkovskii et al. established in the case of the deoxy analogs of Ia-d [12]. Since two new asymmetric centers develop as a result of the cyclization, one should have expected the formation of mixtures of stereoisomeric cyclic products. In fact, from cyano ketones Ia-c under the indicated conditions we obtained mixtures (63-73% overall yields) of 5e-cyanopiperidine-3a,4a-diols IIa-c, 5e-cyanopiperidine-3e,4a-diols IIIa-c, and 5e-cyanopiperidine-3a,4e-diols IVa-c, which were separated by means of column chromatrography. In the mixtures of isomeric piperidinediols IIa-c—IVa-c, which are present in the scheme in the order of the decrease in their chromatographic mobility, cis isomers IIIa-c and IVa-c predominate significantly. 3,4-Dimethyl-1-ethyl-5e-cyanopiperidine-3a,4a-diol (IIb), which was detected in trace amounts in the reaction mixture by thin-layer chromatrography (TLC), could not be isolated in the individual state. On the other hand, a mixture of diphenyl-substituted piperidine-3a,4a-diol and piperidine-3e,4a-diol IId and IIId, in which trans isomer IId predominates, is formed in 86% yield as a result of the cyclization of Id; this may be associated with the more favorable equatorial orientation of both phenyl groups in this isomer.

It should be noted that the ratios of isomers IIIa-c and IVa-c may depend on the length of time that the reaction mixture is allowed to stand. Thus, we showed that 3a,4e-diol IVa, the axial orientation of the 3-OH group in which is probably a consequence of an intramolecular hydrogen bond between the hydroxy group and the nitrogen atom in the cyclized Ia, is converted to an equilibrium mixture of diols IIIa and IVa in a ratio of 1:2 upon prolonged contact with sodium tert-butoxide. Similar treatment of individual isomer IIIa leads to a mixture of IIIa and IVa with a similar composition. The equilibrium may be established via ring inversion and epimerization with respect to the CHC≡N fragment.

The structures of piperidinediols II-IV were confirmed by the results of elementary and spectral analysis, as well as by the results of oxidation of a number of the diols with periodic acid.

The IR spectra contain absorption bands of hydroxy groups at 3425-3605 cm^{-1} and of a nitrile group at 2240 cm^{-1}, and the band of carbonyl absorption that is characteristic for the spectra of Ia-d is absent. A comparison of the spectra of dilute solutions of isomeric diols IIa, c, d and IVa-c shows that the bands at 3425-3485 cm^{-1} correspond to an axial 3-OH group included in an intramolecular hydrogen bond with the nitrogen atom of the piperidine ring. The absorption bands at 3520-3566 cm^{-1} in the IR spectra of 3e,4a-diols IIIa-d are due to intramolecularly bonded hydroxy groups, whereas in the spectra of 3a,4e-diols IVa-c they belong to an equatorial 4-OH group that is linked intramolecularly by a hydrogen bond with the oxygen atom of the axial 3-OH group. An absorption band of an axial 4-OH group linked by a weak intramolecular hydrogen bond with the equatorial cyano group also appears in the spectra of 3a,4a-diols IIa, c, d and 3e-4a-diols IIIa, b at 3565-3575 cm^{-1}, or a band of a free 4-OH group at 3600-3605 cm^{-1} is observed.

A characteristic feature of the PMR spectra of II-IV is a quartet of the 5-H proton, which is deshielded under the influence of the adjacent cyano group, at 3.06-4.61 ppm. The width of this signal, viz., 15-16 Hz, indicates an axial orientation of the 5-H atom and,

TABLE 1. Characteristics of the Compounds Obtained

Compound	bp (pressure, hPa) or mp, °C	R_f[a]	ν_{OH}, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)	Found, %			Empirical formula	Calc., %			Yield, %
					C	H	N		C	H	N	
Ia	125(2)[b]		3470	1,20 (3H, s, 3-CH_3); 2,20 (3H, s, $COCH_3$); 2,26 (4H, m, CH_2CH_2); 2,44 and 2,78 (2H, dd, J=13, NCH_2), 5,74 (1H, s, OH)	58,5	8,7	15,3	$C_9H_{16}N_2O_2$	58,7	8,8	15,2	91
Ib	118(5)[c]		3155	0,93 (3H, t, J=7, β-CH_3); 1,07 (3H, s, 3-CH_3); 2,09 (3H, s, $COCH_3$); 2,34—2,70 (4H, m, CH_2CH_2); 2,44 and 2,78 (2H, dd, J=13, NCH_2); 2,68 (2H, q, J=7, α-CH_2); 3,85 (1H, s, OH)	60,4	9,2	14,4	$C_{10}H_{18}N_2O_2$	60,6	9,2	14,1	88
Ic	Oil	0,76	3426	1,38 (3H, s, 2-CH_3); 2,17 (3H, s, NCH_3); 2,25—2,92 (4H, m, CH_2CH_2); 2,47 and 3,30 (2H, dd, J=14, NCH_2); 4,20 (1H, s, OH); 7,29—7,53 (3H, m) and 8,05—8,20 (2H, m, aromatic protons)	68,5	7,4	11,7	$C_{14}H_{16}N_2O_2$	68,3	7,4	11,4	96
Id	82		3400	2,18 (3H, s, NCH_3); 2,27—2,80 (4H, m, CH_2CH_2); 2,49 and 3,64 (2H, dd, J=13, NCH_2); 4,83 (1H, s, OH); 7,10—7,56 (8H, m) and 7,77—8,20 (2H, m, aromatic protons)	73,7	6,8	9,1	$C_{19}H_{20}N_2O_2$	74,0	6,5	9,1	76
IIa	153	0,69	3605, 3490	1,27 (3H, s, CH_3); 1,56 (3H, s, CH_3); 2,06 (3H, s, NCH_3); 2,28 and 2,60 (2H, dd, J=11, 2-H); 2,36—2,80 (2H, m, 6-H); 3,40 (1H, q, $J_{5a,6a}$=10, $J_{5a,6e}$=5, 5-H); 4,83 (2H, br.s, 2 OH)	58,9	8,9	15,0					8
IIIa	104	0,56	3605, 3575, 3525	1,35 (3H, s, CH_3); 1,48 (3H, s, CH_3); 2,05 (3H, s, NCH_3); 2,38 and 2,63 (2H, dd, J=10, 2-H); 2,48—2,74 (2H, m, 6-H); 3,06 (1H, q, $J_{5,6a}$=10, $J_{5,6e}$=5, 5-H); 5,34 (2H, br.s, 2 OH)	58,9	8,8	15,3	$C_9H_{16}N_2O_2$	58,7	8,8	15,2	27
IVa	95	0,19	3520, 3470	1,22 (3H, s, CH_3); 1,34 (3H, s, CH_3); 2,05 (3H, s, NCH_3); 2,12—2,36 (2H, m, 2-H_a, 6-H_a); 2,47 (1H, q, J_{gem}=12, $J_{2e,6e}$=1,5, dq, $J_{2e,6e}$=1,5, $J_{5,6e}$=4, 6-H_e); 2,66 and 2,78 (1H, $J_{5,6e}$=4, 5-H); 5,44 (1H, q, $J_{5,6a}$=11, s, OH); 5,72 (1H, s, OH)	58,4	8,5	15,3					28
IIIb	Oil	0,52	3605, 3575, 3530	0,83 (3H, t, J=7, β-CH_3); 1,28 (3H, s, CH_3); 1,42 (3H, s, CH_3); 2,23 (2H, q, J=7, α-CH_2); 2,34—2,72 (4H, m, 2- and 6-H); 2,97 (1H, q, $J_{5,6a}$=11, $J_{5,6e}$=4,5, 5-H); 5,58 (2H, br.s, 2 OH)	60,4	9,3	14,1	$C_{10}H_{18}N_2O_2$	60,6	9,2	14,1	30
IVb	90	0,29	3525, 3480	0,83 (3H, t, J=7, β-CH_3); 1,25 (3H, s, CH_3); 1,37 (3H, s, CH_3); 2,11—2,30 (2H, m, 2- and 6-H_a); 2,28 (2H, q, J=7, α-CH_2); 2,64 (1H, q, J_{gem}=12, $J_{2e,6e}$=1,5, 2-H_e); 2,87 and 2,98 (1H, m, $J_{2e,6e}$=1,5, $J_{5,6e}$=4, 6-H_e); 3,54 (1H, q, $J_{5,6a}$=11, $J_{5,6e}$=4, 5-H); 5,38 (2H, br.s, 2 OH)	60,5	9,1	14,0					43
IIc	145	0,81	3600, 3440	1,30 (3H, s, CH_3); 2,07 (3H, s, NCH_3); 2,36 and 3,18 (2H, dd, J=11, 2-H); 2,75—2,87 (2H, m, 6-H); 3,57 (1H, q, $J_{5,6a}$=9, $J_{5,6e}$=7, 5-H); 5,56 (2H, br.s, 2 OH)	68,4	7,4	11,5					7
IIIc	184	0,58	3560	1,21 (3H, s, CH_3); 2,12 (3H, s, NCH_3); 2,52 and 2,79 (2H, dd, J=11, 2-H); 2,64—2,92 (2H, m, 6-H); 4,62 (1H, t, J=8, 5-H); 5,01 and 5,48 (2H, s, 2 OH)	68,5	7,1	11,4	$C_{14}H_{18}N_2O_2$	68,3	7,4	11,4	49
IVc	189	0,23	3533, 3435	1,26 (3H, s, CH_3); 2,14 (3H, s, NCH_3); 2,28—3,82 (1H, q, $J_{5,6a}$=12, $J_{5,6e}$=4,5, 5-H); 5,82 (2H, br.s, 2 OH)	68,2	7,1	11,3					11
IId	149	0,57	3565, 3425	2,33 (3H, s, CH_3); 2,65 and 3,62 (2H, dd, J=11, 6-H); 4,62 (1H, q, $J_{5,6a}$=10, $J_{5,6e}$=5,5, 5-H); 5,80 (2H, br.s, 2 OH)	74,3	6,7	9,1	$C_{19}H_{20}N_2O_2$	74,0	6,5	9,1	57
IIIc	178	0,42	3566	2,30 (3H, s, CH_3); 3,10 and 3,25 (2H, dd, J=12, 6-H); 4,03 (1H, q, $J_{5,6a}$=10, $J_{5,6e}$=5,5, 5-H); 5,82 (2H, br.s, 2 OH)	74,2	6,6	9,1					29

[a] On Al_2O_3 with elution by ether—hexane (4:1) (Ic, IId, IIId), ether—hexane (7:1) (IIc-IVc), and ethyl—isopropyl alcohol (30:1) (IIa; IIIa, b; IVa, b). [b] n_D^{20} 1.4620. [c] n_D^{20} 1.4612.

consequently, an equatorial orientation of the cyano group. For some of the phenyl-substituted piperidinediols (IIc, IIIc) the constants of spin-spin coupling of the 5-H proton with the protons of the 6-CH_2 group have close values; this constitutes evidence for distortion of the chair conformation.

As expected, diaxial diols II are oxidized very slowly by periodic acid as compared with isomers III and IV; this is characteristic for cyclic vicinal glycols with a trans orientation of the hydroxy groups [13].

EXPERIMENTAL

The IR spectra of solutions of the substances in CCl_4 (0.001 M) were recorded with a Specord 75 IR spectrometer. The PMR spectra of solutions in CCl_4 (Ib-d) or pyridine (Ia, II-IV) were obtained with a Varian HA-100 spectrometer (100 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The compositions of the reaction mixtures and the purity of the compounds obtained were monitored by TLC on activity II Al_2O_3 in ether–hexane or ether–isopropyl alcohol systems with development by iodine vapors.

The acyloxiranes were obtained by oxidation of the corresponding unsaturated ketones with alkaline hydrogen peroxide [14].

The characteristics of the synthesized compounds are presented in Table 1.

4-[N-Alkyl-N-(2-cyanoethyl)amino]-3-hydroxy-3-methyl-2-butanones (Ia, b), 2-Hydroxy-2-methyl-3-[N-methyl-N-(2-cyanoethyl)amino]-1-phenyl-1-propanone (Ic), and 2-Hydroxy-3-[N-methyl-N-(2-cyanoethyl)amino]-1,2-diphenyl-1-propanone (Id). A solution of 0.05 mole of the corresponding acyloxirane and 0.05 mole of the 3-alkylaminopropionitrile in 30 ml of isopropyl alcohol was refluxed for 10-15 h, after which the alcohol was removed at reduced pressure, and the residue was distilled in vacuo (Ia, b) or crystallized from hexane–isopropyl alcohol (10:1) (Id). Compound Ic was isolated in the form of a viscous uncrystallizable oil by chromatography of the residue with a column packed with Al_2O_3 by elution with ether–hexane (4:1).

Methyl- and Phenyl-Substituted 1-Alkyl-5-cyanopiperidine-3,4-diols (IIa, c, d; IIa-d; IVa-c). A solution of 0.03 mole of cyano ketone Ia-d in 25 ml of dimethoxymethane was added dropwise at 18-20°C to a stirred suspension of 0.04 mole of sodium tert-butoxide in 100 ml of dry dimethoxymethane, after which stirring was continued for 10-12 h. The reaction mixture was then neutralized with 0.04 mole of glacial CH_3COOH, and the dimethoxymethane was evaporated at reduced pressure. The residue was treated with 20 ml of water, and the aqueous mixture was extracted with chloroform. After removal of the chloroform, the residue was chromatographed with a column packed with Al_2O_3 by elution with ether–isopropyl alcohol (30:1 (IIa; IIIa, b; IVa, b), ether–hexane (7:1) (IIc-IVc), or ether–hexane (4:1) (IId, IIId). After removal of the solvents, individual piperidinediols II-IV were crystallized from hexane–isopropyl alcohol (10:1).

Isomerization of Piperidine-3a,4e-diol (IVa). A 1.8-g (0.01 mole) sample of IVa was added to a suspension of sodium tert-butoxide, obtained from 0.35 g (0.015 mole) of sodium, in dry dimethoxymethane, after which the reaction mixture was stirred for 48 h and worked up as described above. After removal of the $CHCl_3$, the residue was chromatographed with a column packed with Al_2O_3 by elution with ether–isopropyl alcohol (30:1) to give 0.53 g (29%) of IIIa and 1.12 g (62%) of IVa. According to data from the PMR spectrum of the mixture obtained, the ratio of IIIa and IVa was 35:65.

Oxidation of Piperidinediols II-IV by Periodic Acid. This reaction was carried out by means of a standard solution of this oxidizing agent in glacial CH_3COOH. The percentage of the oxidized vicinal diol was determined by the method in [15]. In the course of the 30 min necessary for the oxidation of cis-diols IIIa and IVa at 65°C trans-diol IIa underwent 5-8% oxidation under the same conditions. Similarly, at 60°C cis-diols IIIc and IVc were oxidized by periodic acid in 3 h, whereas trans isomer IIc underwent 1-3% oxidation during this time.

LITERATURE CITED

1. M. Koyama and S. Sakamura, Agric. Biol. Chem., 38, 1111 (1974).
2. T. Yu. Il'yuchenok, M. N. Romanchak, A. M. Zvonok, I. G. Tishchenko, L. S. Stanishevskii, L. M. Frigidova, Yu. V. Zav'yalov, K. S. Shadurskii, Z. B. Berezovskii, A. S. Zakharevskii, and A. V. Miklevich, Khim.-farm. Zh., No. 12, 40 (1978).

3. T. N. Maksimova, V. B. Mochalin, and V. B. Unkovskii, Khim. Geterotsikl. Soedin., No. 6, 783 (1980).
4. V. Petrov and O. Stephenson, J. Pharm. Pharmacol., 14, 306, 522 (1962); Chem. Abstr., 58, 501, 6829 (1963).
5. R. E. Lyle and W. E. Krueger, J. Org. Chem., 30, 394 (1965).
6. J. E. Saavedra, J. Org. Chem., 44, 4516 (1979).
7. N. Bregant, J. Janculev, and S. Ghyczy, Ark. Kemi, 27, 189 (1955); Chem. Abstr., 50, 12043 (1956).
8. L. S. Stanishevskii, I. G. Tishchenko, A. Ya. Guzikov, A. M. Zvonok, and L. A. Khil'manovich, Zh. Org. Khim., 11, 643 (1975).
9. A. M. Zvonok, A. P. Lugovskii, and L. S. Stanishevskii, Vestnik Belorussk. Gosudarstv. Univ., Ser. 2, No. 1, 66 (1983).
10. A. M. Zvonok, A. P. Lugovskii, V. A. Mashenkov, and L. S. Stanishevskii, Zh. Org. Khim., 18, 2108 (1982).
11. V. I. Tyvorskii, L. S. Stanishevskii, and I. G. Tishchenko, Khim. Geterotsikl. Soedin., No. 3, 404 (1981).
12. E. T. Golovin, E. P. Badosov, A. P. Nikiforova, A. B. Khasirdzhev, and B. V. Unkovskii, Zh. Org. Khim., 10, 1265 (1974).
13. E. L. Eliel, N. Allinger, S. J. Angyal, and G. Morrison, Conformational Analysis, Wiley (1965).
14. V. I. Tyvorskii and I. G. Tishchenko, All-Union Institute of Scientific and Technical Information Deposited Paper No. 5797-81 Dep.; Ref. Zh. Khim., 11Zh191 (1982).
15. S. Siggia and J. G. Hanna, Quantitative Organic Analysis via Functional Groups [Russian translation], Khimiya, Moscow (1983), p. 41.

ARYLATION, ALKYLATION, REDUCTION, AND PYROLYSIS OF 1H-1-METHYLINDENO[2,1-b]PYRIDINE

A. T. Soldatenkov, M. V. Bagdadi, V. O. Fedorov, and N. S. Prostakov

UDC 547.665'828:542.953.5'941:543.422

Nucleophilic substitution (phenylation with phenyl lithium) of 1H-1-methylindeno[2,1-b]pyridine occurred at the $C_{(2)}$ and $C_{(4)}$ positions, and electrophilic substitution (methylation and benzylation with halogen derivatives) at $C_{(9)}$. Reduction of the starting anhydrobases gave 1-methyl-1,2,3,9a-tetrahydro-1-azafluorene, and pyrolysis gave 1-azafluorene and 1-azafluorenone.

In a continuation of our work on NH-indenopyridines [1, 2], we have studied the pyrolysis, reduction, and substitution reactions of some anhydrobases such as 1H-1-methylindeno 2, 1-b pyridine (I).

According to quantum mechanical calculations [3], nucleophilic substitution of the indenopyridine I should occur at positions $C_{(4)}$ and $C_{(2)}$. Arylation of compound I with phenyl lithium gave 1H-1-methyl-2-phenyl- and 4-phenylindeno[2,1-b]pyridine (II and III) in approximately equal amounts. A small amount of a crystalline substance, which, from mass-spectral data was assigned the structure 1H-1-methyl-2,4-diphenylindeno[2,1-b]pyridine was also obtained. In the PMR spectra of the anhydrobase II, the 4-H proton signal is further downfield and has a greater coupling constant (8.14 ppm, $J_{3,4}$ = 7.1 Hz) compared with the 2-H proton of its isomer III (7.71 ppm, $J_{2,4}$ = 6.7 Hz); this is characteristic for anhydrobases of this type [2]. The long-wave absorption maximum in the UV spectrum of compound II undergoes a bathochromic shift (608 nm) compared with that of compound III (590 nm).

P. Lumumba People's Friendship University, Moscow 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1212-1214, September, 1986. Original article submitted May 15, 1985.

 0009-3122/86/2209-0980$12.50