THE SPATIAL STRUCTURE OF THE ISOMERIC DIMETHYL ESTERS OF 4-HYDROXYPIPERIDINE-2,6-DICARBOXYLIC ACID

K. F. Turchin, E. S. Nikitskaya, Yu. N. Sheinker, and M. V. Rubtsov

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Three isomeric dimethyl esters of 4-hydroxypiperidine-2,6-dicarboxylic acid have been isolated. The spatial structures of all three isomeric esters and of the acids corresponding to them have been established on the basis of NMR spectra. It has been shown that while the isomers I and II exist in the form of only one conformation each, isomer III in neutral and acid media apparently consists of an equilibrium mixture of two (or more) conformers. The information obtained on the spatial structure of the isomeric esters shows that the cyclization of these compounds with benzylamine and p-nitrobenzaldehyde takes place with the inversion of the piperidine ring.

Dimethyl esters of 4-hydroxypiperidine-2,6-dicarboxylic acid have been obtained by the hydrogenation of chelidamic acid in an aqueous alkaline medium in the presence of a nickel catalyst with subsequent esterification of the hydrogenation product with methanol [1]. From the resulting mixture of isomeric esters a crystalline isomer with mp 134–135° C (I) [2] was obtained. In a study of the spatial structure of this isomer, on the basis of a series of chemical reactions it was concluded that the compound has the chair form, the methoxycarbonyl group being in the cis position and the "hydroxyl group located on the same side of the plane of the molecule as the methoxycarbonyl groups"* [2, 3].

Continuing the work begun, we have isolated another two isomers from the mixture of esters—a crystalline one with mp 98–100° C (II) and a liquid one with bp 140–141° C (0.3 mm) (III). The isomeric esters form three different hydrochlorides and on saponification with dilute hydrochloric acid give the hydrochlorides of the isomeric 4-hydroxypiperidine-2,6-dicarboxylic acids (**Ia**, **IIa**, and **IIIa**). The purity of the isomeric compounds was checked by means of descending paper chromatography in chloroform (paper impregnated with 40% methanolic formamide).

As has been shown previously [2], the isomer I does not give a crystalline bicyclic compound with p-nitrobenzaldehyde [4]. On the other hand, isomers II and III do form such compounds. These results permit the assumption that the hydroxyl group in the isomers **II** and III is on the side opposite to that of the hydroxyl group in the isomer **I**.

A detailed study of the spatial structure of the isomeric esters isolated and of the acid corresponding to them has been carried out by ^1H NMR spectroscopy.

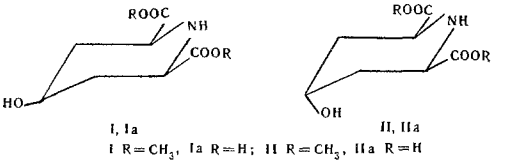
Table 1 gives the values of the chemical shifts (CS), δ, obtained and the spin-spin coupling constants (SSCC), J, of the protons of the piperidine nucleus and the methyl protons of the $COOCH_3$ groups for the isomeric esters I and II and the acids corresponding to them **Ia** and **IIa**. The assignment of the signals in the spectra of all these compounds causes no difficulties of any kind: the signals of the axial protons at C_3 and C_5 ($H_{3a, 5a}$) are found in the strongest field and then come the equatorial protons at these carbon atoms ($H_{3e, 5e}$); the signals of the protons at C_2 and C_6 (H_2 and H_6) are in the 3.5–4.5 ppm region. Finally, the signals in the weakest field relate to the proton at C_4 (H_4) (Fig. 1).

A consideration of the spectra shows that the protons at C_2 and C_6 give a single signal both in I and **Ia** and in II and **IIa** in all the media studied. In these isomers the signals of the protons of the methoxycarbonyl groups at C_2 and C_6 also coincide. This shows the equivalence of positions 2 and 6 (and also 3 and 5) and the similar orientation of the substituents (the two COOR groups) in positions 2 and 6. Consequently, the molecules of each of the isomers are symmetrical with respect to the plane passing through the O—C_4—H and N—H bonds and the COOR groups have the cisoid arrangement.

As is well known, for saturated six-membered rings the chair formation with an equatorial arrangement of the largest substituents is preferred. If it is assumed that the piperidine ring in the isomers studied also has the chair form, the results with respect to CS and SSCC permit the spatial structure of the isomers **I**, **Ia**, II, and IIa to be established unambiguously.

Thus, in the isomer I (**Ia**) the signals present in the strongest field (axial protons at $C_{3(5)}$) show a pattern of spin-spin splitting corresponding to the existence of three large J constants (~11–13 Hz) of which one is obviously J_{gem}, and the other two must represent $J_{H_{3(5)a}H_{2(6)a}}$ and $J_{H_{3(5)a}H_{4a}}$. In the isomer II (and IIa), the signals of the axial protons $H_{3(5)}$ are split as a result of two large (11–13 Hz) and one small (3 Hz) constants, while a consideration of the signals from the protons at $H_{2(6)}$ and H_4 shows that the small constant is due to interaction with the H_{4e} proton.

It follows unambiguously from these facts that in the isomer I (and **Ia**), both the COOR groups and the OH group have the equatorial positions and in the isomer II (and IIa), while the COOR groups retain their equatorial positions, the hydroxyl group assumes the axial position.



I, Ia II, IIa

I R=CH_3, Ia R=H; II R=CH_3, IIa R=H

*What is meant is the plane passing through the three carbon atoms C_2, C_4, and C_6 that bear the substituents.

Table 1

Values of the CS (δ, ppm) and SSCC (J, Hz) of the Protons in the Spectra of **I**, **Ia**, **II**, and **IIa**

Solvent	I		Ia		II	IIa	
	$CDCl_3$	CD_3OD (+HCl)	1*N* NaOD	1*N* DCl	$CDCl_3$	1*N* NaOD	1*N* DCl
CS							
$\delta_{H_{3a(5a)}}$	1.35	1.60	1.08	1.69	1.65	1.45	1.92
$\delta_{H_{3e(5e)}}$	2.27	2.72	2.14	2.59	2.10	1.94	2.31
$\delta_{H_{2(6)}}$	3.41	4.25	3.10	4.17	3.89	3.41	4.29
δ_{H_4}	~3.80	~3.85	3.68	4.10	4.35	4.27	4.39
δ_{RCH_3}	3.77	3.88	—	—	3.77	—	—
SSCC							
$J_{H_4H_{3a(5a)}}$	11—13	11—13	11.2	11.2	2—3	3	3
$J_{H_4H_{3e(5e)}}$	2—4	2—4	4.6	4.6		3	3
$J_{H_2H_{3a}}$	12.5	13.0	12.0	13.4	10.5	12.7	13.3
$(J_{H_6H_{5a}})$							
$J_{H_2H_{3e}}$	3	3	2.8	3.4	2.5	3.0	3.4
$(J_{H_6H_{5e}})$							
$J_{H_{3a,3e}}$	11—13	12.5	12	13	2.5	14	14
$(J_{H_{5a,5e}})$							

Table 2

Values of the CS (δ ppm) and SSCC (J, Hz) of the Protons in the Spectra of **III** and **IIIa**

Растворитель	III		IIIa		
	$CDCl_3$	CD_3OD (+HCl)	1*N* NaOD	1*N* DCl	CD_3OD +DCl
CS,					
$\delta_{H_{3a}}$	1.64—2.24	1.85—2.35	1.24	2.13—2.32	2.05—2.30
$\delta_{H_{5a}}$			1.45		
$\delta_{H_{3e}}$			2.15		
$\delta_{H_{5e}}$					
δ_{H_2}	3.65	4.40	3.16	4.44	4.27
δ_{H_6}	4.03	4.66	3.52	4.62	4.57
δ_{H_4}	3.87 3.77	4.13 3.83	3.61	4.19	4.05
δ_{RCH_3}	3.81	3.89	—	—	—
SSCC					
$J_{H_4H_{3a}}$	(8)		10.7	(4.5) quintet	(4.2) quintet
$J_{H_4H_{3e}}$	(4)		4.7	(4.5)	(4.2)
$J_{H_2H_{3a}}$	(8)	(5.3)	11.5	(5.7) triplet	(5.3) triplet
$J_{H_2H_{3e}}$	(4.2)	(3.9)	3	5.7	(5.3)
$J_{H_6H_{5a}}$	(6)	(4.5)	5	(6.2)	(5.8)
$J_{H_6H_{5e}}$	(5)	(11.0)	2.7	(8.5)	(8.3)
$J_{H_{3a}H_{5e}}$			12.5		

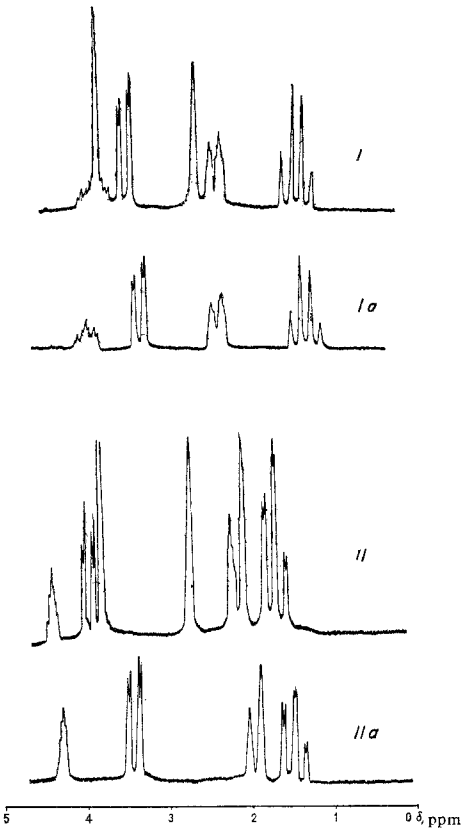


Fig. 1. NMR spectra of the esters I and II and the acids Ia and IIa corresponding to them (the esters in $CDCl_3$, and the acids in 1N NaOD; the assignment of the signals is given in Table 1; the signal at 2.7 ppm in the spectra of the esters is due to OH and NH).

The signals of all the other protons are present in the fields corresponding to this idea. Thus, in all four compounds the signals present in a somewhat weaker field than for the $H_{3a(5a)}$ protons have only one large constant (11–13 Hz) and appear in the form of a doublet of poorly resolved multiplets due to the small

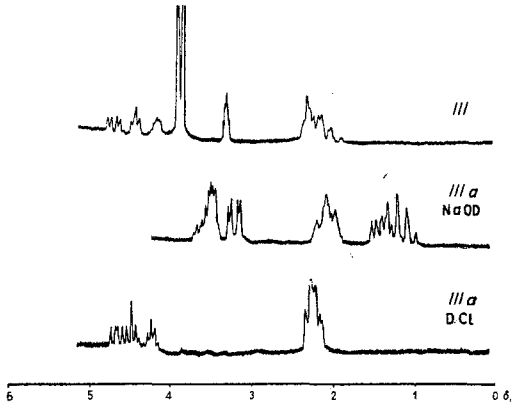
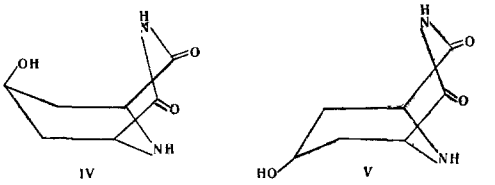


Fig. 2. NMR spectra of the ester III in CD_3OD + DCl and of the acid IIIa corresponding to it in 1 N NaOD and 1 N DCl (the assignment of the signals is given in Table 2; the signal at 3.3 ppm in the spectrum of the ester is due to the residual protons of the solvent CHD_2OD).

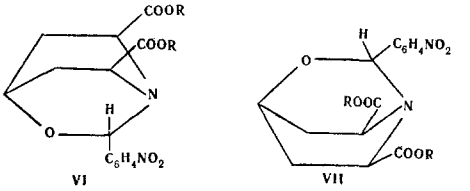
constants, as is to be expected for equatorial protons (the large constant J_{gem} and the small constants $J_{H_{3(5)e}H_{2(6a)}}$ and $J_{H_{3(5)e}H_{4e}}$). Furthermore, in the isomer II, the H_4 proton gives a signal in a weaker field than in the isomer I (in the same solvents), which agrees with the idea of its equatorial position in the isomer II and its axial position in the isomer I.

It follows from the results obtained that the isomeric compounds studied exist under the conditions of the measurements in the form of one conformation each (or, at least, this conformation is markedly predominating). This is understandable, since chair-chair inversion would lead, both for I (Ia) and for II (IIa) to an energetically unfavorable diaxial arrangement of the voluminous COOR groups. So far as concerns the boat form, this could be regarded as possible only for the isomer I (Ia), since in this case it is possible to expect the stabilization of such a form through an intramolecular OH...N hydrogen bond [5–7]; however, the marked closeness of the J constants for the isomers I and II and their very small change on passing from certain solvents (and pH values) to others permits the conclusion that under the conditions described the boat form is absent (or is present in insignificant amounts).

In addition to this, it follows from the results obtained that, in the cyclization of the isomer I with benzylamine, inversion of the piperidine ring into another chair (IV) or boat (V) form with the diaxial arrangement of the two COOR groups takes place, since the closure of the second ring would be impossible if these groups were in the diequatorial position.



Inversion of the ring must also take place in the reaction of the isomer II with p-nitrobenzaldehyde, and in the bicyclic derivative VI formed the piperidine ring must have the boat form with the exoaxial arrangement of the COOR groups. This form is free from steric hindrance between the p-nitrophenyl ring and the ester groups and therefore the cyclization reaction takes place readily. In contrast to this, the isomer I does not take part in the cyclization reaction since the boat conformation with the exoequatorial orientation of the COOR groups, VII, is unfavorable because of the steric repulsion shown, and in the formation of the other boat form, in which both COOR groups are exoaxial, the hydroxyl is in the exoequatorial position and closure with the formation of the bicyclic compound becomes impossible.



Thus, the results obtained on the spatial structures of the isomeric esters I and II (and the acids Ia and IIa corresponding to them) satisfactorily explain the

Table 3

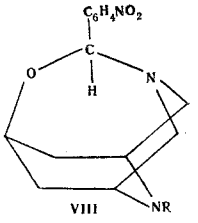
Sums of the Constants in the Isomers III and IIIa

Sums, Hz	Solvent		
	D_2O+NaOD	D_2O+DCl CD_3OD+DCl	$CDCl_3$
$J_{H_4H_{3e}}+J_{H_4H_{3e}}$	15.4	8—9	12
$J_{H_2H_{3a}}+J_{H_2H_{3e}}$	14.5	11.4—10	12
$J_{H_6H_{5a}}+J_{H_6H_{5e}}$	7.7	11—14	11—14

cyclization reaction of these compounds to form bicyclic derivatives and show that the corresponding reactions take place with inversion of the piperidine ring. It follows from this that a study of the cyclization reactions of the esters discussed cannot be used to establish the conformations in which these esters exist. In view of this, the data of the present communication permit the conclusions drawn previously [2] on the steric structure of the isomer I and, to a certain extent, that of the bicyclic compound IV obtained by its reaction with benzylamine, to be refined.

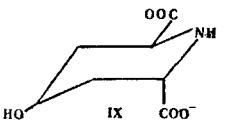
As already mentioned, in the previous paper [2] the ester I was ascribed the chair form "with the OH pres-

ent on the same side of the chain of the molecule as the methoxycarbonyl groups." There can be two such forms—with the triequatorial and with the triaxial arrangement of all the substituents. In the present work the triequatorial nature of the substituents in this isomer has been shown unequivocally. In the bicyclic compound, the diaxial orientation of the C_2—CO and C_6—CO bonds with respect to the piperidine ring is obviously the only one possible; so far as concerns the hydroxyl, it may be assumed with equal success as having the axial position in structure IV and the equatorial position in structure V. Data on the formation of the tricyclic compound VIII [3] cannot support conformation IV, since the reaction with p-nitrobenzaldehyde takes place with the inversion of the piperidine ring and substance VIII can also be obtained from the bicyclic compound V (after reduction of the methoxycarbonyl groups and debenzylation).



VIII

Passing to a consideration of the spectra of III (and IIIa) (Table 2, Fig. 2), we must first of all mention the difference in CS for the protons at C_2 and C_6 ($\Delta\delta$ 0.25–0.30 ppm) and for the $COOCH_3$ groups ($\Delta\delta$ 0.04–0.06 ppm), which shows the asymmetry of the molecule of this isomer. This asymmetry can be explained only by a transoid arrangement of the COOR groups in the isomer III, in contrast to the cisoid diequatorial arrangement that exists in the isomers considered above. The transoid orientation of the COOR groups makes possible the formation of a bicyclic compound by the reaction of III with p-nitrobenzaldehyde, since in the bicyclic compound formed one of the COOR groups is always orientated in such a way that the p-nitrophenyl ring can be arranged without any steric hindrance on the part of this group. The determination of the conformation of III and IIIa proved to be associated with considerable difficulties. As follows from Table 2, only for IIIa and only in an alkaline medium does it prove possible to make an unambiguous assignment of the signals to the H_{3a}, H_{5a}, and $H_{3,5e}$ protons. In all other cases, the signals of these protons overlap and give a complex multiplet the distance between the extreme peaks of which varies from 20 (IIIa, DCl) to 60 Hz (III, $CDCl_3$). By comparing the CS values of the H_{3a}, H_{5a}, $H_{3,5e}$ and, particularly, H_4 protons in the spectrum of IIIa with the corresponding values for Ia it may be concluded that in an alkaline medium the chair conformation with the OH group in the equatorial position and the axial-equatorial orientation of the COO^- groups (IX) is characteristic for IIIa (compare δ_{H_4} for the acids Ia, IIa, and IIIa in 1 N NaOD). The same conclusion follows from a consideration of the SSCC. The spectra of III and IIIa in acid (D_2O + +DCl, CD_3OD + DCl) and neutral* (III in $CDCl_3$) media differ markedly from the spectrum of IIIa in an alkaline medium (Table 3, Fig. 2a, b). In the strong-field region (H_3H_5 resonance), only one multiplet is observed with a distance between the extreme peaks of 20–60 Hz. Thus, the CS of the protons present at C_3 and C_5 are fairly close. In this case, on the basis of a first-order analysis only the value of the sum of the two SSCC, and not the constants themselves, are correctly determined.** All this permits only certain considerations relative to the possible conformation of the isomer III in an acid medium and in $CDCl_3$ to be expressed.



IX

It must be mentioned in the first place that in the isomers III and IIIa the values of the sums of the constants $J_{H_4H_{3a}}+J_{H_4H_{3e}}$, $J_{H_2H_{3a}}+J_{H_2H_{3e}}$ and $J_{H_6H_{5a}}+$ $+J_{H_6H_{5e}}$ change substantially on passing from an alkaline to neutral and acid media (Table 3).

These differences cannot be explained by any electronic effects connected with a change in the state of the ionogenic groups, since the corresponding SSCC values (and their sums) for the isomers I and II depend on the solvent to a far smaller extent.

Thus, it may be assumed that the conformation of the isomer III predominating in an alkaline medium (chair, OH and one of the COOR groups equatorial, the other COOR axial, IX, Fig. 3) is not the only one in acid and neutral media, and that under these conditions we are dealing with an equilibrium of two or more conformers rapidly changing into one another. However, the values of the sums of the SSCC values that we have found do not make it possible to determine just which of the eight conformers possible in principle (two inverted chair and six boat forms) exist in equilibrium with one another, although it may be assumed that in an acid medium the predominant form is the inverted chair (with an axial OH group). It may be mentioned that the greater ease of inversion of the ring for isomer III as compared with isomers I and II is, generally speaking, perfectly explicable, since the axial-equatorial arrangement of the largest substitu-

*Since the strong signals of the two methyl groups interfere with the determination of the structure of the signal of the H_2, H_4, and H_6 protons in a neutral medium ($CDCl_3$), the study of the ester was carried out on the corresponding derivatives with $COOCD_3$ groups.

**In favor of the existence of a virtual interaction in the case discussed, is the nature of the signal from one of the $>\overset{H}{C}-COOR$, protons, which has the form of a symmetrical triplet. In Table 2, the measured intervals between the peaks which, apparently, are not equal to J_{AX} and J_{BX}, are given in brackets.

ents (COOR) will remain the same on chair-chair inversion (the COOR groups will merely change their orientation). The difference in the energies of the two chair forms of the isomer III is therefore due only to the somewhat more suitable equatorial arrangement of the hydroxyl in one of these forms (which, thanks to this, exists as practically the only one for IIIa in an alkaline medium).

In addition to this, the presence of boat forms, as well, in the conformational equilibrium for the isomer III is extremely likely, since some of them—for example, those corresponding to the exoequatorial position of all three substituents—can be fairly favorable in respect of energy.

Some considerations may be given on the question of why the suitability of one of the chair conformations for IIIa appears in the form of a practically complete predominance only in an alkaline medium.

Obviously, this is connected with the appearance under these conditions of the two charged COO^- groups, tending to occupy the most remote position both from one another and from the hydroxyl, which may be partially ionized when a strongly alkaline medium (1 N NaOH) is used. Under these conditions, the most suitable conformation is that denoted by IX, with an equatorial hydroxyl. For the ester III itself and the acid IIIa in neutral and acid media there is no charge on the COOR group and this decreases the difference in the energies of the isomers to such an extent that the compounds exist in the form of an equilibrium mixture of two (or more) conformational isomers.

EXPERIMENTAL

Isolation of the isomers. The solid substance was filtered off from a mixture of the isomeric esters (22.7 g) [1] and was recrystallized from ethyl acetate. This gave 12.1 g (52.2% of the mixture) of the isomer I in the form of a colorless crystalline substance with mp 134–135° C. Found, %: C 50.00; H 7.18; N 6.37. Calculated for $C_9H_{15}NO_5$, %: C 49.76; H 6.96; N 6.44, **Hydrochloride**—colorless crystalline substance with mp 210–212° C. Found, %: Cl 14.02; N 5.45. Calculated for $C_9H_{15}NO_5 \cdot HCl$, %: Cl 13.97; N 5.52.

The mother solution from four filtrations (40 g) was dissolved in dil (1 : 1) HCl and the impurities of a nonbasic nature were extracted with ether; the acid solution was then treated with an excess of 50% potassium carbonate solution and was extracted with chloroform. This gave 16.45 g of a light yellow viscous liquid with bp 150–160° C (0.5 mm). The liquid was dissolved in 60 ml of absolute ethanol, the solution was acidified with ethanolic hydrogen chloride, and the precipitate that deposited (15.5 g) was filtered off and recrystallized from 50 ml of butanol and then from 40 ml of absolute ethanol. This gave 6.22 g of the hydrochloride of the isomer III in the form of a colorless crystalline substance with mp 172–174° C. Found, %: Cl 13.78; N 5.35. The base III formed a viscous colorless liquid with bp 140–141° C (0.3 mm). Found, %: C 49.90; H 6.90; N 6.33.

The butanolic mother solution from the filtration of the hydrochloride of III was evaporated to dryness and the residue was twice crystallized from 20 ml of methanol. This gave 4.3 g of the hydrochloride of the isomer II in the form of a colorless crystalline substance with mp 175–176° C. Found, %: Cl 13.87; N 5.54.

A mixture of the hydrochloride of the isomers II and III melted at 152–155° C.

The base II formed a colorless crystalline substance with mp 98–100° C (from ethyl acetate).

Saponification of the esters. The saponification of the isomeric esters was carried out with a tenfold amount of dil (1 : 1) HCl at the boil for 4 hr. At the end of the reaction, the acid aqueous solutions were evaporated to dryness in vacuum, and the residues were triturated with ether. The colorless crystalline hydrochlorides of the isomeric 4-hydroxypiperidine-2,6-dicarboxylic acids were obtained in yields of 82–87%.

Ia) mp 240–242° C. Found, %: Cl 16.03; N 6.17.
IIa) mp 254–256° C. Found, %: Cl 15.86; N 6.41.
IIIa) mp 185–186° C. Found, %: Cl 15.60; N 6.91.
Calculated for $C_7H_{11}NO_5 \cdot HCl$, %: Cl 15.71; N 6.20.

Reaction of the isomers II and III with p-nitrobenzaldehyde. The reaction was carried out as described previously [3]. The isomer II (0.45 g) gave 0.62 g (86%) of a bicyclic compound in the form of a yellow crystalline substance with mp 159–161° C. Found, %: C 54.83; H 5.22; N 7.64. Calculated for $C_{16}H_{18}N_2O_7$, %: C 54.85; H 5.18; N 7.99.

The isomer III (0.65 g) gave 0.91 g (86.6%) of the bicyclic product in the form of a light yellow crystalline substance with mp 129–131° C. Found, %: C 54.75; H 5.27; N 7.83.

The IR spectra of the bicyclic compounds contain absorption bands in the 1730 and 1530 cm^{-1} regions (ester group and aromatic nitro group) but no absorption bands in the 3200–3500 cm^{-1} region corresponding to secondary amine and hydroxyl groups.

The NMR spectra of the compounds studied were obtained on a JNM-4H-100 spectrometer with a working frequency of 100 MHz. For the solutions in $CDCl_3$ (I, II, III) and in CD_3OD (I, III, IIIa), hexamethyldisiloxane ($\delta = 0.04$) was used as the internal standard. The solutions in D_2O (Ia, IIa, IIIa in alkaline and acid media) were studied with dioxane ($\delta = 3.70$) as the internal standard. Tables 1 and 2 give the values of the CS calculated to TMS ($\delta = 0.00$).

REFERENCES

1. E. S. Nikitskaya, V. S. Usovskaya, E. I. Levkoeva, and M. V. Rubtsov, USSR patent no. 164047; Byull. izobr., no. 14, 20, 1964.

2. E. S. Nikitskaya, E. I. Levkoeva, V. S. Usovskaya, and M. V. Rubtsov, KhGS [Chemistry of Heterocyclic Compounds], 296, 1965.

3. E. S. Nikitskaya, E. I. Levkoeva, V. S. Usovskaya, and M. V. Rubtsov, ZhOrKh, 1, 175, 1965.

4. G. Fodor and K. Nador, J. Chem. Soc., 721, 1953.

5. M. Balasubramanian, N. Padma, Tetrah. Lett., 49, 1963.

6. R. E. Lyle, J. Org. Chem., 22, 1280, 1957.

7. C.-Y. Chen and R. J. W. Le Fevre, J. Chem. Soc., 3467, 1965.

8. N. Bhacca and D. Williams, Applications of NMR Spectroscopy in Organic Chemistry, illustrations from the Steroid Field [Russian translation], Mir, Moscow, 66, 1966.

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Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific-Research Institute, Moscow