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PROCESSES OF HINDERED ROTATION IN N-METHOXY-N-ALKYLAMIDES

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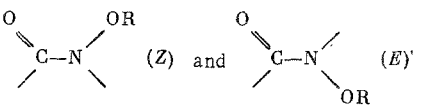
The processes of hindered rotation in the N-alkoxy-N-alkylamides RO(R)N−X (X = COR, N = O, SR, SO_2R) have been investigated intensely by the method of dynamic NMR for more than 10 years [1-3]. The observed inequivalence of the protons or groups in such compounds may be due to the processes of inversion of the N atom or rotation around the N−O, N−X and N−O, or N−X and N−R bonds, which are slow in the NMR time scale.

The main problems are to analyze these processes and to ascertain their nature. The possibility of the hindered inversion of the N atom is ruled out, since the planar configuration of the N atom has been established for N,O-dialkylhydroxamic acids, their thio analogs [4], and the sulfamides $(Me_2N)_2SO_2$ [5] and $PhSO_2(Cl_3CS)$-$NCH(Me)C_{10}H_7$ [6]. Therefore, the observed conformational changes are due only to hindered rotation around the N−substituent bonds. For example, synchronous rotation around N−CO and N−O bonds was detected in $PhCO(PhCO_2)NCH_2Ph$ ($\Delta G^{\neq}$ = 9.8 kcal/mole) [1], hindered rotation around N−CO and N−C bonds was detected in $MeCON(CH_2R)_2$ [for R = t-Bu $\Delta G^{\neq}$ = 11.9 kcal/mole (N−C)] [7], and such rotation around N−CO and N−S bonds was detected in $X-C_6H_4S(MeO_2C)NCH_2Ph$ [for X = p-Me $\Delta G^{\neq}$ = 12.1 kcal/mole (N−CO) and 9.1 kcal/mole (N−S)] [3].

In the present work we used the method of dynamic NMR to investigate the N-methoxy-N-alkylamides listed in Tables 1-3. The low-temperature PMR spectra of II (see Table 1, Fig. 1) reveal the inequivalence of the geminal methylene and methyl protons, which is caused by hindered rotation around the N−substituent bonds. The activation parameters of the hindered rotation in II were found from the merging of the signals of the indicator groups (see Table 1). The dependence of the values of $\Delta G^{\neq}$ on the nature of the substituent at the C=O group in IIa-IId indicates that the values found for $\Delta G^{\neq}$ correspond to hindered rotation around the amide bond. The lowering of $\Delta G^{\neq}$ in IIc and IId in comparison to IIa and IIb is attributed to the competitive weakening of the amide conjugation due to the interaction of the resonance-positive substituents with the C=O group. In the PMR spectra of IIa-IId the separated signals always have identical intensities, and the methylene protons produce a spectrum of the AB type (see Table 1 and Fig. 1). Therefore, in the present case, the magnetic inequivalence is caused not by the "freezing out" of the amide rotamers



but by the chirality of the compounds with a predominant (> 98%) Z or E configuration. The chirality of compounds IIa-IId is possible only if besides the hindered amide rotation there is at least one more hindered process, i.e., rotation around the N−O or N−C bond. The disappearance of the geminal inequivalence when the size of the N-alkyl substituent is reduced in I (see Table 1) indicates that hindered rotation around the N−C bond is responsible for the chirality of IIa-IId, although the limiting process in all cases is the amide rotation.

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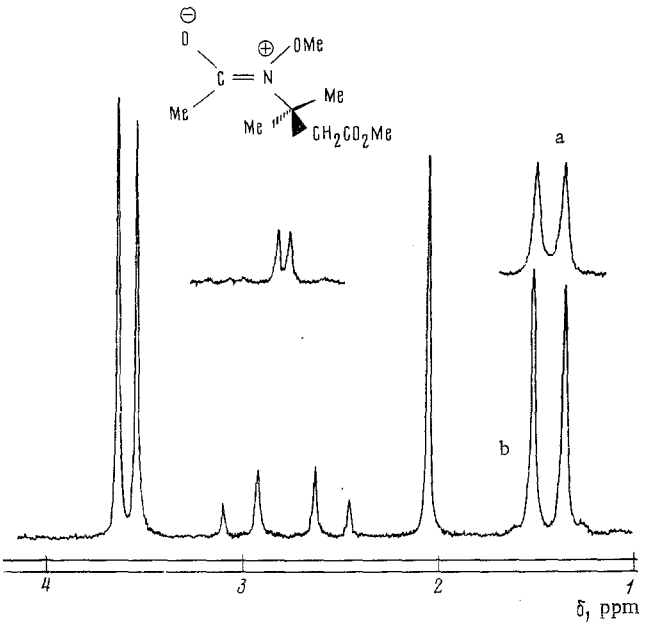

Fig. 1. PMR spectrum of the methyl ester of β-(N-acetyl-N-methoxyamino)isovaleric acid (IIa) in $CHFCl_2$ at 20 (a) and −50°C (b).

The observed geminal inequivalence of the Me_2C and CH_2 protons (the AB spectrum) is attributed to the following. The amide conjugation causes hindered rotation around the CO−N bond and fixation of the skeleton of the amide group in a plane. Therefore, the methyl group at CO prevents the rotation of the tertiary alkyl group at N and is oriented in the gap between its substituents Me and CH_2CO_2Me. As a result, the geminal groups are inequivalent, and the conformation as a whole is chiral. For this reason the methylene protons are also inequivalent due to the asymmetric induction of the chiral fragment of the molecule. The chirality of the compounds is unequivocally proved by the experiment with the optically active shift reagent $Eu(tfc)_3$ in the example of IIa. In this case, the PMR spectrum at 0°C shows two equivalent sets of MeO, CH_2, and Me_2C signals. The value of $\Delta G^{\neq}$ for amide rotation was determined on the basis of the merging of the Me_2C signals and coincided with the value found without the addition of the shift reagent (see Table 1).*

The predominance of one configuration for compounds IIa-IId has already been noted above. Signals of rotamers were likewise not found in the PMR spectra of N-methoxy-N-methylamides IV-VI upon cooling in various solvents (see Table 2). This is difficult to explain when we compare them to O,N-diacylhydroxylamines, such as MeCON(Me)OCOMe, whose PMR spectrum in $CDCl_3$ displays signals of rotamers in a 5:1 ratio upon cooling [1]. However, taking into account the data on the E configuration (100%) of MeC(S)−N(Me)OMe and the similar ratio of E and Z isomers HCON(Me)OMe (75% E) and HC(S)N(Me)OMe (84% E) [4], we may assume that compounds IV-VI also have an E configuration. This is supported by the data on the shift induced by an aromatic solvent for IV (see Table 2). As the size of the N-alkyl substituent is increased, for example, in HC(S)−N(OMe)R, the relative concentration of the E isomer decreases sharply (R = Me, 84; R = $PhCH_2$, 76; R = i-Pr, 51; R = t-Bu, 0%) [4]. Therefore, it may be concluded that all the compounds of type II have a Z configuration. Hence the sharp lowering of the barrier to rotation in IIe in comparison to IIa-IId (see Table 1) and HCON(OMe)Me ($\Delta G^{\neq}$ = 14.6 kcal/mole [4]) becomes understood. The value of $\Delta G^{\neq}$ for IIe corresponds to the barrier to rotation around the N−C bond and is not limited by the amide barrier owing to the small steric hindrances of the formyl proton in the Z form. The further decrease in the steric hindrances in III (the sp^2 lone pair of the Z NO group) results in free rotation around the N−C bond (see Table 1). The Z configuration of III follows from the data in [2].

In contrast to II, III (see Table 1), and IV-VI (see Table 2), the low-temperature spectra of N-methoxy-N-alkylcarbamoyl chlorides VII and VIII and N-methoxy-N-methylnitrosamine (IX) show signals of E and Z isomers, and the barriers to hindered amide rotation were found for the first time on the basis of their

*The determination of $\Delta G^{\neq}$ for rotation around a CO−aryl bond in the presence of a chiral shift reagent was accomplished for the first time in the example of 2,6-disubstituted benzamides in [10].

TABLE 1. PMR Spectra and Barriers to Hindered Rotation in the N-Methoxy-N-alkylamides $X(MeO)NCH_2CH_2CO_2Me$ (I) and $X(MeO)NCMe_2CH_2CO_2Me$ (II-III)

Compound	X	Solvent	δ[a], ppm, J, Hz				Observed group	Δν, Hz	T_m °C	$\Delta G^{\neq}_{T_m}$ ±0.25, kcal/mole
			Me_2C	CH_2	MeO; MeO_2C	others				
(I)[b]	MeCO	$C_6D_5CD_3$	–	2,27 (12,8) CH_2CO 3,65 (6,8) CH_2N	3,01 (48,7) 3,23 (17,2)	1,75 (16,7) MeCO	–	–	–	–
		$C_6D_5CD_3$	1,15; 1,33 (5,0)	2,69 (2,0); at −90° Δν=24, J_{AB}=13	3,08 (23,6) 3,17 (42,1)	1,73 (11,7) MeCO	Me_2C	17,5	38,0	16,0
(IIa)	MeCO	$C_6D_5CD_3$ (0°)[c]	3,36; 3,41 3,71; 4,05	4,75; 5,06	3,86; 3,92 4,60	2,11 (MeCO)	Me_2C	19,0	37,5	15,9
		CCl_4	1,32; 1,46	2,72; at −20° Δν=17, J_{AB}=12	3,50; 3,65	1,98 (MeCO)	Me_2C CH_2, J_{AB}=12	13,5 5,5	35,5 41,0	16,0 15,9
(IIb)	CF_3CO	$C_6D_5CD_3$	1,10; 1,23	2,50; at −40° Δν=23,0, J_{AB}=14	3,21, 3,30 (J_{HF}=0,7)	–	Me_2C	12,0	48,5	16,8
(IIc)	PhCO	$C_6D_5CD_3$	1,40	2,88; at −80° Δν=85, J_{AB}=15,5	2,95; 3,28	7,02 (Ph)	Me_2C	13,5	−18,0	13,0
(II d)	Ph(Me)CH–NHCO	$C_6D_5CD_3$	1,38	2,61	3,16; 3,23	1,20MeCH, J=7,1, 4,93$\overline{CH}$, 5,96NH, J_{NHCH}=8,0, 7,03Ph,	Me_2C	23,0	−28,5	12,3
		$(CD_3)_2CO$[d]	1,35	2,68; at −70° Δν=25, J_{AB}=14	3,48; 3,55	1,40MeCH, J=7 4,88$\overline{CH}$, 7,3Ph	MeO_2C	3,8	−38,0	12,5
(IIe)	H	$C_6D_5CD_3$ $CHFCl_2$	1,13 1,45	2,40 2,62	3,26; 3,47 3,63; 3,82	9,0CH –	CH_2, J_{AB}=17,3	– 30,0	– −78,0	– 9,2
(III)	NO[e]	$C_6D_5CD_3$	1,26	2,36	3,17; 3,40	–		–	–	–

[a] The shift induced by an aromatic solvent, i.e., the SIAS effect, $\Delta\delta = \delta(CCl_4) - \delta(C_6H_6)$, Hz, is given in parentheses.
[b] The spectrum remains unchanged upon cooling in $C_6D_5CD_3$ (−100°C) and $(CD_3)_2CO$ (−90°C).
[c] With an addition of the chiral shift reagent $Eu(tfc)_3$ in a 0.25 mole ratio relative to the sample.
[d] Signals of diastereomers are observed in $(CD_3)_2CO$ at −70°C; MeO and CO_2Me (3.42, 3.49, 3.50, 3.51 ppm).
[e] The spectrum remains unchanged in $C_6D_5CD_3$, $(CD_3)_2CO$, CD_3OD, CH_2Cl_2 (−90°C), CCl_4 (−20°C), C_6F_6 (−10°C), as well as with the addition of the shift reagent $Eu(dpm)_3$ (0.2 relative to the sample) at −40°C in $C_6D_5CD_3$.

TABLE 2. PMR Spectra and Barriers to Hindered Rotation in the Amides X–N(Me)OMe (IV-VII, IX) and X–N(i-Pr)OMe (VIII)

Compound	X	Solvent	Rotamer ratio (t, °C)	δ[a], ppm, J, Hz		Observed group	Δν, Hz	T_m, °C	$\Delta G^{\neq}$, ($\Delta \vec{G}^{\neq}$), kcal/mole
				MeN	MeO				
(IV)[b]	MeCO	$C_6D_5CD_3$	–	2,75(22,1) 1,65(14,6) MeCO	2,98 (55,7)	–	–	–	–
		$CDCl_3$	–	3,11 2,05 MeCO	3,62	–	–	–	–
(V)[b]	$(CF_3)_2CHCO$	CCl_4	–	3,19	3,68;4,70 CH, J_{HF} = 7,0	–	–	–	–
(VI)[b]	PhCO	$(CD_3)_2CO$	–	3,21	3,41	–	–	–	–
(VII)	COCl	$C_6D_5CD_3$	6(–50°)	2,61	3,09	MeO	4,0	–31,0	13,1 (13,9)
(VIII)	COCl	$C_6D_5CD_3$	4(–50°)	0,85 MeC 4,03HC	3,27	MeO	3,8	–43,0	12,5 (13,0)
(IX)	N=O	CCl_4	4[c] (–10°)	3.60	3,75	MeO[d]	10,0	13,0	14,9 (15,9)
		$(CD_3)_2CO$	4[c] (–10°)	3,73	3,73	MeO[d]	9,0	15,0	15,2 (16,0)

[a] The SIAS effect, $\Delta\delta = \delta(CCl_4) - \delta(C_6H_6)$, Hz, is given in parentheses.
[b] The spectra remain unchanged: IV in $C_6D_5CD_3$ (–100°C), $CDCl_3$ (–40°C), $(CD_3)_2CO$ (–30°C), and CCl_4 (–20°C); V in CCl_4 (–20°C), $(CD_3)_2CO$ (–90°C); VI in $(CD_3)_2CO$ (–90°C) and in CCl_4 (–20°C).
[c] Coincides with [2] (the ratio is ~4 in $CDCl_3$ at –30°C), in [8] the ratio is ~7 in $CDCl_3$ at –60°C.
[d] Merges with the MeN signal at T_m.

merging. The significant lowering of the barriers to amide rotation in N-methoxy-N-methylamides in comparison to the N-dimethyl analogs (Table 4) is apparently due to the reduction of the p character of the electron pair and, thus, to the +M capacity of the amide N atom under the influence of the –I effect of the MeO substituent [15]. The significant variation of the values of $\Delta\Delta G^{\neq}$ (see Table 4), which could hardly be attributed to the different measurement conditions and calls for further study, should be noted.

As in the case of the N-methoxy-N-alkylamides (see Tables 1 and 2), the low-temperature PMR spectra of p-toluenesulfonamides Xa-Xd reveal the geminal inequivalence of the CH_2N and Me_2C protons (see Table 3), which may be attributed to the hindered rotation around one of the three N–substituent bonds.

The possibility of hindered rotation around the N–C bond in Xa–Xd is ruled out because of the maintenance of the inequivalence of the CH_2N protons as the size of the N-alkyl substituent is reduced in Xb–Xd (see Table 3). Therefore, the values of $\Delta G^{\neq}$ found for p-toluenesulfonamides Xa and Xc (see Table 3) should be assigned to rotation around the N–O or N–S bond.

EXPERIMENTAL

The PMR spectra were measured on a Tesla BS-487C spectrometer (80 MHz), and the internal reference was HMDS. The concentration of the samples was ~15%. In the case of the dynamic measurements, the temperature in the spectrometer pickup was monitored with the aid of standard samples (methanol and ethylene glycol). The rate constants of hindered rotation were determined at the merging temperatures of the exchanging groups: $k = \pi\Delta\nu/\sqrt{2}$, for a spectrum of the AB type $k = (\pi/\sqrt{2})(\Delta\nu^2 + 6J^2)^{1/2}$. The values of $\Delta\nu$ were extrapolated to the merging temperature T_m of the signals. The change in free energy of activation $\Delta G^{\neq}$ were found according to [16] from the formula

$$\Delta G^{\neq} = 4{,}57 \cdot T_m (10{,}32 + \lg T_m - \lg k)$$

The error in the determination of $\Delta G^{\neq}$ was ≤ 0.3 kcal/mole with consideration of the measurement of $\Delta\nu \pm 2$ Hz and $T_m \pm 3°$.

The entropy change of activation $\Delta S^{\neq}$ in such systems for the process of hindered rotation was assumed to be close to zero, as in [16].

The specific rotation was measured on a Perkin–Elmer-141 polarimeter.

N-Methoxy-N-methylacetamide (IV). A solution of 8.2 g (84 mmole) of $MeO(Mo)NH_2 \cdot HCl$ [17] in 10% aqueous KOH was given an addition of 7.06 g (90 mmole) of MeCOCl at 0°C. The product was extracted by

TABLE 3. PMR Spectra and Barriers to Hindered Rotation in the p-Toluenesulfonamides TsN(OMe)R (Xa-Xd) and TsN(CH_2Ph) i-Pr (XI)

Compound	R	δ[a], ppm, J, Hz				Observed group	Δν, Hz	T_m, °C	$\Delta G^{\neq}_{T_m}$, kcal/mole
		CH_2N	MeO_2C	MeO	other				
(Xa)	$CMe_2CH_2CO_2Me$	2,52 (CH_2CO)	3,20	3,40	1,26Me_2C, 1,85MeC_6H_4, 6,70, 7,70C_6H_4, J=8,1	Me_2C	5,8	−4	14,3±0,25
(Xb)	$CH_2CH_2CO_2Me$	3,02 2,17 (CH_2CO)	3,21	3,56	1,87MeC_6H_4, 6,75, 7,55C_6H_4, J=8,2	CH_2N[b]	–	–	–
(Xc)	CH_2CO_2Me	3,86	3,23	3,53	1,91MeC_6H_4, 6,81, 7,61C_6H_4, J=8,2	CH_2N[c]	~17	~−34	~13,0
(Xd)	CH_2CO_2Et	3,48	–	3,86	0,80$MeCH_2$, J=7, 3,76CH_2O, 1,86MeC_6H_4, 6,73, 7,50C_6H_4, J=8,4	CH_2N[b]	–	–	–
(XI)	–	4,05	–	–	0,60MeCH, J=7,0, 3,96CH, 1,88MeC_6H_4, 7,10(Ph), 6,73, 7,52C_6H_4, J=8,3	CH_2N[d]	–	–	–

[a] In $C_6D_5CD_3$.
[b] The CH_2N, MeO, and MeO_2C signals overlap upon cooling.
[c] In $CHCl_2F$; at T_m the CH_2N and MeO signals partially overlap; at −90°C J_{AB} = 17; $\Delta\nu$ = 99 Hz.
[d] Broadens at −100°C; in R_2NSO_2Cl $\Delta G^{\neq}$(N−S) = 11.4 for R = Et and 11.0 kcal/mole for R = Bz [9].

TABLE 4. Barriers to Amide Rotation

Compound	Solvent	T_m, °C	$\Delta G^{\neq}$	$\Delta\Delta G^{\neq}$	Literature cited
			kcal/mole		
$HCONMe_2$	Pure liquid	129,5	20,9	–	[11]
HCON(Me)OMe	$CDCl_3$	19,5	14,6	6,3	[4]
MeCON(Me)OC(O)Me	$CDCl_3$	–16,0	14,2	–	[1]
$HCSNMe_2$	o-$Cl_2C_6H_4$	160,0	24,1	–	[12]
HCSN(Me)OMe	$(CD_3)_2CO$	110,0	19,6	4,5	[4]
$ClCONMe_2$	CCl_4	–	16,5	–	[13]
ClCON(Me)OMe	$C_6D_5CD_3$	–31,0	13,0	3,5	
$ONNMe_2$	Pure liquid	186,0	23,0	–	[14]
ONN(Me)OMe	$(CD_3)_2CO$	15,0	15,1	7,9	

ether, dried by $MgSO_4$, and distilled. The yield was 2.9 g (33.3%), bp 93-94°C (100 mm), n_D^{20} 1.4243. Found: C 47.09; H 8.87; N 13.28%. Calculated for $C_4H_9O_2N$: C 46.59; H 8.80; N 13.58%.

N-Methoxy-N-methyl-α-monohydrohexafluoroisobutyramide (V). A solution of 5.9 g (33 mmole) of bis(trifluoromethyl)ketene in 20 ml of ether at −78°C was given an addition of a solution of 1.83 g (30 mmole) of methoxymethylamine in 10 ml of ether. The mixture was left to stand for 48 h at 20°C. After the removal of the ether, the residue was distilled. The yield was 5.6 g (78.1%) of V, bp 62.5-63°C (7 mm), νCO 1706 cm^{-1}. Found: N 6.02%, Calculated for $C_6H_7O_2NF_6$: N 5.86%.

N-Methoxy-N-methylbenzamide (VI), bp 112°C (5 mm) (compare [15]).

N-Methoxy-N-methylcarbamoyl Chloride (VII). A solution of 49 g (0.5 mole) of $COCl_2$ in 100 ml of ether was given a dropwise addition of a solution of 6 g (0.1 mole) of MeO(Me)NH and 10.1 g (0.1 mole) of Et_3N in 50 ml of ether over the course of 1 h with cooling (−10 to −20°C) and stirring. The mixture was left to stand overnight at ~20°C, the precipitate was separated, the ether was driven off in a vacuum, and the residue was distilled. The yield was 5.54 g (44.9%) of VII, bp 59-60°C (18 mm), n_D^{20} 1.4405. Found: C 42.71; H 7.02; N 16.54%. Calculated for C_3H_6NOCl: C 42.85; H 7.19; N 16.63%.

N-Methoxy-N-isopropylcarbomoyl Chloride (VIII). Chloride VIII was obtained in an analogous manner from MeO(i-Pr)NH [17], 64.5% yield, bp 50°C (6 mm). Found: C 39.57; H 6.60; H 9.10%. Calculated for $C_5H_{10}NO_2Cl$: C 39.62; H 6.65; N 9.24%.

N-Methoxy-N-methylnitrosamine (IX), bp 59-60°C (30 mm) (compare [18]).

Methyl β-(N-Acetyl-N-methoxyamino)propionate (I). a) A mixture of 5.7 g (0.12 mole) of $MeONH_2$ [19] and 8.6 g (0.1 mole) of methyl acrylate was held for 96 h at 28°C and distilled. This yielded: 1) 9.87 g (74.2%) of methyl β-methoxyaminopropionate, bp 91-93°C (36 mm) (compare [20]). PMR spectrum (CCl_4, δ, ppm): 3.35 and 3.56 (MeO and MeO_2C), 2.03 and 2.41 [$(CH_2)_2$]. Found: 45.12; H 8.40; N 10.55%. Calculated for $C_5H_{11}NO_3$: C 45.08; H 8.32; N 10.51%. 2) 2.7 g (24.5%) of N-methoxybis(β-carbomethoxyethyl)amine, bp 148-151°C (18 mm). PMR spectrum (CCl_4, δ, ppm): 3.36 (MeON), 3.55 (MeO_2C), 2.41 and 2.49 [$(CH_2)_2$]. Found: C 49.38; H 7.81; N 6.52%. Calculated for $C_9H_{17}NO_5$: C 49.31; H 7.82; N 6.39%.

b) A solution of 1.33 g (10 mmole) of methyl β-methoxyaminopropionate and 2.53 g (25 mmole) of Et_3N in 30 ml of ether was given an addition of 1.94 g (25 mmole) of MeCOCl in 5 ml of ether, and the mixture was stirred for 2 h and left to stand overnight. The precipitate was separated and washed with ether, the ether was removed from the filtrate, and the residue was distilled. The yield was 1 g (57.2%) of I, bp 66-67°C (1 mm). Found: C 48.05; H 7.37; N 8.06%. Calculated for $C_7H_{13}NO_4$: C 47.97; H 7.48; N 7.99%.

Methyl β-(N-Acetyl-N-methoxyamino)isovalerate (IIa). a) A mixture of 3.76 g (80 mmole) of $MeONH_2$ and 4.3 g (38 mmole) of methyl β,β-dimethylacrylate [21] was heated in a sealed ampul for 14 days at 90°C. Distillation yielded 1.8 g of $MeONH_2$ and 3.97 g (65.3%) of methyl β-methoxyaminoisovalerate, bp 65°C (10 mm), n_D^{18} 1.4250. Found: C 52.28; H 9.31; N 8.62%. Calculated for $C_7H_{15}NO_3$: C 52.16; H 9.38; N 8.69%.

b) A solution of 966 mg (6 mmole) of the ester synthesized in 15 ml of pyridine was given an addition of 549 mg of MECOCl with stirring (10°C), and the mixture was left to stand overnight at ~20°C and then poured into 50 ml of ice water. The product was extracted with ether. After washing with water, drying by $MgSO_4$, and removing the ether in a vacuum, distillation yielded 530 mg (43.5%) of IIa, bp 73°C (1 mm). Found: C 53.07; H 8.53; N 7.08%. Calculated for $C_9H_{17}NO_4$: C 53.19; H 8.43; N 6.89%.

Methyl β-(N-Trifluoroacetyl-N-methoxyamino)isovalerate (IIb). A 1.86-g portion (14 mmole) of CF_3COCl was condensed in a solution of 966 mg (6 mmole) of methyl β-methoxyaminoisovalerate and 606 mg (6 mmole) of Et_3N in 20 ml of ether at −77°C. The mixture was left to stand overnight at −77°C and then for 6 days at ~20°C. After the salt was separated and the ether was driven off in a vacuum, the residue was distilled. The yield was 1.23 g (79.6%) of IIb, bp 62-63°C (1 mm). Found: C 42.29; H 5.33; N 5.53%. Calculated for $C_9H_{14}NO_4F_3$: C 42.03; H 5.49; N 5.45%.

Methyl β-(N-Benzoyl-N-methoxyamino)isovalerate (IIc). A mixture of 0.32 g (2 mmole) of methyl β-methoxyaminoisovalerate and 0.28 g (2 mmole) of PhCOCl in 10 ml of pyridine was held for 24 h at 20°C, poured into 25 ml of ice water, and extracted with ether. The extract was washed with water and dried with $MgSO_4$, the ether was driven off in a vacuum, and the residue was chromatographed in a column (silica gel, the eluent was $CHCl_3$). The yield was 0.46 g (86.5%) of IIc. Found: C 63.21; H 6.59; N 5.28%. Calculated for $C_{14}H_{19}NO_4$: C 63.38; H 7.22; N 5.28%.

Methyl β-(N-(S)-α-Phenylethylcarbamoyl-N-methoxyamino)isovalerate (IId). A solution of 251 mg (2.6 mmole) of methyl β-methoxyaminoisovalerate and 229 mg (1.6 mmole) of (S)-α-phenylethyl isocyanate in 5 ml of ether was held for 6 days at 20°C, the ether was driven off in a vacuum, and the residue was chromatographed in a column (silica gel, the eluent was $CHCl_3$). The yield was 350 mg (72.7%) of IId, $[\alpha]_D^{20}$ −7.34° (c 0.72, MeOH). Found: C 62.11; H 7.95; H 9.01%. Calculated for $C_{16}H_{24}N_2O_4$: C 62.32; H 7.84; N 9.08%.

Methyl β-(N-Formyl-N-methoxyamino)isovalerate (IIe). A solution of 0.64 g (4 mmole) of methyl β-methoxyaminoisovalerate, 0.28 g (6 mmole) of formic acid, and 1.24 g (6 mmole) of dicyclohexylcarbodiimide in 20 ml absolute CH_2Cl_2 was held for 24 h at 20°C. The precipitate was separated, the CH_2Cl_2 was removed from the filtrate in a vacuum, and the residue was distilled. The yield was 0.46 g (60.7%) of IIe, bp 89°C (1 mm). Found: C 50.98; H 7.52; N 7.38%. Calculated for $C_8H_{15}NO_4$: C 50.78; H 7.99; N 7.40%.

Methyl β-(N-Nitroso-N-methoxyamino)isovalerate (III). A solution of 1.66 g (24 mmole) of $NaNO_2$ in 4 ml of water was added with stirring over the course of 15 min to a mixture of 1.3 g (8 mmole) of methyl β-methoxyaminoisovalerate and 1.44 g (24 mmole) of $MeCO_2H$ at 0°C. The mixture was stirred for an additional 1.5 h and left to stand overnight at 20°C. The product was extracted with ether, the extract was dried by $MgSO_4$, the solvent was driven off in a vacuum, and the product was distilled. The yield was 0.59 g (38.7%) of III, bp 87° (1 mm). Found: C 44.14; H 7.42; N 14.73%. Calculated for $C_7H_{14}N_2O_4$: C 44.21; H 7.42; N 14.78%.

Methyl β-(N-p-Toluenesulfonyl-N-methoxyamino)isovalerate (Xa). A mixture of 161 mg (1 mmole) of methyl β-methoxyaminoisovalerate and 191 mg (1 mmole) of p-toluenesulfonyl chloride in 1 ml of pyridine was held for 48 h at 20°C and poured into 10 ml of ice water. The precipitate was separated and recrystallized from hexane. The yield was 250 mg (79.2%) of Xa, mp 73-74°C. Found: C 53.28; H 6.64; N 4.60%. Calculated for $C_{14}H_{21}NO_5S$: C 53.32; H 6.71; N 4.44%.

Methyl β-(N-p-Toluenesulfonyl-N-methoxyamino)propionate (Xb). A mixture of 612 mg (4 mmole) of methyl β-methoxyaminopropionate and 950 mg (5 mmole) of p-toluenesulfonyl chloride in 10 ml of pyridine was held for 1 h at 0°C, left to stand overnight at 20°C, and poured into 60 ml of ice water. The precipitate was separated, washed with water, dried, and recrystallized from hexane. The yield was 820 mg (71.2%) of Xb, mp 57-58°C. Found: C 49.98; H 5.94; H 4.91%. Calculated for $C_{12}H_{17}NO_5S$: C 50.16; H 5.96; N 4.87%.

Methyl N-p-Toluenesulfonyl-N-methoxyaminoacetate (Xc). a) Methyl N-methoxyaminoacetate was obtained under the conditions in [22], 6.2% yield, bp 51-52°C (9 mm).

b) Under the conditions of the synthesis of Xa 520 mg (63.3%) of Xc were recovered from 357 mg (3 mmole) of the ester obtained and 570 mg (3 mmole) of p-toluenesulfonyl chloride. The mp was 73-74°C (from hexane). Found: C 48.41; H 5.83; N 5.06%. Calculated for $C_{11}H_{15}NO_5S$: C 48.32; H 5.53; N 5.12%.

Ethyl N-p-Toluenesulfonyl-N-methoxyaminoacetate (Xd). Under the conditions of the synthesis of Xa, 133 mg (1 mmole) of ethyl N-methoxyaminoacetate [22] and 190 mg (1 mmole) of p-toluenesulfonyl chloride yielded 150 mg (54.1%) of Xd, mp 56-57°C (from hexane). Found: C 51.91; H 6.08; N 4.98%. Calculated for $C_{12}H_{17}NO_5S$: C 51.97; H 6.18; N 5.05%.

N-Benzyl-N-isopropyl-p-toluenesulfonamide (XI). Under the conditions of the synthesis of Xa, 1.49 g (10 mmole) of N-benzyl-N-isopropylamine and 1.90 g (10 mmole) of p-toluenesulfonyl chloride yielded 1.85 g (61%) of XI, mp 97-98°C (from hexane). Found: C 67.21; H 6.83; N 4.68%. Calculated for $C_{17}H_{21}NO_2S$: C 67.29; H 6.98; N 4.62%.

CONCLUSIONS

1. The chirality of N-tert-alkyl-N-methoxyamides due to rotation around the N–CO and N–C bonds which is slowed in the NMR time scale has been discovered, and its dependence on the type of N-alkyl substituent and the type of substituents at the C=O group has been studied.

2. The barriers to hindered amide rotation in N-methoxy-N-methylnitrosamine and N-methoxy-N-alkylcarbamoyl chlorides have been determined.

3. The hindered process in N-methoxy-N-alkyl-p-toluenesulfonamides corresponds to rotation around the N–O or N–S bond.

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