ASYMMETRIC NITROGEN.

68.* GEMINAL SYSTEMS.

42.* DIASTEREOMERIC NH-DIALKOXYAMINES WITH AN ASYMMETRIC NITROGEN ATOM IN AN OPEN CHAIN

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UDC 541.63:543.422.25:547.495

Progress in the investigation of asymmetric trivalent N atoms depends on the development of methods for synthesis and optical activation of a wide range of configurationally stable compounds [2], including those with an asymmetric N atom in an open chain [2-4]. These compounds are used in asymmetric syntheses for construction of chiral centers at C and S atoms [2] and for studying stereochemical problems and reaction mechanisms at trivalent N atoms [2, 5]. In this respect the possibility of existence in optically active form of compounds with an asymmetric nitrogen atom in the NH group is of principal importance. The lack of success in separating the enantiomers of secondary amines, attempted even about 100 years ago (see [6]), is explained by their fast interconversion due to inversion of the N atom as well as HN exchange. These two processes are substantially hindered in the NH-dialkoxyamines synthesized by us [7], raising the hope of their separation into optical isomers.

Separation of stereoisomers is facilitated by the presence of a functional group which provides an auxiliary chiral center. However, functionally substituted NH-dialkoxyamines were not previously known. Aliphatic NH-dialkoxyamines were obtained by alkaline hydrolysis or alcoholysis of 1,1-dialkoxy-3,3-dimethylureas [7]. Attempts at alcoholysis of the described functionally substituted N,N-dialkoxyureas of the type B [8] [Scheme (1)] in order to synthesize the corresponding NH-dialkoxyamines were unsuccessful, apparently due to proton abstraction from the α-position to ester group by base and further transformations of the anion so generated. Thus, the base catalyzed fragmentation of compounds $\rangle NOCH_2CO_2R$ is known [9]:

$$\underset{(A),\ n=1,2}{Me_2NCON(Cl)O(CH_2)_nCO_2Me} \xrightarrow{ROH} \underset{(B)}{Me_2NCON(OR)O(CH_2)_nCO_2Me} \xrightarrow{MeOH/MeONa} HN(OR)O(CH_2)_nCO_2Me \qquad (1)$$

Moreover, it was shown earlier [8] that while alcoholysis of N-chloro-N-alkoxyurea (A) (n = 2) is realized easily with formation of N,N-dialkoxyurea (B), from urea (A) (n = 1) the product of nucleophilic substitution of the Cl atom is formed in insignificant yield, since nucleophilic attack at the carbonyl group dominates. The decreased susceptibility of N-chloro-N-alkoxyurea (A) (n = 1) to nucleophilic substitution at Cl is explained by the weakened $n_{\pi(O)} - \sigma^*_{N-Cl}$ orbital interaction responsible for the mobility of Cl in geminal ONCl systems due to stabilization of the $n_\pi(O)$-orbitals by the electronegative substituent at the α-carbon atom of the n-alkoxy group [8]. Considering the two above limitations on the preparation of N,N-dialkoxyureas and their alkaline hydrolysis, we synthesized the functionally substituted diastereomeric NH-dialkoxyamine (IV) [Scheme (2)]:

$$HBr\cdot NH_2OC(Me)_2CO_2H \xrightarrow[2.\ SOCl_2]{1.\ KOH} [HCl\cdot NH_2OC(Me)_2COCl] \xrightarrow{S\text{-}PEA}$$

$$\longrightarrow \underset{S\text{-(I)}}{NH_2OC(Me)_2CONHC(Me)(H)(Ph)} \xrightarrow{Me_2NCOCl} \underset{S\text{-(II)}}{Me_2NCONHOC(Me)_2CONHC(Me)(H)(Ph)} \longrightarrow$$

*For previous communication, see [1].

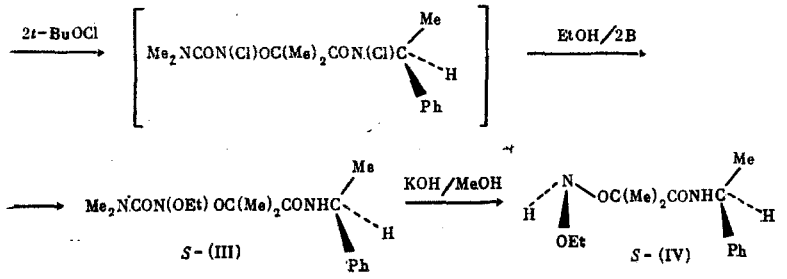
Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2788-2792, December, 1988. Original article submitted July 16, 1987.

0568-5230/88/3712-2513$12.50

TABLE 1. Barriers of Inhibited Processes in 1,1-Dialkoxy-3,3-dimethylurea (III) and NH-Dialkoxyamine (IV) (80 MHz, $C_6C_5CD_3$)

Compound	Observed group	$\Delta\nu$, Hz (J_{AB}, Hz)	T_c, °C	k, sec^{-1}	$\Delta G^{\neq}_{inv}(\Delta G^{\neq}_{rot})$ at T_c, kcal/mole[a]
(III)	$Me_A(Me_B)N$[b]	5.8	−1	12.88	(14.5)
	Me_AN[c]	4	−40	8.88	12.5[d]
	Me_BN[c]	7	−30	15.54	12.8[d]
	CH_2{Me}	2.8(8.1)	−13	76.06	12.9[d]
(IV)	MeCH	1.7	64	3.77	18.9

[a]Determined as in [10].
[b]Nonequivalent due to inhibited amide rotation (see Fig. 1).
[c]Two signals of diastereomers are observed (see Fig. 1).
[d]Barriers of inversion of the N^1 nitrogen atom according to various indicator groups, spread of values caused by determination error of quantities $\Delta\nu$ and T_c.



(2)

where PEA is α-phenylethylamine and B is γ-collidine.

As was expected, replacement of the ester group in N-chloro-N-alkoxyura (A) (n = 1) by the less electron accepting amide group promotes smooth nucleophilic substitution at the Cl atom. The absence in N,N-dialkoxyurea (III) of labile protons on the N-alkoxy group ensures its unambiguous alkaline hydrolysis to (IV). It is also necessary to note that chlorination of N-alkoxyurea (II) by excess t-BuOCl followed by treatment of the product formed with an alcohol solution of 2 moles of base leads to N,N-dialkoxyurea (III) and 2 moles of base hydrochloride. This indicates intermediate formation upon chlorination of the corresponding N,N'-dichloro derivative, in which the N−Cl bonds are polarized in opposite directions and show different properties. This example illustrates the exceptional character of the N−Cl bond in N-chloro-N-alkoxyureas [8].

In the PMR (80 and 400 MHz) of N,N-dialkoxyurea (III) at 20°C geminal anisochronism of the diastereotopic methyl protons (Me_2C) is observed, which is caused by the presence of the chiral carbon center. For the methylene protons this is not observed due to their significant distance from the chiral center. Upon cooling below −1°C the Me_2N signal splits due to inhibited rotation around the Me_2N-CO bond, the barrier to which was found from the coalescence of the signals (Fig. 1, Table 1). It is first order as in other 1,1-dialkoxy-3,3-dimethylureas [10]. At −50°C in the PMR spectrum of (III) signals of two diastereomers (doubling of proton signals of all groups) and geminal anisochronism of the methylene protons are observed. This can be explained by slow inversion of the nitrogen chiral center, since in 1,1-dialkoxyureas the inversion barrier of the N^1 atom is ~10-11 kcal/mole [10]. From the coalescence of the proton signals of the diastereomers (Me_2N and CH_2) (III) a similar value for the epimerization barrier was found (Fig. 1, Table 1). The above experiment for (III) is the first observation of diastereomers with an symmetric acyclic amide N atom. Previously observed diastereomers with asymmetric amide N atoms were N-carbamoyl derivatives of diaziridines and oxaziridines [11].

In the PMR spectrum of NH-dialkoxyamine (IV) (Fig. 2) diastereomers (1:1) are observed under normal conditions due to the high configurational stability of the chiral NH nitrogen. From the coalescence of the methyl signals (MeCH) of the diastereomers the inversion barrier was determined for the N atom (Table 1). From the value of the inversion rate constant the epimerization half life of (IV) at 20°C was calculated as 8.5 sec. Nevertheless, by one crystallization under ordinary conditions, compound (IV) was enriched in one diastereomer to a

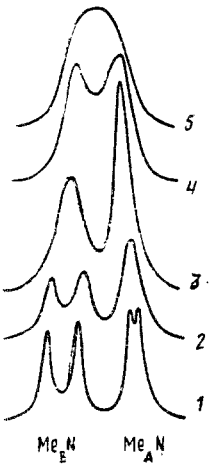


Fig. 1

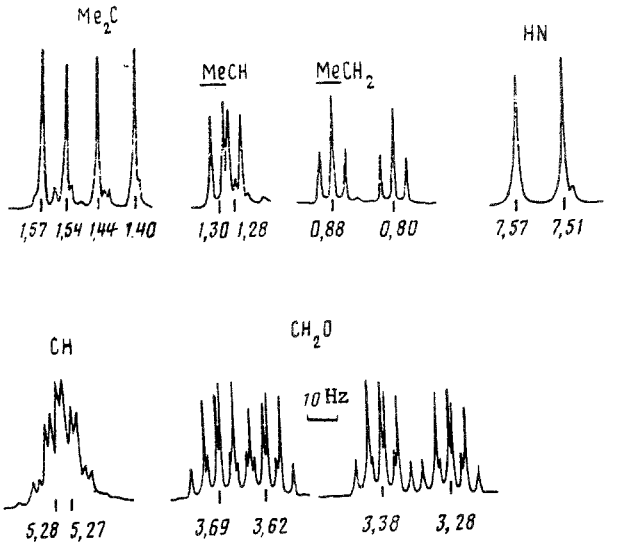


Fig. 2

Fig. 1. Temperature dependence of the PMR spectrum (80 MHz, $C_6D_5CD_3$) of the compound (III) Me_2N group: 1) −50°C, groups Me_A and Me_B of the diastereomers nonequivalent due to inhibited amide rotation; 2) −40°C, fast epimerization according to signals of diastereomers with lower $\Delta\nu$ (Me_A); 3) −30°C, fast epimerization also according to the signals with high $\Delta\nu$ (Me_B); 4) −5°C, only amide rotation inhibited; 5) −1°C, amide rotation and epimerization fast on the NMR time scale.

Fig. 2. PMR spectrum (400 MHz, $C_6D_5CD_3$, 20°C) of NH-dialkoxyamine (IV) (signals recorded at different intensities).

ratio of ~1.5 (PMR at −40°C in $CDCl_3-C_6D_5CD_3$, by HN and $MeCH_2$ signals).

EXPERIMENTAL

PMR spectra were obtained on a Bruker WP-80SY (80 MHz) and a Bruker WM-400 (400 MHz) spectrometer relative to TMS. Optical rotation was measured on a Polamat-A polarimeter.

In the synthesis S-(−)-PEA with $[\alpha]_D$ −33.7° (neat) and optical purity of 83% was used. The hydrobromide of α-aminooxylisobutyric acid as obtained according to [12] in 78% yield with an mp of 160-162°C.

S-α-Phenylethylamide of α-Aminooxyisobutyric Acid S-(I). A solution of 4 g (20 mmoles) of the hydrobromide of α-aminooxyisobutyric acid in 10 ml of MeOH was neutralized with a solution of 1.12 g (20 mmoles) of KOH in 10 ml of MeOH. The salt precipitate was separated and the filtrate was evaporated under vacuum. To the residue 16 ml of $SOCl_2$ was added dropwise at 0°C with stirring. The mixture was stirred for 1 h at 20°C and 2.5 h at 40°C. Excess $SOCl_2$ was removed under vacuum and the residue was dissolved in 20 ml of abs. $CHCl_3$. The obtained solution was added dropwise at 0°C with stirring to a solution of 7.26 g (60 mmoles) of S-(−)-PEA in 100 ml of abs. $CHCl_3$. The mixture was left for a night, then diluted with 20 ml of H_2O and saturated with CO_2. The organic phase was separated, dried over $MgSO_4$, and evaporated under vacuum. The residue was chromatographed on a column (Al_2O_3 neutr. according to Bruckmann, eluent: ether−benzene, 1:1). The product was crystallized from a CCl_4−pentane mixture. There was obtained 3.25 g (73.1%) of S-(I) with mp of 85°C, $[\alpha]_D$ −70.7°C (1.4 MeOH). PMR spectrum (80 MHz, $CdCl_3$; δ, ppm; J, Hz): 1.33, 1.35 (Me_2C), 1.44 (MeCH, ^3J = 6.9), 4.98 (NH_2), 5.08 (CH, J_{CHNH} = 7.1), 6.58 (NH), 7.25 (Ph). Found: C 64.94; H 8.34; N 12.43%. $C_{12}H_{18}N_2O_3$. Calculated: C 64.84; H 8.16; N 12.60%.

S-α-Phenylethylamide of α-(N-dimethylcarbamoylaminooxy)isobutyric Acid S-(II). A solution of 0.88 g (3.9 mmoles) of S-(I), 0.43 g (4 mmoles) of dimethylcarbamoyl chloride and 0.4 g (4 mmoles) of Et_3N in 30 ml of abs. MeCN was kept for 3 days at 20°C and then refluxed for 7 h. The residue was separated, the filtrate evaporated under vacuum, and the residue extracted with C_6H_6. The extract was evaporated under vacuum and the residue crystallized from CCl_4. There was obtained 0.67 g (57.9%) of S-(II) with mp of 125°C, $[\alpha]_D$ −39.6° (1.4

MeOH). PMR spectrum (400 MHz, $CDCl_3$): 1.42, 1.49 (Me_2C), 1.44 (MeCH, ^3J = 7.1), 2.86 (Me_2N), 5.02 (CH, J_{CHNH} = 7.6), 7.30 (Ph), 8.79 (NH). Found: C 60.90; H 7.82; N 14.41%. $C_{15}H_{23}N_3O_3$. Calculated: C 61.41; H 7.90; N 14.32%.

S-α-Phenylethylamide of α-(N-dimethylcarbamoyl-N-ethoxyaminooxy)isobutyric Acid S-(III). To a suspension of 0.67 g (2.3 mmoles) of S-(II) in 20 ml of an $Et_2O-C_6H_6$ mixture (1:3) at 0°C 0.65 g (6 mmoles) of t-BuOCl was added. The mixture was stirred until complete dissolution of the starting compound and evaporated under vacuum in the cold. To the residue at −78°C a solution of 0.28 g (2.3 mmoles) of γ-collidine in 10 ml of EtOH was added. The mixture was kept for 1 h at 0°C and 0.5 at 20°C, then evaporated under vacuum, and the residue extracted with Et_2O. The extract was evaporated under vacuum and the residue chromatographed on a column (Al_2O_3 neutr. according to Bruckmann, Et_2O eluent). There was obtained 0.5 g (64.4%) of S-(III) (oil), $[\alpha]_D$ = −26.4° (0.9 C_6H_6). PMR spectrum (80 MHz, $C_6D_5CD_3$, 20°C): 0.80 (MeCH$_2$, ^3J = 7.2), 1.29 (MeCH, ^3J = 7.1), 1.42, 1.50 (Me_2C), 2.40 (Me_2N), 3.55 (MeCH$_2$), 5.15 (CH, J_{CHNH} = 7.5), 8.05 (NH). PMR spectrum (80 MHz, $C_6D_5CD_3$, −50°C): 0.69, 0.78 (MeCH$_2$, ^3J = 7.2), 1.20, 1.29, 1.34, 1.44, 1.56, 1.63 (Me_2C, MeCH), 2.14, 2.15 and 2.25, 2.32 (Me_2N), 3.33, 3.77 (MeCH$_2$, J_{AB} = 8.1, Δν 3 Hz), 5.18 (CH), 8.47, 8.65 (NH). Found: C 60.86; H 8.21; N 12.31%. $C_{17}H_{27}N_3O_4$. Calculated: C 60.51; H 8.06; N 12.45%.

S-α-Phenylethylamide of α-(N-ethoxyaminooxy)isobutyric Acid S-(IV). A solution of 1.48 g (4.4 mmoles) of S-(III) and 0.25 g (4.4 mmoles) of KOH in 10 ml of MeOH was kept over night at 20°C, saturated with CO_2, and evaporated under vacuum, the residue was extracted with Et_2O and the extract evaporated under vacuum. The residue was chromatographed on a column (Al_2O_3 neutr. according to Bruckmann, eluent Et_2O−pentane, 2:1) and the product crystallized from pentane−CCl_4 (2:1). There was obtained 0.35 g (29.9%) of S-(IV) with mp of 68-69°C, $[\alpha]_D$ −67.8° (with C_6H_6). PMR spectrum (400 MHz, $CDCl_3$): 0.92, 1.03 (MeCH$_2$, ^3J = 7.1), 1.24, 1.29 and 1.30, 1.34 (Me_2C), 1.32, 1.33 (MeCH, ^3J = 6.9), 3.49, 3.75 and 3.64, 3.84 (MeCH$_2$, J_{AB} = 9.3), 4.91, 4.92 (MeCH, J_{CHNH} = 7.1), 6.79 (CONH), 7.75, 7.80 (NH). Found: C 63.14; H 8.38; N 10.45%. $C_{14}H_{22}N_2O_3$. Calculated: C 63.14; H 8.33; N 10.52%.

CONCLUSIONS

1. For the first time a diastereomerically enriched acyclic NH-dialkoxyamine with asymmetric nitrogen atom in the NH group was obtained.

2. By low-temperature PMR spectra the diastereomers of a 1,1-dialkoxyurea with asymmetric amid enitrogen atom were observed.

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