cis–trans Isomerism of Thioncarbamate Esters

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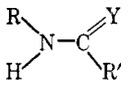
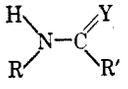
Hindered rotation due to the partial double-bond character of the nitrogen–carbonyl bond is the cause of a form of *cis–trans* isomerism of N-alkylamides[1] and thioamides.[2] This can usually be detected in the nmr



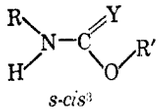
s-cis[3]



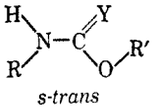
s-trans

spectra of such compounds either by observation of both of the possible isomers, or of a single preferred form. The former is the case, for example, with N-alkylformamides[4] and thioacetanilides,[5] whereas the latter condition prevails with N-alkylacetamides (and higher amides)[4] and thiopivalanilides.[5] Although solvent, temperature, and concentration may all affect the isomer ratio, it can be said in general for these secondary amides and thioamides that the *s-cis* conformation is preferred even when R is a bulky group, and, if R′ is bulky, it is the exclusive conformation.

Since carbamate esters,[6] like carboxylic esters,[7] have been shown in those cases examined to have the *s-cis* conformation of alkyl group and carbonyl oxygen, the resultant lessening of steric hindrance might make the *s-trans* conformation of the N-alkyl group and the carbonyl oxygen less unfavorable than it has been found to be in amides. However, nmr spectra of methyl N-alkylcarbamates[8] showed no evidence for two isomeric



s-cis[3]



s-trans

forms, and ethyl N-(*p*-methylphenylsulfamylmethyl)-carbamate,[9] which apparently shows some isomerism in the ester function, displayed none due to the amide bond. A barrier to rotation does exist in N,N-dimethylcarbamates, but it must be less than that in amides since it was observed only at subzero temperatures for alkyl esters,[10] although with electron-withdrawing aryl esters[10,11] even at room temperature. The barrier seems to be even lower in thiolcarbamates.[11]

No reports have been published on the isomerism of thioncarbamate esters. Provided there is a sufficient barrier to rotation in these compounds, the greater size of the sulfur atom should make the *s-trans* conformation more favorable than in the corresponding carbamate esters. This factor of size is not, however, sufficient to change the preferred conformation of thioncarboxylic esters, which has been found[12] to be *s-cis*.

Results and Discussion

We have examined nine N-alkylthioncarbamate esters and found in their nmr spectra clear evidence for the coexistence of two isomeric forms. For example, in the spectrum of O-ethyl methylthiocarbamate as a 1 *M* solution in carbon tetrachloride at 36°, each of the four types of proton in the ester portion of the molecule as well as the amide portion, exhibits two signals. That this is not due to tautomerism follows from the splitting of both N–C*H*$_3$ resonances into doublets. We have also excluded the remote possibility that we are dealing with a case of thiol–thion isomerism by converting the thioncarbamate into the isomeric thiol form. The infrared spectrum of the latter shows very strong carbonyl absorption (1660 cm^{-1}) which is missing in the spectrum of the thioncarbamate. Also the nmr spectrum has single signals for each of the proton types and is not identical with either of the isomeric thioncarbamates.

In carbon tetrachloride and chloroform-*d* where the spectra of O-ethyl methylthiocarbamate are similar the differences in chemical shifts for the two sets of N–CH$_3$ and N–H protons are much larger than those of the O-alkyl protons which supports the interpretation that the isomerism is about the amide-type bond rather than the ester-type bond. Furthermore, in benzene-d_6 the difference in shifts of the N–CH$_3$ groups is even larger, whereas that for the O-alkyl protons is so small as to be unmeasurable in our spectra.

By integration of the N–CH$_3$ signals it was found that the isomer ratio in carbon tetrachloride and chloroform was 64:36, in benzene 67:33, and in pyridine 76:24. At lower temperatures (to −16°) in chloroform the isomer ratio approached 50:50. Within the temperature range studied (−16 to +50°) the chemical shifts were not temperature dependent (at least in chloroform) except for the N–*H* of the two isomers; for the major isomer this varied from δ 7.0 to 6.6, and for the minor isomer from 8.0 to 7.2. The coupling constants for the N–CH$_3$ and N–H protons of the two isomers were slightly different, J = 4.7 Hz for the major and 5.1 Hz for the minor isomer.

Chemical-shift data in four solvents for the other esters examined and isomer ratios where determined are given in Table I. It is remarkable that in the esters with larger alkyl groups the terminal methyls, far removed from the nitrogen–thiocarbonyl bond, still gave separate signals for each isomer, although not in all solvents.

In pyridine no N–H proton was observed, probably due to masking by solvent protons. In the amino esters the N–*H* signals were not separated; perhaps they become indistinguishable by some interaction with the basic amino groups. Some other evidence for an intramolecular effect of the tertiary amino group comes from the isomer ratio which was usually significantly smaller in the aliphatic solvents than in pyridine, but

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(2) W. Walter and G. Maerten, *Ann.*, **669**, 66 (1963).
(3) For consistency the terms *cis* and *trans* are used in this paper to designate the relationship of the carbonyl oxygen or sulfur (Y in the formulas) and the N-alkyl or O-alkyl groups.
(4) L. A. LaPlanche and M. T. Rogers, *J. Am. Chem. Soc.*, **86**, 337 (1964).
(5) I. D. Rae, *Can. J. Chem.*, **45**, 1 (1967).
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(8) E. H. White, M. C. Chen, and L. A. Dolak, *J. Org. Chem.*, **31**, 3038 (1966).
(9) S. van der Werf, T. Olijnsma, and J. B. F. N. Engberts, *Tetrahedron Letters*, No. 8, 689 (1967).
(10) E. Lustig, W. R. Benson, and N. Duy, *J. Org. Chem.*, **32**, 851 (1967).
(11) T. M. Valega, *ibid.*, **31**, 1150 (1966).
(12) H. Lumbroso and P. Reynaud, *Compt. Rend.*, **262C**, 1739 (1966).

TABLE I

CHEMICAL SHIFTS[a,b] OF THIONCARBAMATE ESTERS

Solvent[c]	1		Esters						Isomer ratio *cis/trans*
			CH_3	NH	C(S)O	CH_3			
$CDCl_3$			3.08 2.88	6.6 7.2		3.98 4.07			62:38
CCl_4			3.05 2.88	6.5 7.6		3.93 4.03			63:37
C_6D_6			2.63 2.23	5.6 6.9		3.75			66:34
C_5H_5N			3.16 2.83			4.03 4.09			73:27
	2		CH_3	NH	C(S)O	CH_2	CH_3		
$CDCl_3$			3.08 2.87	6.5 7.1		4.50 4.56	1.30 1.37		64:36
CCl_4			3.03 2.87	6.5 7.6		4.43 4.50	1.30 1.37		64:36
C_6D_6			2.65 2.28	5.7 6.9		4.41	1.05		67:33
C_5H_5N			3.13 2.81			4.58 4.62	1.21 1.26		76:24
	3		CH_3	NH	C(S)O	CH_2	CH	$(CH_3)_2$	
$CDCl_3$			3.08 2.88	6.5 7.2		4.20 4.27		1.02 0.91	58:42
CCl_4			3.03 2.88	6.6 7.7		4.14 4.22		1.03 0.92	62:38
C_6D_6			2.66 2.30	5.6 7.0		4.25		0.81	66:34
C_5H_5N			3.13 2.82			4.35 4.40		0.92 0.82	75:25
	4		CH_3	NH	C(S)O	CH_2	CH_2CH	$(CH_3)_2$	
$CDCl_3$			3.08 2.86	6.5 7.2		4.47 4.52		0.95	60:40
CCl_4			3.03 2.86	6.4 7.7		4.39 4.47		0.97 0.95	60:40
C_6D_6			2.67 2.32	5.7 7.0		4.50		0.82	65:35
C_5H_5N			3.13 2.82			4.60 4.65		0.82 0.88	80:20
	5		CH_3	NH	C(S)O	$C(CH_3)_3$			
$CDCl_3$			3.00 2.78	6.4 7.0		1.63 1.68			62:38
CCl_4			2.95 2.78	6.3 7.5		1.60 1.67			62:38
C_6D_6			2.60 2.24	5.3 6.9		1.58			70:30
C_5H_5N			3.08 2.75			1.67 1.73			76:24
	6		$(CH_3)_2C$	NH	C(S)O	CH_3			
$CDCl_3$			1.35 1.50	6.9		4.08 3.90			
CCl_4			1.38 1.45	7.3 6.2		4.01 3.88			
C_6D_6			1.02 1.28	7.2		3.81			33:67
C_5H_5N			1.31 1.60			4.10 3.93			37:63
	7		CH_3	NH	C(S)O	CH_2	CH_2	$N(CH_3)_2$	
$CDCl_3$			3.03 2.87	7.6		4.56 4.61	2.63 2.69	2.28 2.30	74:26
CCl_4			2.97 2.85	7.9		4.50 4.52	2.59 2.64	2.27	75:25
C_6D_6			2.80 2.45	7.4		4.53 4.58	2.38 2.41	2.02 2.04	
C_5H_5N			3.12 2.83	9.8		4.71 4.78	2.58 2.66	2.17 2.22	74:26
	8		CH_3	NH	C(S)O	CH_2	$(CH_2)_2$	$N(CH_3)_2$	
$CDCl_3$			3.05 2.85	7.5		4.46 4.52		2.23	67:33
CCl_4			3.00 2.85	7.6 7.9		4.39 4.46		2.20	67:33
C_6D_6			2.80 2.38	7.1		4.50 4.53		2.02	
C_5H_5N			3.14 2.83	9.7		4.66 4.72		2.08 2.15	80:20
	9	CH_3	CH_2	NH	C(S)O	CH_2	CH_2	$N(CH_3)_2$	
$CDCl_3$		1.20 1.17	3.55 3.31	7.2		4.54 4.60	2.63 2.70	2.28	
CCl_4		1.19 1.15	3.49 3.29	7.6		4.48 4.54	2.59 2.64	2.25	
C_6H_6		0.92 0.77	3.42 2.93	5.9		4.57 4.63	2.42 2.45	2.05	
C_5H_5N		1.20 1.12	3.69 3.33			4.72 4.76	2.59 2.67	2.17 2.22	

[a] Values are in parts per million downfield from tetramethylsilane on Varian A-60A spectrometer. [b] Shift of major isomer given first. [c] The solute is 1 *M* at 37°.

became equal in the various solvents for O-2-dimethylaminoethyl methylthiocarbamate (7).

In an earlier work[13] we had recorded the spectrum of O-ethyl *p*-chlorothiocarbanilate in chloroform-*d* and had seen no evidence for isomerism. Repetition in benzene and pyridine still showed but one set of signals for each type of proton. This may represent either an overwhelming preference for one isomer or an intramolecular effect of a benzene ring similar to that of benzene as a complexed solvent.

We also recorded the spectrum of 2-dimethylaminoethylmethyldithiocarbamate which also showed two isomeric forms. In pyridine at 36° the ratio was 90:10.

From the data at hand deductions can be made as to the particular conformation to be assigned to the major and minor isomers, either by comparison of the chemical shifts with those of known compounds or by the method of solvent-induced shifts.[14]

For amides the alkyl group *cis* to the carbonyl oxygen has been determined[4,15] to resonate at higher field than the *trans* group. However, in a recent comparison[16] of N,N-dimethylacetamide with the corresponding thioamide it was concluded that the magnetic anisotropy of thiocarbonyl is opposite that of carbonyl. This is substantiated by work[17] on N-methyl-N-benzylthio-

(13) R. A. Bauman, *J. Chem. Eng. Data*, **11**, 274 (1966).

(14) J. Ronayne and D. H. Williams, *Chem. Comm.*, 712 (1966).

(15) D. L. Hooper and R. Kaiser, *Can. J. Chem.*, **43**, 2363 (1965).

(16) H. Paulsen and K. Todt, *Angew. Chem. Intern. Ed. Engl.*, **5**, 899 (1966).

(17) W. Walter, G. Maerten, and H. Rose, *Ann.*, **691**, 25 (1966).

TABLE II

SOLVENT-INDUCED SHIFTS

($\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$; $\Delta' = \delta_{CCl_4} - \delta_{C_5H_5N}$)

1		CH_3	NH	C(S)O	CH_3		
Δ		0.45 0.65	1.0 0.3		0.23 0.32		
Δ'		−0.11 0.05			−0.10 −0.06		
2		CH_3	NH	C(S)O	CH_2	CH_3	
Δ		0.43 0.59	0.8 0.2		0.09 0.15	0.25 0.32	
Δ'		−0.10 0.06			−0.15 −0.12	0.09 0.11	
3		CH_3	NH	C(S)O	CH_2 CH	$(CH_3)_2$	
Δ		0.42 0.58	0.9 0.2		−0.05 0.02	0.21 0.10	
Δ'		−0.10 0.06			−0.21 −0.18	0.11 0.10	
4		CH_3	NH	C(S)O	CH_2	CH_2CH	$(CH_3)_2$
Δ		0.41 0.54	0.8 0.2		−0.03 0.02		0.13
Δ'		−0.10 0.04			−0.21 −0.18		0.15 0.07
5		CH_3	NH	C(S)O	$C(CH_3)_3$		
Δ		0.40 0.54	1.1 0.1		0.05 0.10		
Δ'		−0.13 0.03			−0.07 −0.06		
6		$(CH_3)_3C$	NH	C(S)O	CH_3		
Δ		0.33 0.22	−0.3		0.27 0.10		
Δ'		0.07 −0.15			−0.09 −0.05		
7		CH_3	NH	C(S)O	CH_2	CH_2	$N(CH_3)_2$
Δ		0.23 0.42	0.2		0.03 0.03	0.25 0.28	0.26 0.26
Δ'		−0.15 0.02	−1.9		−0.21 −0.26	0.01 −0.02	0.10 0.05
8		CH_3	NH	C(S)O	CH_2	$(CH_2)_2$	$N(CH_3)_2$
Δ		0.25 0.47	0.4		−0.04 −0.01		0.21
Δ'		−0.14 0.02	−2.1		−0.27 −0.26		0.12 0.05
9	CH_3	CH_2	NH	C(S)O	CH_2	CH_2	$N(CH_3)_2$
Δ	0.28 0.40	0.13 0.38	1.3		−0.03 −0.03	0.21 0.25	0.23
Δ'	−0.01 0.03	−0.20 −0.04			−0.24 −0.22	0 −0.03	0.08 0.03

TABLE III

ANALYTICAL DATA FOR THIONCARBAMATES

Compound	Formula	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
3	$C_{16}H_{13}NOS$	Liquid	48.95	48.90	8.90	9.14		
4	$C_7H_{15}NOS$	Liquid	52.13	52.15	9.38	9.45		
5	$C_6H_{13}NOS$	55.5	48.95	48.71	8.90	8.95		
6	$C_6H_{13}NOS$	53.5	48.95	48.77	8.90	8.59		
7	$C_6H_{14}N_2OS$	66	44.41	44.51	8.70	8.85	17.27	16.95
8	$C_7H_{16}N_2OS \cdot HCl$	129.5	39.52	40.02	8.06	8.38	13.17	12.91
9	$C_7H_{16}N_2OS \cdot HCl$	113	39.52	39.72	8.06	8.15	13.17	13.18

formamide in which it was found that each of the groups, methyl and methylene, appeared at higher field in the spectrum when it was *trans* to the sulfur. If this can be extended to thioncarbamates, then the major isomer in all of our compounds save one (O-methyl *t*-butylthiocarbamate will be discussed separately at the end) has the *s-cis* conformation.

Satisfying confirmation for this assignment comes from the study of solvent-induced shifts of our compounds. The computed shifts are presented in Table II. As an empirical generalization it has been stated that, if a plane be passed through the carbonyl carbon for benzene-induced shifts[18] or through the atoms α to the carbonyl for pyridine-induced shifts,[19] then protons lying in front of the plane show very small or negative shifts, and protons lying well behind the plane show positive shifts. Although the rules were derived for rigid cyclic and true double-bonded structures, the consistency of the data in Table II demonstrates their applicability to open-chain molecules when there is some restriction of rotation. Thus, in each of the thioncarbamates (again excepting only **6**) the protons of the alkyl group attached to the carbamate nitrogen show a larger or more positive solvent shift for the minor isomer. For the carbamate proton the opposite is true whenever differentiation is possible. The conclusion, therefore, is that the *s-cis* isomer predominates in thioncarbamates of the type studied here.

It is also possible to draw some conclusions concerning the ester portion of the molecule. The near-equality of the solvent shifts for the O-alkyl protons in the two forms is inconsistent with the existence of both *cis* and *trans* conformations of the ester bond. Furthermore, the magnitude of the shifts, near zero for benzene and substantially negative for pyridine, agree with the assignment of an *s-cis* conformation to the single existing form. An exception is O-*t*-butyl methylthiocarbamate (**5**), for which the solvent shifts suggest that the bulky alkyl group assumes either an *s-trans* or some intermediate conformation.

The other *t*-butyl compound examined, O-methyl *t*-butyl thiocarbamate (**6**) is also an exception to the

(18) J. D. Connolly and R. McCrindle, *Chem. Ind.*, 379 (1965).

(19) D. H. Williams, *Tetrahedron Letters*, 2305 (1965).

above assignment. Here both the chemical shifts and solvent-induced shifts indicate the major isomer to have the *s-trans* conformation about the nitrogen–thiocarbonyl bond. Whereas in formamides the presence of the *t*-butyl group increases only slightly the amount of *s-trans* isomer,[4] the effect here is more profound, and a 2:1 preference for the ordinarily less favorable conformation is shown.

Experimental Section

The thioncarbamates were prepared by reaction of ethyl or methyl isothiocyanate with an alkoxide either in excess of alcohol or in xylene (for the amino alcohols). They were shown to be homogeneous by gas chromatography on Apiezon L at 150° or lower (on-column decomposition occurs at higher temperatures). Infrared spectra on liquid films or Nujol mulls (Beckman IR-12) showed bands at 3250–3285, 1530–1550, 1330–1335, and 1200–1225 cm^{-1}, which are typical of thioncarbamates.[18] Analytical data for previously unreported compounds are in Table III.

S-Ethyl Methylthiocarbamate.—Following a procedure[20] for unsubstituted carbamates a mixture of 3.0 g of O-ethyl methylthiocarbamate and 3.9 g of iodoethane was warmed on the steam bath until gas chromatography indicated that the reaction was complete (1 hr). The mixture was distilled and the product was collected at 104° (0.8 mm). Nmr signals in $CDCl_3$ appeared at δ 2.87 (doublet CH_3N), 5.7 (broad NH), 3.05 (quartet SCH_2), 1.29 (triplet $C\text{-}CH_3$).

Anal. Calcd for C_4H_9NOS: C, 40.31; H, 7.61. Found: C, 40.00; H, 7.55.

2-Dimethylaminoethyl Methyldithiocarbamate.—A solution of 15.0 g (0.105 mole) of 2-dimethylaminoethanethiol hydrochloride in 15 ml of water was neutralized with 210 ml of 1 *N* sodium hydroxide solution and then treated immediately with 8.1 g (0.11 mole) of methyl isothiocyanate dissolved in a few ml of methanol. Following 30 min of stirring at room temperature, the reaction mixture was treated with 105 ml of *N* hydrochloric acid. After 1 hr the solid which had formed was removed by filtration, dried, and recrystallized from benzene–Skellysolve B. The yield was 9.7 g (54%), mp 110–112°.

Anal. Calcd for $C_6H_{14}N_2S_2$: C, 40.41; H, 7.91; N, 15.71. Found: C, 40.53; H, 7.92; N, 15.58.

Registry No.—1, 14128-35-9; 2, 817-73-2; 3, 14128-37-1; 4, 14128-38-2; 5, 14128-39-3; 6, 14128-40-6; 7, 14128-41-7; 8, 14128-42-8; 9, 14128-43-9; *s*-ethyl methylthiocarbamate, 14128-44-0; 2-dimethylaminoethyl methyldithiocarbamate, 14128-45-1.

Acknowledgment.—The author is indebted to Mr. Michael Camara for assistance in the preparative work and to Mr. Gilbert Suarez for recording the nmr spectra.

(20) H. L. Wheeler and B. Barnes, *Am. Chem. J.*, **22**, 141 (1899).

The Reaction of 2-(N,N-Dimethylamino)-1,4-diphenyl-1,4-butanediol with Acid. A Novel Tetralone Formation[1a]

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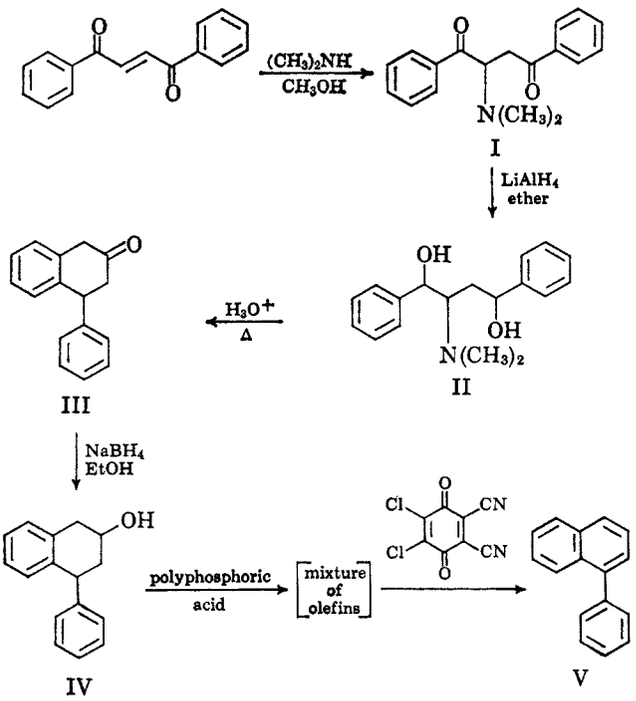
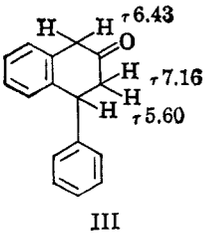
Reduction of 2-(N,N-dimethylamino)-1,4-diphenyl-1,4-butanedione[2] (I) with excess lithium aluminum hydride in ether gave 2-(N,N-dimethylamino)-1,4-diphenyl-1,4-butanediol (II) as a mixture of stereoisomers, mp 89–124° (Scheme I). Treatment of II

SCHEME I



with refluxing aqueous hydrochloric acid, hydrobromic acid, or sulfuric acid afforded a neutral compound (III) of molecular formula $C_{16}H_{14}O$. Compound III was a colorless liquid: bp 127–128.5° (0.07 mm); $n^{23}D$ 1.6030. The infrared spectrum of a solution of III in carbon tetrachloride showed strong absorption at 5.80 μ, indicating the presence of a nonconjugated ketone. The ultraviolet spectrum of III (λ_{max} 263 mμ, ϵ 1000) suggests the presence of a substituted phenyl group as the only chromophore.

In order to assign a structure to compound III, it was desirable to convert it into a hydrocarbon having the same carbon skeleton. This was accomplished as follows. Reduction of ketone III with sodium borohydride gave a quantitative yield of alcohol IV, mp 122–123.5°. Treatment of IV with polyphosphoric acid at 95° gave a mixture of two olefins; dehydrogenation of this crude mixture with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene, followed by chromatography of the products on an alumina column, afforded 1-phenylnaphthalene, identified by comparison of physical and spectral properties with an authentic sample. The nmr spectrum of III in $CDCl_3$ showed absorption at τ 2.7–2.9 (complex multiplet, 9 H), 5.60 (triplet, 1 H), 6.43 (singlet, 2 H), and 7.16 (doublet, 2 H). A likely structure for III is therefore 4-phenyl-2-tetralone. The observed nmr splitting pattern is consistent with the suggested structure and the



III

(1) (a) First presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967; (b) to whom inquiries should be addressed.

(2) R. E. Lutz, P. S. Bailey, and N. H. Shearer, Jr., *J. Am. Chem. Soc.*, **68**, 2224 (1946).