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Thiocyanations. 5. Nuclear Magnetic Resonance Analysis of the Stereochemistry of α,β-Dithiocyanates and α-Isothiocyanato-β-thiocyanates[1,2]

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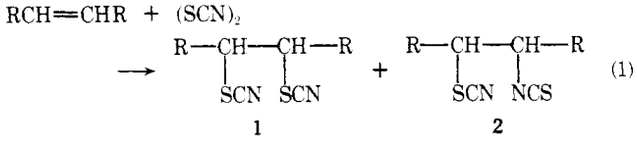
The stereochemical structures of 3,4-dithiocyanatohexanes as representative examples of aliphatic α,β-dithiocyanates could not be determined by direct conformational NMR analysis because of symmetry but were resolved by cyclization to and configurational analysis of their 2-imino-1,3-dithiolane salt derivatives. The aromatic 1,2-dithiocyanatophenylpropanes which have C–H asymmetry are subject to conformational analysis. Conformational analysis is also applicable to resolution of structures of the isomeric 3-isothiocyanato-4-thiocyanatohexanes.

Although the stereochemical structures of *vic*-dithiocyanate adducts were initially investigated by McGhie and co-workers,[4] our recent study of olefin thiocyanations emphasized the need for a reexamination of their structural assignments.[2]

On the basis of chemical evidence, McGhie and co-workers[4] proposed a trans addition of thiocyanogen to olefins to explain the reaction's stereochemistry; i.e., formation of erythro adducts from trans olefins and threo adducts from cis olefins. Their structural assignments for these adducts were based on the known pseudohalogen nature of thiocyanogen and on a comparison of a series of melting points of related isomeric dibromides, epoxides, and thiiranes. Such criteria are often inconsistent[4] and can be misleading; therefore, this approach to a determination of stereochemical assignments is provisional and not definitive for it is now recognized that the stereochemistry of electrophilic addition depends upon the structure of the olefin, the nature of the reagent, and the reaction conditions.[5]

McGhie[4] and earlier investigators[6] had examined only *vic*-dithiocyanate adducts as these were the sole products isolated from the addition of thiocyanogen to cis and trans olefinic compounds. However, more recently two independent investigations of the product distribution obtained by thiocyanations in acetic acid solution showed that formation of the *vic*-dithiocyanate adduct is accompanied by formation of several ancillary coproducts,[2,7] principally adduct **2**,



suggesting a further need for clarification of the reaction's stereochemistry.

A more direct and definitive method than chemical analysis of acquiring stereochemical determinations may be provided using NMR spectroscopy. However, a direct determination of the vicinal coupling constants is difficult for dithiocyanate adducts of aliphatic olefins because of their high degrees of symmetry. We undertook the present investigation to determine conclusively the stereochemical geometries of dithiocyanate adducts using *erythro*- and *threo*-3,4-dithiocyanatohexanes as the representative models. The stereochemical structures of the *vic*-dithiocyanate adducts were unequivocally confirmed by examination of the chemical shifts and the C-13 satellite spectra of their cyclic derivatives, the salts of 2-imino-1,3-dithiolanes. The coupling constants were also determined for the related erythro and threo isomers of 3-isothiocyanato-4-thiocyanatohexane and the 1,2-dithiocyanato-1-phenylpropane. The assignments were derived by correlation of the constants with the stereochemical conformations.

While our work was in progress, Guy and co-workers[7] reported assignments of several related dithiocyanate adducts. However, they did not report any NMR data or discuss the mode of analysis used that would allow independent confirmation of their assignments.

Results and Discussion

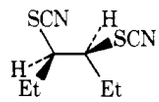
Configuration Assignment. In the earlier stages of this work differentiation of adducts **3** and **4** (eq 2 and 3) by NMR analysis was limited because of symmetry considerations. Therefore, a method of cyclic derivatization of **3** and **4** was developed whereby the stereochemistry of the asymmetric C–S bonds in these compounds was maintained. Cyclization would freeze the structures into a more limited and discrete number of conformations for each configuration. The desired derivatives of the erythro (**3**) and threo (**4**) forms of 3,4-dithiocyanatohexanes were accordingly obtained by facile cyclization to the corresponding 2-imino-1,3-dithiolane salts of methanesulfonic acid (**5** and **6**, respectively; eq 2 and 3).[8] The cyclization was smoothly attained in methanesulfonic acid as solvent–catalyst. No alteration of the precursor's C–S bonds at the point of carbon attachment in the alkane chain occurs since these asymmetric bonds do not participate in the reaction.

Chemical shifts of the salts **5** and **6** were obtained and the stereochemical assignments were proven by comparison with published assignments for known cyclic analogues (Table I). In each example the chemical shift of vicinal methine protons of the trans isomers appear ~0.2 ppm upfield relative to cis isomers. This difference has been noted for many cis–trans isomeric pairs of planar three- to five-membered ring com-

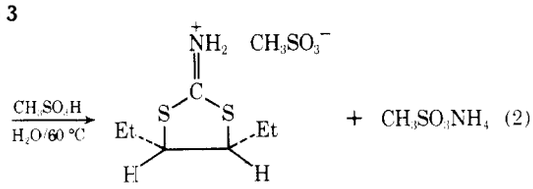
Table I. Chemical Shifts of Substituted 1,3-Dithiolane and 1,3-Dioxolane Derivatives

Compd	δ, ppm (methine protons) cis	trans	c − t
4,5-Diethyl-1,3-dithiolane-2-iminium methanesulfonate[a]	4.50 (4.13)[b]	4.30 (4.07)[b]	0.20 0.06
4,5-Dimethyl-1,3-dithiolane-2-thione[c,d,e]	4.38	4.11	0.27
4,5-Dimethyl-1,3-dioxolan-2-one[e,f]	5.84	5.66	0.18

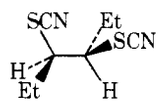
[a] Measured at 60 MHz in D_2O with DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) as internal standard. [b] Measured in $CSCl_3$. [c] C. G. Overberger and A. Drucker, *J. Org. Chem.*, **29**, 360 (1964). [d] E. J. Corey and R. B. Mitra, *J. Am. Chem. Soc.*, **84**, 2938 (1962), also established the configuration by an independent synthesis of L(−)-*trans*-4,5-dimethyl-1,3-dithiolan-2-one from *trans*-4,5-dimethyl-1,3-dithiolane-2-thione, the latter being the only isomer of the two geometric structures capable of supporting optical activity. [e] Measured at 60 MHz in CCl_4 with Me_4Si as internal standard. [f] Reference 9.



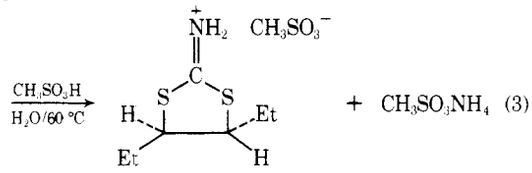
erythro **3**



cis **5**



threo **4**



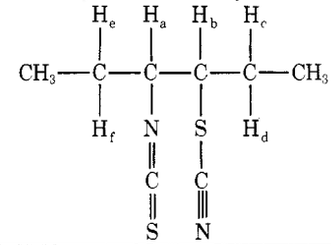
trans **6**

pounds.[10] The stereochemical assignment made for the cis isomer **5** confirms the stereochemistry of the precursor erythro dithiocyanate **3**; similarly the established trans stereochemistry of isomer **6** confirms the identity of the threo dithiocyanate **4**.

Configuration of **5** and **6** was further verified through analysis of the corresponding natural abundance ^{13}C proton satellites. Homonuclear decoupling of each of the methylene proton resonances at δ 1.93 yielded a methine singlet whose low-field ^{13}C satellite doublet could be easily analyzed for the methine J_{vic}. The stereochemistry of **5** was established by the large cis coupling J_{vic} = 10.7 Hz for this five-membered ring compound ($J_{^{13}C-H}$ = 164 Hz). Likewise, the trans configuration of **6** was confirmed by J_{vic} = 2.7, $J_{^{13}C-H}$ = 170 Hz.[11] The data also support McGhie's[4] assignments and confirm his proposal of a stereochemical trans addition of thiocyanogen to olefins.

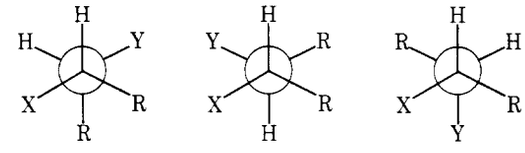
Conformational Assignments. A. 3-Isothiocyanato-4-thiocyanatohexanes. In contrast to symmetrical 3,4-dithiocyanatohexanes, the differences in chemical shift of *vic*-methine protons in the isomeric 3-isothiocyanato-4-thiocyanatohexanes enabled direct conformational analysis of the stereochemical isomers.[12] Table II records the results of a first-order analysis of these isothiocyanatothiocyanate isomers. Newman projections of the threo (**7**) and erythro (**9**) diastereoisomeric conformer are depicted below (exclusive of mirror images for each conformer).

Table II. NMR First-Order Analysis of 3-Isothiocyanato-4-thiocyanatohexanes[a]



Compd	Proton H_a δ, ppm	Coupling constant, Hz	Proton H_b δ, ppm	Coupling constant, Hz
Erytho adduct (from *trans*-3-hexene)	3.95 (double triplets)	J_{ab} = 5.4[b] J_{ae} = 5.4 J_{af} = 7.0	3.2 (double overlapping quartets)	J_{ab} = 5.4[b] J_{bc} = 4.2 J_{bd} = 9.0
Threo adduct (from *cis*-3-hexane)	4.05 (double quartet)	J_{ab} = 3.7[b] J_{ae} = 6.0 J_{af} = 7.2	3.2 (double quartet)	J_{ab} = 3.7[b] J_{bc} = 6.0 J_{bd} = 8.1

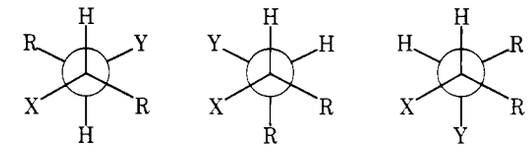
[a] All methine coupling constants were verified by reproduction of the spectra of the methine hydrogens H_a, H_b using LAOCN 3[13] on an ab spin system representing protons a–f. [b] Verified by decoupling of methylene protons.



a b c

threo:

7, R = Et; X = SCN; Y = NCS
8, R = Me; X, Y = Br



a b c

erythro:

9, R = Et; X = SCN; Y = NCS
10, R = Me; X, Y = Br

In general for conformers having trans methine protons, such as **7b** and **9a**, a large J_{vic} value of 10–12 Hz is anticipated whereas the remaining conformers with gauche methine protons are expected to have small J_{vic} values of 1–3 Hz. Our observed J_{HH} of 3.75 Hz for **7** closely approximates the value of 3.15 Hz found by Anet[9] for *dl-threo*-2,3-dibromobutane (**8**). The erythro adduct **9**, however, gave the significantly lower value of 5.4 Hz for J_{vic} in comparison with Anet's[9] 7.85 Hz for the corresponding dibromide **10**. Anet[9] had obtained weighted averages of conformer populations for the latter compounds by considering the steric and electronic effects of adjacent bromines. His studies of the conformer population of threo adduct **8** showed that it contained predominantly **8a**, with a minor **8b** contribution, whereas the erythro adduct **10** was a mixture comprised of 66% conformer **10a** and 34% conformer

Table III. Coupling Constants and Methyl Chemical Shifts of 1,2-Disubstituted 1-Phenylpropanes[a]

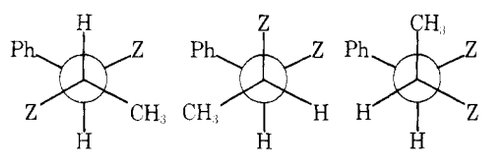
	J_{vic}, Hz		δ_{CH_3}, ppm		
	Erythro	Threo	Erythro	Threo	$\Delta\delta_{CH_3}$
1,2-Dithiocyanato-1-phenylpropane	10.2	9.0	1.9	1.5	0.4
1,2-Dibromo-1-phenylpropane[b]	11.0	5.5	2.0	1.6	0.4
1,2-Dichloro-1-phenylpropane[c]	8.0	5.7	3.6	3.4	0.2

[a] Spectra measured at 60 MHz with CCl_4 as the solvent and Me_4Si as internal standard. [b] Reference 14. [c] Reference 15.

10b. On the other hand, electrostatic interactions in *vic*-isothiocyanatothiocyanates would not be expected to contribute greatly to the establishment of relative conformer populations. Therefore, conformational assignments in this class of adducts would be determined primarily on the basis of steric interactions. The similarity in J_{vic} values for the threo adducts **7** and **8** indicated that the conformer populations were nearly the same. The erythro isomer **9**, however, gave a J_{vic} value 2.4 Hz smaller than that reported for **10**, which indicated that the relative contribution by **9a** decreased and contributions from **9b** and **9c** correspondingly increased. Reduced steric interactions in conformers **9b** and **9c**, relative to the corresponding *vic*-dibromides, would account for the decrease in conformational preferences for **9a** in the erythro isomer **9**.

B. *erythro*- and *threo*-1,2-Dithiocyanato-1-phenylpropanes. In contrast to aliphatic dithiocyanates, the asymmetry in aryl-substituted dithiocyanates made these compounds amenable to direct NMR analysis. Conformational analysis was carried out with dithiocyanate adducts derived from *cis*- and *trans*-1-phenylpropene. For conformational determinations, *vic*-dithiocyanates were compared with the known stereochemical structures of analogous *vic*-dibromides[14] and *vic*-dichlorides.[15] Our data for the thiocyanated adducts were compared with published values for halogenated adducts (Table III).

The Newman projections for the three primary conformations of the erythro adduct **11** are illustrated below. Conformer **11a** was expected to be the rotamer of lowest energy because of the all-trans structure in which the bulky groups are maximally separated (dihedral angle 180°). The observed average



erythro:			
Z = –SCN	11a	11b	11c
Z = –Br or Cl	12a	12b	12c

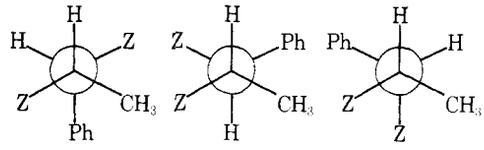
J_{vic} (10.2 Hz) for **11** is comparable to J_{vic} (11.0 Hz) reported for the analogous dibromide adduct **12** and is significantly larger than 8.0 Hz for the erythro dichloride adduct (Table III).

The following conformations for threo-substituted adducts indicate, from the coupling constant (9.0 Hz) for **13**, that the trans rotamer **13b** must contribute significantly to the average population of this isomer. The coupling constants of threo dibromide and dichloride adducts **14** are much lower in value in comparison with adduct **13**. Such a trend indicates that rotamers **14a** and **14c** best represent the conformational population of the two dihalides. The lower values of threo

Table IV. Solvent Effect on Vicinal Coupling Constant of 1,2-Dithiocyanato-1-phenylpropanes

Solvent	J_{vic}, Hz Erythro	Threo
CCl_4	10.2	9.0
Benzene	9.7	9.0
$CDCl_3$	9.5	8.6
Dimethyl sulfoxide	10.7	10.0

dihalide adducts suggest a counterbalance of steric and electronic interactions, the latter attaining paramount importance



threo:			
Z = –SCN	13a	13b	13c
Z = –Br or Cl	14a	14b	14c

in determining conformational preference in vicinal dihalide systems.[9] However, in thiocyanate adducts the steric requirement is more important and appears to outweigh polarity effects. The predominance of trans rotamers in **11** and **13** suggests that the spatial interactions of the linear thiocyanate functionality are contributed primarily by the sulfur moiety for which steric repulsions appear similar to those of methyl groups.

The data in Table III for the methyl resonance of each isomer show the same trend observed for the corresponding dihalides; the methyl proton resonances of all threo adducts are observed at higher field relative to the erythro adducts. In a previous study[14] of dibromide adducts, the higher field positions of the $-CH_3$ resonances in the threo adduct were attributed to the shielding effects of the phenyl groups. Should this effect solely account for the higher field position of the $-CH_3$ resonances, the $\Delta\delta CH_3$ (11–13) should be larger than expected since the threo adduct **13** should exist predominantly as conformer **13b**, in which shielding of the $-CH_3$ by phenyl would be maximal.

The unexpectantly large J_{vic} obtained for **13** with $CHCl_3$ prompted a further NMR study of the isomers in several polar and nonpolar solvents. When a solute molecule interacts with solvent, J_{vic} is expected to decrease as the solvent medium is changed from low to high dielectric constant,[9,16] owing to a shift in the conformer population equilibrium, i.e., **11a → 11b + 11c** and **13a → 13b + 13c**. However, the data in Table IV show an increase in the average J_{vic} for both the erythro **11** and threo **13** adducts upon changing the solvent from CCl_4, benzene, and $CDCl_3$ to Me_2SO, i.e. to solvents of higher dielectric constants. Clearly, these results are inconsistent with the effects normally expected in solvent-dependence studies of vicinal coupling constants. None of the data presently available account for the fact that both isomers **11** and **13** have similar conformational preferences in all the solvents tested.

Experimental Section

Equipment. The thiocyanogen adducts were separated by countercurrent distribution (CCD) in a 200 cell Post Automatic[17] instrument with acetonitrile as stationary phase and hexane as mobile phase.

NMR spectra were obtained with a Jeolco C-60H spectrometer. The chemical shifts of adducts in organic solvents are reported relative to tetramethylsilane whereas shifts obtained in D_2O are relative to DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate). Coupling

constants were confirmed, when necessary, by reconstruction of the spectra using the LAOCN 3 program modified for an IBM 1130 computer. ^{13}C proton satellites were measured on a Brucker WH-90 Fourier transform pulsed NMR spectrometer using block averaging techniques to overcome dynamic range problems. Only the low-field satellites were accessible for measurement. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer.

Samples were analyzed with a Model 810 F & M gas chromatograph using the following columns: (A) SS colum 0.25 in. × 6 ft, saturated $AgNO_3$/ethylene glycol on 60/80 mesh Anakrom ABS; (B) SS column 0.25 in. × 8 ft, 10% DEGS on 60/80 mesh Anakrom ABS; (C) Glass column 0.25 in. × 4 ft, 5% DEGS on 60/80 mesh Anakrom ABS.

Reagents. The olefins (*cis*-3-hexene, *trans*-3-hexene, *cis*-β-methylstyrene, and *trans*-β-methylstyrene) were from Chemical Samples Co. The isomeric purity of each sample was determined by GLC with column A. The lead thiocyanate used to generate thiocyanogen was prepared by a previously described method.[18]

Thiocyanation of Olefins. The α,β-dithiocyanate and α-isothiocyanato-β-thiocyanate adducts were prepared as follows. Lead thiocyanate (125 g, 0.38 mol) and acetic acid (2 L) were added to a three-neck flask equipped with a true-bore stirrer and maintained under nitrogen. The mixture was stirred for 10 min, bromine (31 g, 0.19 mol) was added, and stirring was continued until the solution became colorless. Olefin (0.097 mol) was added, and the mixture stirred overnight to ensure complete reaction, then filtered. The filtrate was shaken with water to destroy excess thiocyanogen, and the aqueous layer extracted with ethyl ether. The extract was water washed, dried over anhydrous $MgSO_4$, and concentrated to a thick, amber liquid. The adducts in the mixture were thereby separated by CCD. Individual components were checked for purity by GLC using column B. Elemental analyses were satisfactory for all compounds described. The following compounds were isolated in this manner.

erythro-3,4-Dithiocyanatohexane (**3**) was isolated as a white, crytalline solid: mp 62–63 °C; IR (KBr) 2150 cm^{-1} (SCN).

threo-3,4-Dithiocyanatohexane (**4**) was isolated as an amber-colored, viscous oil, IR (neat) 2150 cm^{-1} (SCN).

threo-3-Isothiocyanato-4-thiocyanatohexane (**7**) from the addition of thiocyanogen to *cis*-3-hexane was recovered as a brown liquid: IR (neat) sharp –SCN peak at 2150 cm^{-1} and broad –NCS peak at 2080 cm^{-1}.

erythro-3-Isothiocyanato-4-thiocyanatohexane (**9**), from the addition of thiocyanogen to *trans*-3-hexene, was separated as a brown, oily liquid: IR (neat) sharp –SCN peak at 2160 cm^{-1} and broad –NCS peak at 2080 cm^{-1}.

threo-1,2-Dithiocyanato-1-phenylpropane (**11**) was isolated as a viscous oil from the addition of thiocyanogen to *cis*-β-methylstyrene. The purity of this sample was checked by GLC using column C, IR (neat) 2160 cm^{-1} (SCN).

erythro-1,2-Dithiocyanato-1-phenylpropane (**13**) from the addition of thiocyanogen to *trans*-β-methylstyrene was isolated as a white, crystalline solid: mp 110–111 °C; IR (KBr) 2160 cm^{-1} (SCN).

cis- and *trans*-4,5-diethyl-1,3-dithiolane-2-iminium methanesulfonate (**5** and **6**) were obtained by cyclization of **3** and **4** in methanesulfonic acid as described in part 3 of this series.[8]

Registry No.—**3**, 30647-63-3; **4**, 61521-96-8; **5**, 61521-98-0; **6**, 61522-00-7; **7**, 61522-01-8; **9**, 61522-02-9; **11**, 60212-01-3; **13**, 60212-00-2; *cis*-3-hexene, 7642-09-3; *trans*-3-hexene, 13269-52-8; *cis*-β-methylstyrene, 766-90-5; *trans*-β-methylstyrene, 873-66-5; methanesulfonic acid, 75-75-2; lead thiocyanate, 592-87-0; thiocyanogen, 505-14-6.

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Pteridines. 40. Some Reactions of 2-Amino-3-cyano-5-bromomethylpyrazine and 2-Amino-3-cyano-5-methylpyrazine[1]

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Some chemistry of 2-amino-3-cyano-5-bromomethylpyrazine (**1**) and 2-amino-3-cyano-5-methylpyrazine (**2**) has been explored to determine their usefulness as intermediates for the preparation of C-6 substituted pteridines. In general, new carbon–carbon bonds can be formed at the 5 position of **1** if weakly basic nucleophiles are employed. The synthetic potential of **2** was less than expected, however, owing to the nonacidity of the 5-methyl protons. By contrast, 2-amino-3-cyano-6-methylpyrazine could be alkylated to give 2-amino-3-cyano-6-*n*-propylpyrazine. A general discussion is given of the reactivity of both **1** and **2**.

Previous papers in this series have detailed an unambiguous approach to the synthesis of 6-substituted pteridines (i.e., L-*erythro*-biopterin, xanthopterin, methotrexate, folic acid, Asperopterin B), by guanidine cyclization of a 2-amino-3-cyano- (or carboalkoxy-) pyrazine suitably substituted at position 5. These latter critical intermediates were prepared in turn by an unequivocal cyclization of aminomalononitrile or an ester of α-aminocyanoacetic acid with an α-ketoaldoxime followed by deoxygenation of the resulting pyrazine 1-oxide.[3]

One obvious disadvantage of this procedure for the preparation of pteridines possessing complex side chains at position 6 (pyrazine position 5) was the inaccessibility of the requisite α-ketoaldoxime intermediates. We have therefore investigated the possible utility of two readily accessible pyrazines, 2-amino-3- cyano-5-bromomethylpyrazine (**1**)[4] and 2-amino-