

Temperature-Dependent Optical Rotatory Dispersion Measurements of Methyl (*R*)-(-)-1,2-Dithiane-4- carboxylate.

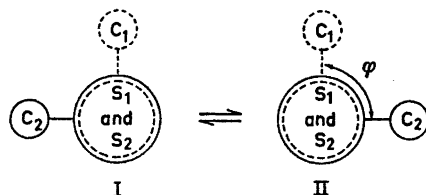
The Absolute Configuration of the Disulphide Group *

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The ORD curves of (*R*)-(-)-1,2-dithiane-4-carboxylate have been studied at different temperatures. Low temperature NMR measurements have given the conformational free energy difference ($-\Delta F$) between the axial and equatorial conformers. These data have permitted calculation of the ORD curves for the pure, nonisolatable axial and equatorial forms. It has also been possible to assign a negative Cotton effect, associated with the lowest frequency disulphide absorption band, to the presence of a disulphide group twisted in the sense of a left-handed helix.

An organic disulphide, R-S-S-R, is most stable when the dihedral angle $\Lambda(\varphi)$ is about 90° .¹ This can produce two different molecular conformations — making up the equimolar mixture of I and II.



* This work has been previously presented in the Laboratory of Chemical Biodynamics Quarterly Report, Lawrence Radiation Laboratory (LCBQ-16 (1967) 5).

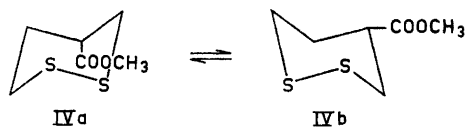
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These two forms are optical antipodes, and their stabilities depend upon the height of the barrier hindering the free rotation about the disulphide bond. Usually the barrier has a value between 10–15 kcal,¹⁻⁴ which is too small to allow a long-lived independence in solution, and as yet a separation of the enantiomers of a disulphide has not been accomplished.

The cyclic 6-membered disulphide, 1,2-dithiane, exists in solution as an equimolar mixture of the enantiomeric chair forms III a and III b.^{5, cf. 6-9}



If a substituent, *e.g.* the carbomethoxy group, is introduced in the 1,2-dithiane ring, the derivative will contain two asymmetric elements, the dithiane-ring itself and the asymmetric carbon. The two forms IV a and IV b



are no longer enantiomers, and they do not have equal energy and do not exist in equimolar amounts.

The conformational equilibrium in solution is temperature dependent. At low temperatures the more stable form is predominant, and at higher temperatures the two forms tend to approach the same concentration according

$$K = N_e/N_a = \exp(-\Delta F/RT) \quad (1)$$

to eqn. (1), where K is the conformational equilibrium constant, N_e and N_a are the mole fractions of the dithiane derivative in the equatorial and axial conformations, ΔF is the free energy difference, R is the gas constant, and T the absolute temperature.

The axial and equatorial conformers of compound IV must also have different optical rotations. As the equilibrium constant is temperature dependent, a change of temperature changes the optical rotation of the equilibrium mixture.

The molecular optical rotation $[M]$ at a temperature T and wavelength λ is composed of contributions from both the equatorial and the axial conformers according to eqn. (2),

$$[M] = N_e [M_e] + N_a [M_a] \quad (2)$$

where $[M_e]$ and $[M_a]$ denote the molecular optical rotation associated with the equatorial and axial conformer respectively.

Now we also have

$$K = \frac{N_e}{N_a} \text{ and } N_e + N_a = 1$$

which give $N_a = \frac{1}{K+1}$ and $N_e = \frac{K}{K+1}$

Substitution in eqn. (2) gives:

$$[M] = \frac{[M_e]K}{K+1} + \frac{[M_a]}{K+1} \quad (3)$$

or

$$[M] = [M_e] - \frac{[M_e]}{K+1} + \frac{[M_a]}{K+1}$$

or

$$[M] = \frac{1}{K+1} ([M_a] - [M_e]) + [M_e] \quad (4)$$

According to eqn. (4) a plot of $[M]$ vs. $1/(K+1)$ at different temperatures should give a straight line.¹⁰ The slope and intercept of this line give the values for $[M_e]$ and $[M_a]$.

$[M]$ can be measured directly at different temperatures, and nuclear magnetic resonance spectroscopy can be utilized for determination of the K values. Because equatorial and axial substituents exhibit different chemical shifts, the relative amounts of the equatorial and axial conformers, $N_e/N_a = K$, may be determined from the NMR spectrum. Substitution of the K value in eqn. (1) gives the value of ΔF at the temperature of the measurement. If ΔF is constant over the temperature range studied, then eqn. (1) gives the values of K at different temperatures. Thus, if $[M]$ can be measured and $1/(K+1)$ calculated (from knowledge of ΔF through NMR study), we have the variables necessary for a plot of eqn. (4).

1,2-Dithiane-4-carboxylic acid has been prepared¹¹ and resolved into optical antipodes, the configurations of which have been unambiguously determined¹² by desulphurization to 2-methylbutyric acid. The methyl ester, instead of the free carboxylic acid, has been chosen for this study for several reasons. All of the hydrogens in the dithiane ring of the acid give complicated NMR patterns, and the acid was for that reason unsuitable for the NMR studies. The methyl hydrogens of the ester are, on the other hand, not coupled, and give rise to a single sharp peak. By using the ester, the complications associated with dissociation, dimerisation, and hydrogen bonding are also avoided.

Acetonitrile has been chosen as solvent because of its transparency in UV, absence of protons suitable for hydrogen bonding, and availability in deuterated form for NMR measurements.

RESULTS

The NMR spectra of the methyl resonance of methyl 1,2-dithiane-4-carboxylate in acetonitrile- d_3 are shown in Fig. 1. It is obvious that the inter-conversion between the axial and equatorial forms (IV a and IV b) is so rapid at room temperature, that the methyl hydrogens give only one peak as an average absorption from the two conformers. At lower temperatures the peak from the methyl group broadens, and at still lower temperatures it

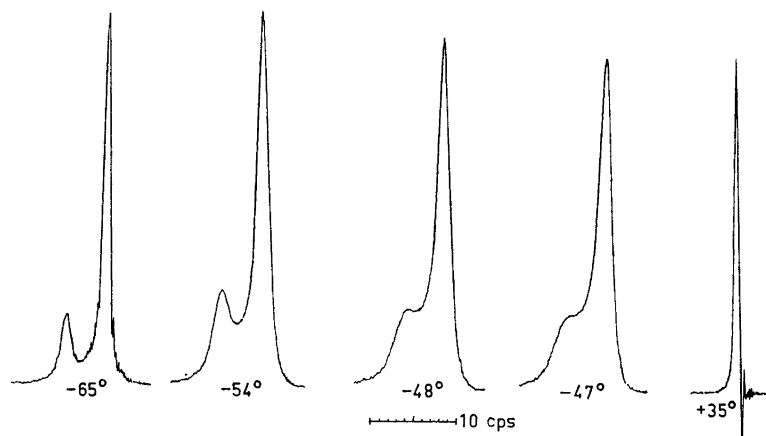


Fig. 1. NMR spectra of the methyl resonance of methyl 1,2-dithiane-4-carboxylate in CD_3CN at -65° , -54° , -48° , -47° , and $+35^\circ$.

separates into two peaks (Fig. 1). The two peaks are separated by about 4.8 cps at -65° , and the ratio between their areas is 76.9:23.1. The free energy difference ($-\Delta F$) between the two forms, calculated from eqn. (1), is 500 cal/mole. In conformity with substituted cyclohexane derivatives, it seems most likely that the equatorial conformer (IV b) is the most stable one and gives rise to the biggest peak. The peak from the axial ester group, the smaller

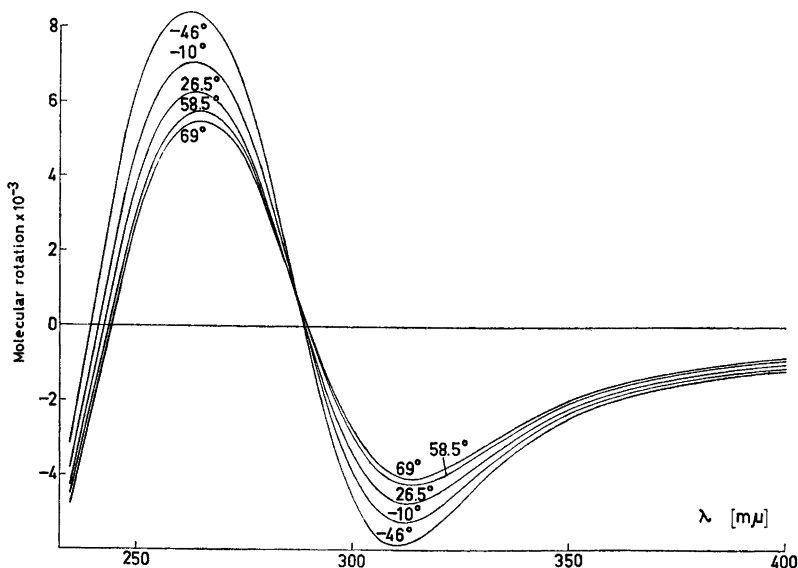


Fig. 2. ORD curves of methyl (*R*)-(-)-1,2-dithiane-4-carboxylate in CH_3CN at $+69^\circ$, $+58.5^\circ$, $+26.5^\circ$, -10° , and -46° .

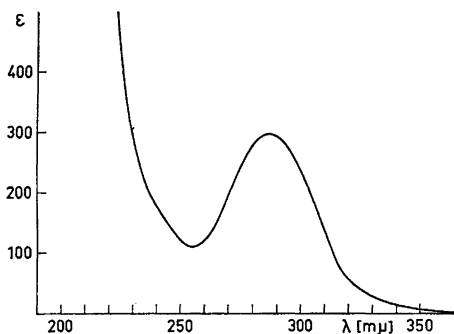


Fig. 3. UV absorption spectrum of methyl 1,2-dithiane-4-carboxylate in CD_3CN .

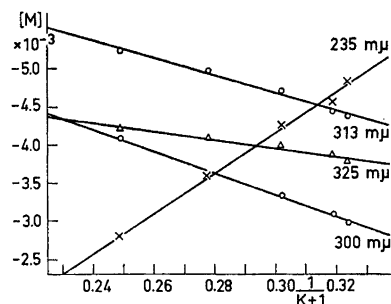


Fig. 4. The linear relation between $[M]$ and $1/(K+1)$ for methyl (*R*)-(-)-1,2-dithiane-4-carboxylate.

peak, is thus downfield compared to the peak from the equatorial ester group. This is also supported by the fact that the chemical shifts of axial protons in other dithiane derivatives are also found at a lower field than those of the corresponding equatorial protons.¹³⁻¹⁵

ORD measurements were made at five different temperatures between 69° and -46° . The change of the optical rotation with change in temperature is seen in Fig. 2. The observed Cotton effect corresponds to the disulphide absorption band¹⁶ at about $287\text{ m}\mu$ (Fig. 3). From Fig. 2 the molecular optical rotation $[M]$ was obtained at the different temperatures and at chosen wavelengths. At these wavelengths a plot of $[M]$ vs. $1/(K+1)$, according to eqn. (4), gave straight lines (examples of which are given in Fig. 4). From these lines, $[M_e]$ and $[M_a]$ were obtained at the chosen wavelengths, and the plotted ORD curves for the pure axial and equatorial conformers are shown in Fig. 5.

DISCUSSION

Cystine has long been known to have an unusually large optical rotation compared to other amino acids. The anomalously high rotation at the sodium D line of other optically active, open chain, and cyclic disulphides, was for the first time pointed out by Fredga in 1950.¹⁷ Djerassi, Fredga and Sjöberg¹⁸ have also investigated the rotatory dispersion of a number of disulphides and diselenides. It has been suggested that the high rotation of disulphides may reside in the fact that the disulphide bridge is intrinsically asymmetric. As a separation of the enantiomers of a disulphide has not yet been accomplished, no direct measurement of the intrinsic optical rotation of a disulphide has been possible.

The curves in Fig. 5 are noteworthy since they give the optical rotatory dispersion of the nonisolatable conformers IV a and IV b, having opposite configurations at the disulphide bridge. We notice that the ORD curves for the equatorial and axial conformers are very roughly mirror images, and that the Cotton effects appear at about the same place as does the disulphide absorption in the ultraviolet (Fig. 3). This shows that the main

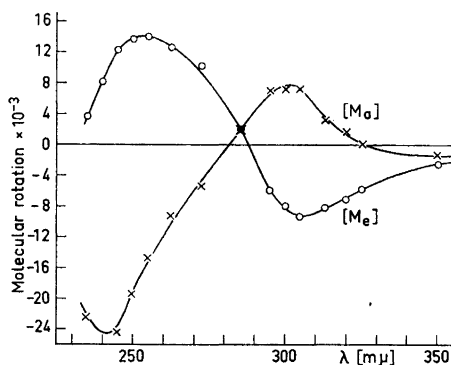


Fig. 5. Calculated ORD curves for the axial and equatorial forms of methyl (*R*)-(-)-1,2-dithiane-4-carboxylate.

contribution to the shape of the ORD curves in this region comes from the asymmetric disulphide grouping.

The contributions to the optical activity attributable to the inherent dissymmetry usually greatly outweigh those that can be attributed to perturbation by asymmetrically disposed substituents.¹⁹ If we in this case form sectors by drawing planes symmetrical to the disulphide bond, the carbomethoxy group in both IV a and IV b will fall in the same sector. Thus, its perturbations of the —S—S— chromophore in the two conformers probably give contributions to the optical rotation which are of the same sign. The opposite sign of the Cotton effects of IV a and IV b must thus be determined by the inherently dissymmetric disulphide chromophore.

Since the absolute configuration at the asymmetric carbon atom of IV is known¹² the configurations of the disulphide group in the axial and equatorial conformers of (-)-IV must be those given by formulas IV a and IV b. The equatorial form IV b has left-handed chirality at the disulphide group, also expressed as in formula II. It is obvious that this left-handed chirality of the disulphide group is associated with a negative Cotton effect (Fig. 5).

The antibiotic gliotoxin has been studied by Beechman *et al.* by means of X-ray crystallography, and its disulphide group has been found to have left-handed chirality.^{20,21} The circular dichroism spectrum shows a negative peak at 340 μ , at about the same place as its ultraviolet absorption. The authors state, however, . . . "but whether the sign is dominated by the skew sense remains unclear. Adjacent asymmetric elements within the molecule may well have a perturbing influence on this chromophore as suggested in the case of the cisoid diene. Absolutely determined model compounds would be valuable here also."

The case studied in this paper may be considered as such a model compound, and there should be no doubt, even if the exact shape of the curve is uncertain, that a negative Cotton effect associated with the lowest frequency disulphide absorption band¹⁶ signifies the presence of a disulphide group twisted in the sense of a left-handed helix.*

* After this work had been accepted for publication I became aware of a CD study of other disulphides by Carmack, M. and Neubert, L. A. *J. Am. Chem. Soc.* **89** (1967) 7134. Their conclusions are in agreement with the postulated rule in this paper.

The disulphide dihedral angle in methyl 1,2-dithiane-4-carboxylate is probably around 60° (*cf.* Ref. 22). The importance of the dihedral angle on the ultraviolet absorption band was for the first time demonstrated by the results of Calvin *et al.*²³ and explained from Bergson's theory of the variation of the orbital energies with the dihedral angle.⁴ The sign of the Cotton effect associated with the disulphide absorption band is dependent upon the sign of the dihedral angle (φ) as explained above. But also the position and magnitude of the Cotton effect depend upon φ . When φ is equal to 0° or 180° the grouping is symmetric and there is, of course no inherent optically active absorption.

In view of the results of this investigation, the absolute configuration of the disulphide group can be considered to be known, and thus studies of ORD or CD curves of other disulphide containing compounds make it possible to draw conclusions regarding the stereochemistry of the disulphide group in these compounds. The disulphide can either be in a stiff ring system, with a fixed —S—S— configuration, or in a flexible compound, where the preferred conformation also determines the preferred configuration of the disulphide bond.

One must, however, be aware that peripheral asymmetry may be capable of affecting the rotatory properties of the disulphide group (*cf.* Refs. 20 and 21), especially if the rotation strength of the disulphide is of low magnitude.

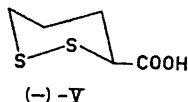
The curve shapes in Fig. 5 must be considered to be more qualitatively than quantitatively correct. The necessary assumptions for drawing the lines expressed by eqn. (4) are, that the Boltzmann distribution holds for the conformers, that ΔF is a constant over the temperature range studied, and that $[M_a]$ and $[M_c]$ are temperature independent. The fact that the points in Fig. 4 fit a straight line reasonably well, shows that the assumption about ΔF holds, and that $[M_a]$ and $[M_c]$ are temperature independent, or if they change, they must change in the same way. Corrections have been made for the concentration changes accompanying the volume variation with temperature. The variations of association with temperature have been ignored, as has also the fact that K has been measured at a higher concentration (a 10 % acetonitrile- d_3 solution was used for the NMR measurements) than that used for the ORD measurements.

The conformational free energy change ($-\Delta F$) for the equilibrium $IVa \rightleftharpoons IVb$ in acetonitrile was calculated to be 0.5 kcal/mole from the NMR measurements. For the corresponding methyl cyclohexanecarboxylate the value 1.1 kcal/mole has been determined in methanol solution.²⁴

CD SPECTRA

Circular dichroism is also a useful tool for studying Cotton effects, and Beychok²⁵ has pointed to the potential usefulness of CD analysis as a way of determining the configurations of —S—S— bonds. The CD curves of (—)-1,2-dithiane-4-carboxylic acid (Fig. 6) and (—)-1,2-dithiane-3-carboxylic acid (Fig. 7) exhibit negative maxima at 286 $m\mu$ (UV: λ_{max} 288 $m\mu$) and 279 $m\mu$

(UV: λ_{\max} 280 $m\mu$), respectively. The configuration at the asymmetric carbon of (–)-1,2-dithiane-3-carboxylic acid (V) has been determined by Claeson.¹²



Thus, the equatorial conformers of both of these two acids have left-handed chirality at the disulphide group. With the assumption that the equatorial conformer of each acid is predominant in ethanol solution, the negative Cotton effects obtained are in agreement with the postulated rule (p. 2434).

Both of these acids also show a positive CD maximum at about 240 $m\mu$, corresponding to a shoulder in the ultraviolet spectrum.

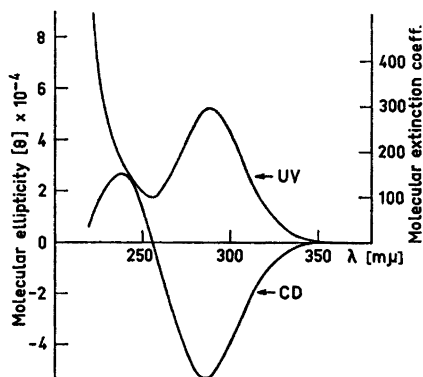


Fig. 6. UV and CD curves of (R)-(-)-1,2-dithiane-4-carboxylic acid in 95 % ethanol solution.

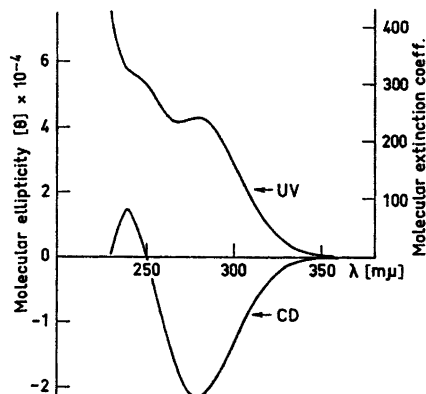


Fig. 7. UV and CD curves of (S)-(-)-1,2-dithiane-3-carboxylic acid in 95 % ethanol solution.

EXPERIMENTAL

The UV spectra were measured with a Cary Model 11 recording spectrophotometer.

The NMR spectra were obtained with a Varian Model A-60 spectrometer with a variable-temperature probe. The spectra were measured as 10 % solutions in acetonitrile- d_3 with TMS as internal reference.

The ORD measurements were made with a Cary 60 spectropolarimeter. The base line was recorded at all temperatures at which the spectra were measured. The spectra were taken to 600 $m\mu$ in order to check for base line shifts. Corrections were made for the change of the volume of the solution with changing temperatures.²⁶ Thermostating for the ORD measurements was done by placing a 2 cm cylindrical cell in an aluminium cell holder through which the thermostating liquid was circulated. The temperature was measured with a copper-constantan thermocouple just before the spectrum was taken. The temperature was known to be better than $\pm 0.5^\circ$ and did not fluctuate beyond those limits. Temperatures above room temperature were obtained using a Haake Model Fe thermal regulator. Temperatures below room temperature were obtained using refrigerated baths or circulating methanol cooled by dry ice.

The CD spectra were recorded in ethanol solution with an instrument designed by Dratz.²⁷

Acetonitrile of Eastman Spectrograde quality was stirred, first over potassium hydroxide and then over phosphorus pentoxide. The acetonitrile was then distilled from phosphorus pentoxide and stored over Linde 5H Sieve.

(R)-(-)-1,2-Dithiane-4-carboxylic acid. The racemic acid was prepared according to Claeson and Langsjoen¹¹ and resolved into optical antipodes by the method described by Claeson.¹²

Methyl (R)-(-)-1,2-dithiane-4-carboxylate. The levorotatory acid, $[\alpha]_D^{25} = -167^\circ$, was transformed to methyl ester with diazomethane and purified by gas liquid chromatography using a 1/4 inch \times 10 feet stainless steel column packed with 5% SE 30 on dimethylchlorosilane (DMCS) treated Chromosorb G. At a column temperature of 200° with a helium flow rate of 40 ml/min, the ester had a retention time of 2.8 min, which is identical with that of racemic methyl 1,2-dithiane-4-carboxylate. The ester gave an infrared spectrum which was indistinguishable from that of the authentic racemic ester. The ester showed levorotation with $[\alpha]_D^{25} = -167^\circ$.

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REFERENCES

1. Foss, O. In Kharasch, N., (Ed.), *Organic Sulfur Compounds*, Pergamon, London 1961, Vol. I, p. 77.
2. Calvin, M. U. S. *Atomic Energy Comm.* UCRL-2438, 1954, p. 3.
3. Bergson, G. and Schotte, L. *Arkiv Kemi* **13** (1958) 43.
4. Bergson, G. *Some New Aspects of Organic Disulphides, Diselenides and Related Compounds*, Abstracts of Uppsala Dissertations in Science **13** (1962).
5. Claeson, G., Androes, G. and Calvin, M. *J. Am. Chem. Soc.* **82** (1960) 4428.
6. Claeson, G., Androes, G. and Calvin, M. *J. Am. Chem. Soc.* **83** (1961) 4357.
7. Lüttringhaus, A., Kabuss, S., Maier, W. and Friebohn, H. *Z. Naturforsch.* **16b** (1961) 761.
8. Isenberg, N. and Herbrandson, H. F. *Tetrahedron* **21** (1965) 1067.
9. Kalf, H. T. and Havinga, E. *Rec. Trav. Chim.* **81** (1962) 282.
10. Equations of similar form as (3) are given by Eliel, E. L. in *J. Chem. Educ.* **37** (1960) 126.
11. Claeson, G. and Langsjoen, A. *Acta Chem. Scand.* **13** (1959) 840.
12. Claeson, G. *Arkiv Kemi. In press.*
13. Abraham, R. J. and Thomas, W. A. *J. Chem. Soc.* **1965** 335.
14. Isenberg, N. and Herbrandson, H. F. *Tetrahedron* **21** (1965) 1067.
15. Kalf, H. T. and Havinga, E. *Rec. Trav. Chim.* **85** (1966) 467.
16. Bergson, G., Claeson, G. and Schotte, L. *Acta Chem. Scand.* **16** (1962) 1159.
17. Fredga, A. *Acta Chem. Scand.* **4** (1950) 1307.
18. Djerassi, C., Fredga, A. and Sjöberg, B. *Acta Chem. Scand.* **15** (1961) 417.
19. Mislow, K. *Introduction to Stereochemistry*, W. A. Benjamin, New York 1966, p. 158.
20. Beecham, A. F., Fridrichsons, J. and Mathieson, A. Mc L. *Tetrahedron Letters* **27** (1966) 3131.
21. Beecham, A. F. and Mathieson, A. Mc L. *Tetrahedron Letters* **27** (1966) 3139.
22. Foss, O. and Reistad, T. *Acta Chem. Scand.* **11** (1957) 1427.
23. Bartrop, J. A., Hayes, P. M. and Calvin, M. *J. Am. Chem. Soc.* **76** (1954) 4348.
24. Eliel, E. L., Allinger, N. L., Angyal, S. J. and Morrison, G. A. *Conformational Analysis*, Interscience, New York 1965, p. 441.
25. Beychok, S. *Science* **154** (1966) 1295.
26. Dreisbach, R. R. *Physical Properties of Chemical Compounds, Advan. Chem. Ser.* **29**, A.C.S., 1961, Vol. III, p. 392.
27. Dratz, E. A., Ph.D., Thesis, University of California, Berkeley 1966.

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