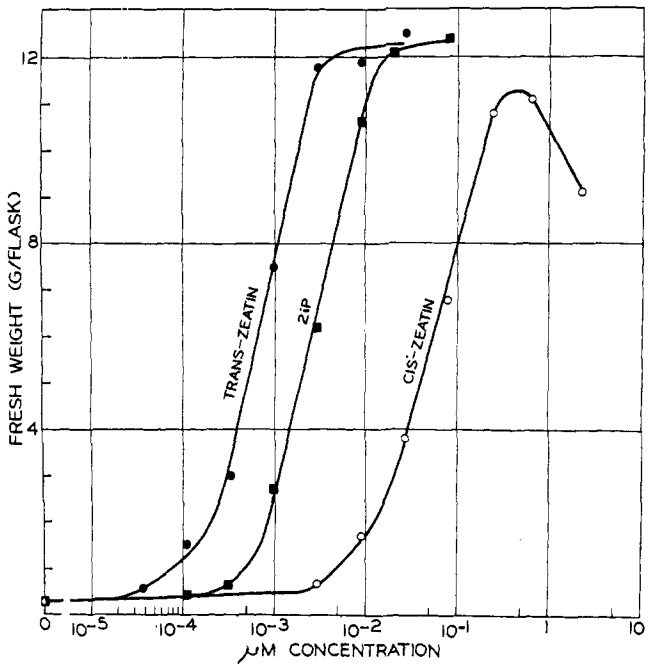


Figure 1. Comparison of cytokinin activities of *trans*- and *cis*-zeatin and of 6-(3-methyl-2-butenylamino)purine (2iP) in the tobacco bioassay. The curves represent mean values from three experiments. Growth period 35 days within the dates June 10–Sept 4, 1970.

thin-layer chromatography on silica: trans, R_f 0.25; cis, R_f 0.32. Final proof that the synthesis had been stereoselective, leading to 6-(4-hydroxy-3-methyl-*cis*-2-butenylamino)purine (**2**), was achieved by hydrogenation of the product over 5% palladium on charcoal to give (±)-dihydrozeatin (**8**),[21,22] identified by direct comparison with an authentic sample prepared by catalytic hydrogenation of zeatin (R_f, melting point, mixture melting point, nmr; picrate melting point, nmr (pyridine-d_5)).[23]

The difference in biological activity between *cis*- and *trans*-zeatin was striking. In the standard tobacco callus bioassay for cytokinin activity,[24] the trans isomer was at least 50 times more active than *cis*-zeatin (Figure 1), a finding consistent with the difference in activity of other N^6-substituted adenines and adenosines showing dependency on the geometrical configuration of the side chain.[11,13]

Acknowledgment. This work was supported at the University of Illinois by a research grant (GM-05829) from the National Institutes of Health, U. S. Public Health Service, and at the University of Wisconsin by a research grant (GB-25812) from the National Science Foundation and by the Research Committee of the Graduate School with funds from the Wisconsin Alumni Research Foundation. We add our thanks to Dr. Sidney M. Hecht for helpful suggestions and for making available very useful spectroscopic data.

Nelson J. Leonard,* Anthony J. Playtis
School of Chemical Sciences, University of Illinois Urbana, Illinois 61801

Folke Skoog, Ruth Y. Schmitz
Institute of Plant Development, Birge Hall University of Wisconsin, Madison, Wisconsin 53706

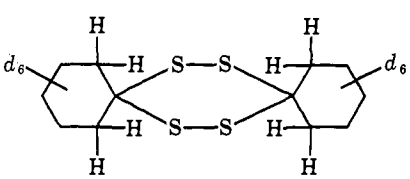
Received February 13, 1971

Conformational Analysis in Multisulfur Heterocycles. VI. 3,3:6,6-Bis(pentamethylene)-*s*-tetrathiane. Slow Pseudorotation in the Twist Conformer of a 6 Ring

Sir:

Since the early postulation by Sachse[1] of chair and flexible (twist) forms for cyclohexane, a wealth of experimental data indicates a general preference for the chair conformer in 6 rings both homocyclic[2] and heterocyclic.[3] Recently, we reported evidence for a low chair–twist energy difference in *s*-tetrathianes and activation parameters for the chair ⇄ twist rate process.[4]

This paper concerns evidence from dnmr spectroscopy for all three of the conformational rate processes possible in a 6 ring, *i.e.*, chair ⇄ chair, chair ⇄ twist, and twist ⇄ twist (pseudorotation[5]) interconversions, being slow on the nmr time scale at −90° in a *single* structure, the deuterated form of 3,3:6,6-bis(pentamethylene)-*s*-tetrathiane (I).



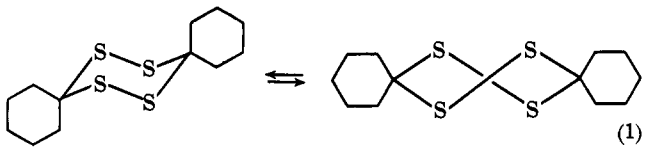
I

The ^1H nmr spectrum (100 MHz) of I in C_2Cl_4 at 80° is a singlet consistent with all protons being rendered equivalent *via* rapid exchange on the nmr time scale (Figure 1). Upon lowering the temperature, the spectrum broadens and separates into three peaks in a manner analogous to that for duplodithioacetone (3,3,6,6-tetramethyl-*s*-tetrathiane)[4] and is totally consistent with a slowing of the *s*-tetrathiane chair ⇄ twist equilibration.[4] The two smaller singlets of equal area (−6°, Figure 1) are assigned to the axial and equatorial methylene groups of the chair conformer of the *s*-tetrathiane ring (C_{2h} symmetry) in I. The lowest field singlet observed at −6° is broadened by exchange processes to be discussed. The large singlet observed at −6° (Figure 1) is assigned to the twist conformer

(1) H. Sachse, *Ber.*, **23**, 1363 (1890); *Z. Phys. Chem. (Leipzig)*, **10**, 203 (1892).
(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1966.
(3) F. G. Riddell, *Quart. Rev., Chem. Soc.*, **21**, 364 (1967); C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 39 (1969); J. B. Lambert, *Accounts Chem. Res.*, **4**, 87 (1971); E. L. Eliel, *ibid.*, **3**, 1 (1970).
(4) C. H. Bushweller, *J. Amer. Chem. Soc.*, **89**, 5978 (1967); **90**, 2450 (1968); **91**, 6019 (1969); C. H. Bushweller, *Tetrahedron Lett.*, 2785 (1968); C. H. Bushweller, J. Golini, G. U. Rao, and J. W. O'Neil, *J. Amer. Chem. Soc.*, **92**, 3055 (1970).
(5) J. B. Hendrickson, *ibid.*, **89**, 7047 (1967).

(21) K. Koshimizu, T. Kusaki, T. Mitsui, and S. Matsubara, *Tetrahedron Lett.*, 1317 (1967).
(22) K. Koshimizu, S. Matsubara, T. Kusaki, and T. Mitsui, *Ag. Biol. Chem.*, **31**, 795 (1967).
(23) The position of the methyl group was confirmed by spin decoupling experiments with both *cis*-zeatin and dihydrozeatin. Moreover, the methyl-position isomers of **1** and **2**, the 6-(4-hydroxy-2-methyl-*trans*-[9] and *cis*-2-butenylamino)purines, along with their dihydro derivative, have now been synthesized and characterized and will be described in a sequel.
(24) E. M. Linsmaier and F. Skoog, *Physiol. Plant.*, **18**, 100 (1965).

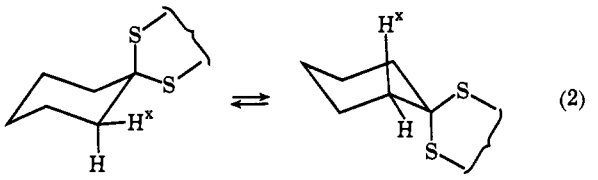
of the *s*-tetrathiane ring (D_2 symmetry) analogous to duplodithioacetone.[5] The tetrathiane twist–chair ratio in I at −12° in CS_2 is 3.3:1.0 giving $\Delta G^\circ = -0.6$ kcal/mol (eq 1). It would be expected at these tem-



(1)

peratures (−6° and above) that the cyclohexane chair ⇄ chair interconversion in I would not be occurring at a slow enough rate to cause any significant changes in the spectrum.[6]

Subsequent examination of I in CS_2 at lower temperatures (−6 to −90°) revealed further changes in the spectrum (Figure 1). From available data,[6] it would be expected that the cyclohexane chair inversion would affect the spectrum of I in the region from −20 to −80° and that under conditions of slow cyclohexane chair interconversion, the various methylene groups in the tetrathiane chair and twist would give AB spectra (eq 2). Indeed, the lowest field singlet for I (tetra-



(2)

thiane chair) observed at −6° (Figure 1) broadens and separates into an AB spectrum of which only one component is observed at −90°. The other singlet resonance due to the chair form of the *s*-tetrathiane ring observed at −6° (Figure 1) broadens substantially from −53 to −72° and disappears under the peaks due to the twist. However, the dominant twist resonance undergoes intriguing changes at lower temperatures (Figure 1) separating not into just one AB pattern but into *two overlapping AB spectra* ($\Delta\nu_{AB} = 63$ Hz, $J_{AB} = 13.5$ Hz; $\Delta\nu_{AB}' = 81$ Hz, $J_{AB}' = 13.5$ Hz). Such spectral changes are certainly grossly consistent with slow cyclohexane flip but the complexity of the spectrum suggests a more complicated situation.

Considering the cyclohexane ring in I, it would be expected that syn-axial nonbonded repulsions involving the large axial sulfur atom would tend to flatten that end of the cyclohexane system attached to the tetrathiane ring. With this in mind, an examination of models of the two equivalent twist forms of I is revealing. Newman projections looking down the H_2C–CS_2 bond indicated by the arrow in eq 3 reveal the equatorial protons in the two twist forms (H_e in II; H_e' in III) to be nonequivalent due to nearest "up" or "down" S–S bonds. The same argument applies to axial H_a and H_a' in II and III. Thus, making the apparently valid assumption that cyclohexane inversion is slow at −90°, the observation of two separate AB spectra for the twist form of I is consistent with *slow twist ⇄ twist interconversion* (eq 3), *i.e., slow pseudorotation*[5] *of the twist.* With slow cyclohexane inversion and fast tetrathiane pseudorotation, H_e and H_e' or H_a'

(6) F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **89**, 760 (1967).

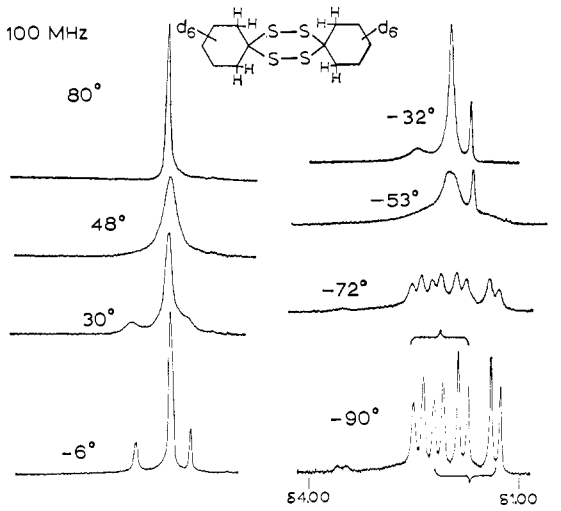
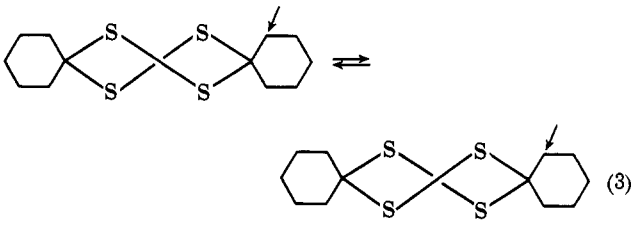
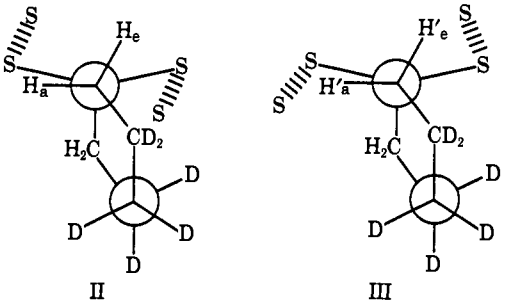


Figure 1. The ^1H nmr spectrum (100 MHz) of 3,3:6,6-bis(pentamethylene)-*s*-tetrathiane (I) as a function of temperature in C_2Cl_4 (80–30°) and CS_2 (−6 to −90°).

and H_a' will be rendered equivalent although axial and equatorial protons would retain their nonequivalence leading to one time-averaged AB spectrum which, of course, is not observed.



(3)



II III

Another rationalization for the observation of two AB patterns for the twist form of I under slow exchange conditions involves the orientation of the cyclohexane rings with respect to one another. In one diastereomer, the two cyclohexane chairs are oriented in the same sense and in the opposite sense for the other diastereomer. In principle, these two diastereomers could give rise to two different AB patterns even in the event of fast twist pseudorotation. Using this model, the relatively large chemical shifts between the different axial or equatorial protons (Figure 1) would require a significant long-range diamagnetic anisotropic effect which we consider to be unlikely. It seems more reasonable that the chemical-shift differences result from the known substantial diamagnetic anisotropy of proximate sulfur–sulfur bonds.[4] However, our data do not unequivocally rule out the possibility of such diastereoisomerism.

Although the nmr spectral transitions for I (Figure 1) do not show clear-cut changes corresponding to cyclohexane flip and tetrathiane twist pseudorotation, the data do provide evidence for slow twist pseudorotation in a 6 ring. A lower limit of about 10 kcal/mol can be assigned to the barrier ($\Delta G^{\pm}$) to pseudorotation in the twist form of an *s*-tetrathiane. This value is dramatically higher than the calculated barrier to pseudorotation in the cyclohexane twist (0.8 kcal/mol)[5] and attests to the significance of vicinal lone pair–lone pair repulsions and a large prow–prow nonbonded repulsion in the transition state for pseudorotation (boat form).[5] Since the pseudorotatory process involves passing vicinal lone pairs on adjacent sulfur atoms, the high barrier to pseudorotation in the twist form of I is consistent with a relatively high calculated cis barrier in H_2S_2 (9.33 kcal/mol)[7] and experimental (dnmr) cis barriers in dialkyl disulfides (8–9 kcal/mol).[8]

Acknowledgment. We are grateful to the National Science Foundation (Grant No. GP-18197) and The Society of Sigma Xi for support.

(7) A. Veillard and J. Demuynck, *Chem. Phys. Lett.*, **4**, 476 (1970).
(8) R. R. Fraser and G. Boussard, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 28–April 2, 1971, No. ORGN 082.
(9) Alfred P. Sloan Research Fellow, 1971–1973.

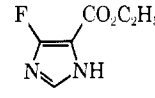
C. Hackett Bushweller,*[9] Geetha U. Rao, Frank H. Bissett
Department of Chemistry, Worcester Polytechnic Institute
Worcester, Massachusetts 01609
Received December 7, 1970

Photochemical Decomposition of Diazonium Fluoroborates. Application to the Synthesis of Ring-Fluorinated Imidazoles

Sir:

Of all possible replacements for hydrogen in carbon–hydrogen bonds, fluorine is unique in effecting the least increase in size while, at the same time, introducing a markedly enhanced electronegativity and a strong hydrogen-bonding potential. Recognition of these properties has induced extensive activity in the synthesis and testing of fluorinated analogs of biologically significant compounds. Such research has provided the biochemist with useful enzyme inhibitors and the pharmacologist with valuable drugs.[1] Despite the key role of the imidazole ring in biological structure and function, no example of a ring-fluorinated imidazole has yet been reported. Accordingly, the development of a synthetic route to such compounds has been a concern of this laboratory for a number of years.

The various procedures in general use for the formation of carbon–fluorine bonds[2] failed, in our hands and undoubtedly in others', to provide a single example of a ring-fluorinated imidazole. We can now report that the photochemical decomposition of diazonium fluoroborates in aqueous fluoroboric acid offers a general route to this series of compounds, as well as to other ring-fluorinated aromatics. A significant feature of the technique is the fact that the diazonium fluoroborate can be generated *in situ* and be subjected, without isolation, to photolysis at room temperature or below; furthermore, the method is readily amenable to moderate scale batches. In the absence of ultraviolet light, none of the diazonium fluoroborates examined provided detectable quantities of fluorinated imidazoles, either in solution or under pyrolytic conditions. The general procedure can be illustrated by several examples.



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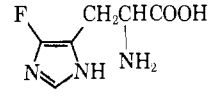

2

2-Fluoroimidazole. A solution of 2-aminoimidazole in aqueous fluoroboric acid (50%) was diazotized by addition of an equivalent amount of sodium nitrite. The resulting diazonium fluoroborate solution was subjected to photolysis (Hanovia mercury vapor lamp, medium pressure, 450 W) at 10–25° until evolution of nitrogen ceased. The solution was neutralized and subjected to continuous ether extraction. The product was separated from a small amount of 2-azidoimidazole[3] by silica gel chromatography and crystallized as the hydrochloride,[4] mp 215–226°; yield 30%.[5]

4-Fluoroimidazole. Because of the instability of 4-aminoimidazole,[6] this compound was generated, *in situ*, from an N-protected derivative. Curtius rearrangement of imidazole-4-carbonyl azide[7] in boiling *tert*-butyl alcohol[8] provided *tert*-butyl imidazole-4-carbamate, mp 142–152° dec. Upon solution of the latter compound in aqueous fluoroboric acid, the blocking group was rapidly removed and the resulting 4-aminoimidazole fluoroborate was treated as described above. Following work-up and purification by sublimation, 4-fluoroimidazole, mp 101–104°, was obtained in 41% yield.

Ethyl 4-Fluoroimidazole-5-carboxylate (1). This compound, mp 155–157.5°, 38% yield, was obtained from ethyl 4-aminoimidazole-5-carboxylate by use of the procedure described for 2 aminoimidazole. Ammonolysis of the fluoro ester provided 4-fluoroimidazole-5-carboxamide, mp 257–260°, of interest with respect to purine biosynthesis.[9]

4-Fluoro-DL-histidine (2). The fluoro ester **1** was reduced with lithium aluminum hydride to 4-fluoroimidazole-5-methanol, mp 136–138°. Reaction of the alcohol with thionyl chloride provided the 5-chloromethyl compound which, without isolation, was used to alkylate ethyl formamidomalonate in the usual manner.[10]

Acid hydrolysis of the alkylation product, mp 120–122°, provided 4-fluorohistidine dihydrochloride (hy-

(1) P. Goldman, *Science*, **164**, 1123 (1969); F. Weygand and W. Oettmeier, *Usp. Khim.*, **39**, 622 (1970); *Russ. Chem. Rev.*, 290 (1970).
(2) M. Hudlicky, "Organic Fluorine Chemistry," Plenum Press, New York, N. Y., 1970; A. E. Pavlath and A. J. Leffler, "Aromatic Fluorine Compounds," Reinhold, New York, N. Y., 1962.
(3) Thermal decomposition of imidazole-2-diazonium fluoroborate in fluoroboric acid leads to 2-azidoimidazole exclusively. The mechanism of formation of the azido derivative is under investigation.
(4) This compound was stored as the hydrochloride since the free base was found to undergo slow decomposition.
(5) Identities and purities of all compounds were confirmed by elemental analysis, nmr and mass spectroscopy, and by tlc.
(6) K. Hofmann, "Imidazole and Its Derivatives," Interscience, New York, N. Y., 1953, p 142.
(7) I. E. Balaban, *J. Chem. Soc.*, 268 (1930).
(8) *Cf.* K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 395 (1969).
(9) The preparation of another analog, 2-fluoro-4-aminoimidazole-5-carboxamide, is in progress.
(10) N. F. Albertson and S. Archer, *J. Amer. Chem. Soc.*, 67, 308 (1945).