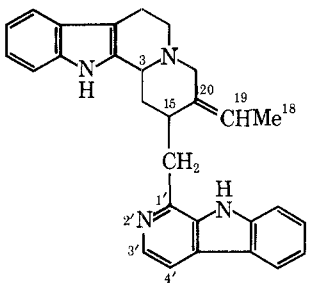
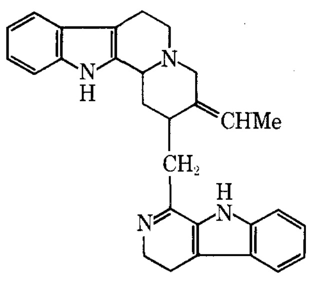
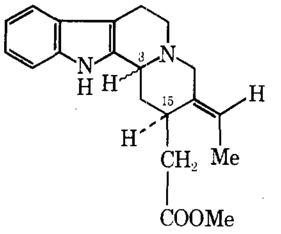


1

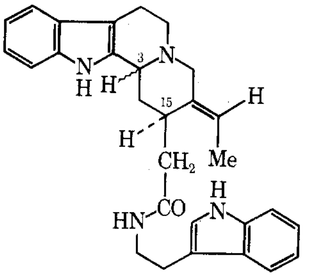


2

a, 3,15 cis, 18-Me cis to C-15
b, 3,15 trans, 18-Me cis to C-15



3a, 3α-H
b, 3β-H



4a, 3α-H
b, 3β-H

residues and a C_9 terpenoid component, dihydrousambarensine features stereochemical relationships characteristic of (1) terpene-derived indole alkaloids bearing ethylidene groups, normally possessing cis geometry, and (2) the emetine type, having the cis relationship of C-3 and C-15. Further, the oxidation levels of the heterorings in natural products **1**, **2**, and tetrahydro-**2** corresponds exactly to those of the isoquinoline units in emetine, psychotrine, and emetamine.[5] These similarities constitute a remarkable overlap of the various structural features which characterize the two alkaloid classes and suggest action on precursor substrates of very similar—perhaps identical—enzyme species.

Acknowledgment. The authors thank Dr. L. Angenot, University de Liege, for providing a sample of natural dihydrousambarensine, and Professor E. E. van Tamelen, Stanford University, for his kind interest in this work.

Supplementary Material Available. The experimental procedures for the reactions described in this investigation will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $2.50 for photocopy or $4.00 for microfiche, referring to code number JOC-75-2572.

References and Notes

(1) L. Angenot and N. G. Bisset, *J. Pharm. Belg.*, **26** (5), 585 (1971); *Chem. Abstr.*, **76**, 72694w (1972).
(2) K. Yamada, K. Aoki, T. Kato, D. Uemura, and E. E. van Tamelen, *J. Chem. Soc., Chem. Commun.*, 908 (1974).
(3) The C-3,C-15 stereochemical assignment has been changed from the original 3β,15α to 3α,15α (personal communication from Dr. L. Angenot; *cf.* L. Angenot, Ph.D. Thesis, University de Liege, 1973, pp 66–69).
(4) H. Yazawa, K. Tanaka and K. Kariyone, *Tetrahedron Lett.*, 3955 (1974).
(5) H. T. Openshaw in "Chemistry of the Alkaloids", S. W. Pelletier, Ed., Van Nostrand-Reinhold, 1970, pp 85–115.

Department of Chemistry
Faculty of Science
Nagoya University
Chikusa, Nagoya, Japan

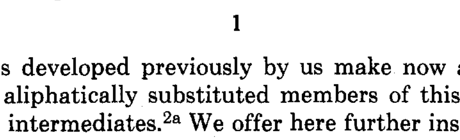
Kiyoyuki Yamada*
K. Aoki
D. Uemura

Received March 11, 1975

Thiocarbonyl Ylides.[1] Stereochemical Properties of 4-*tert*-Butylcyclohexyl Derivatives

Summary: The stereoisomeric thiocarbonyl ylides derived formally from 4-*tert*-butylcyclohexanone undergo ring closure in a conrotatory manner providing spirocyclic thiiranes, which may be desulfurized.

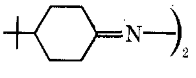
Sir: Thiocarbonyl ylides (1) have revealed their usefulness as tools for theory and as building blocks for synthesis.[2]



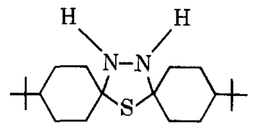
1

Methods developed previously by us make now available various aliphatically substituted members of this class of reactive intermediates.[2a] We offer here further insight into the stereochemical properties of thiocarbonyl ylides and in the following articles some applications of the derived products.[3]

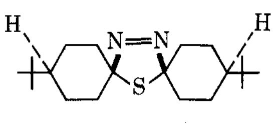
Treatment of the azine (**2**) of 4-*tert*-butylcyclohexanone with hydrogen sulfide under pressure gives a mixture of 1,3,4-thiadiazolidines (**3**). Dehydrogenation of this mixture with dimethylazodicarboxylate gives a mixture of **4**, **5**, and **6**.[4,5] The yield is quantitative based on **2**. Separation of **4** and **5** from **6** is achieved by extraction with *n*-pentane in which **6** is totally insoluble. Chromatography over aluminum oxide allows separation of **4** and **5**. The isomers **4–6** were pure as determined by ^1H NMR and ^{13}C NMR spectroscopy[6] and chromatography.[7]



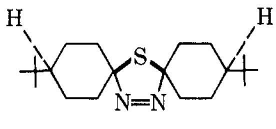
2



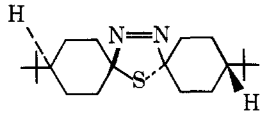
3 (mixture of stereoisomers)



4 (trans,trans), 34%



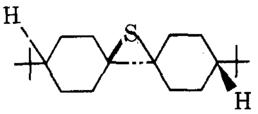
5 (cis,cis), 23%



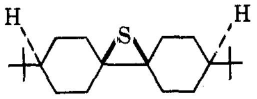
6 (cis, trans), 43%

The stereochemistry of **6** was readily ascertained from the observation of two *tert*-butyl absorptions (δ 0.915 and 0.95 in $CDCl_3$) of equivalent intensity in the ^1H NMR spectrum. Moreover in the proton decoupled ^{13}C NMR spectrum eight lines (four pairs) for the ring carbon atoms were noted demonstrating the nonequivalence of the rings. Distinction between **4** and **5** (*tert*-butyl absorptions at δ 0.90 and 0.92, respectively, in $CDCl_3$) was made on the basis of selective shifts observed in the ^1H NMR spectrum induced by $Eu(FOD)_3$. In **5** the axial hydrogens adjacent to the quaternary ring carbon atoms project into the vicinity of the azo bridge, which provides a good complexing site.[8] Absorptions for these protons[9] are shifted strongly downfield on addition of $Eu(FOD)_3$, but in **4** where this steric feature is absent $Eu(FOD)_3$ influences the ^1H NMR spectra only trivially. The configurational assignment was substantiated independently by oxidizing **4** and **5** to their respective sulfoxides (not shown); here two of the axial protons adjacent to the ring quaternary carbons in the sulfoxide **4** project into the vicinity of the sulfur–oxygen bond and undergo the anticipated downfield shift in C_6D_6 solution.[10] This effect is, as predicted, absent in the sulfoxide of **5**.

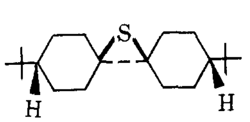
Pyrolysis in boiling methylcyclohexane of **4** or **5** either separately or as a mixture (most convenient for synthetic purposes) gave in quantitative yield a single thiirane **7**, mp 208–214° dec. The observation of two *tert*-butyl absorptions of equal intensity in the ^1H NMR spectrum (at δ 0.915 and 0.95 in $CDCl_3$) as well as clear evidence in the proton decoupled ^{13}C NMR spectrum for the nonequivalence of the cyclohexyl rings established the cis,trans structure.



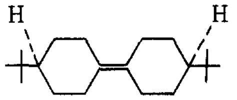
7 (cis, trans)



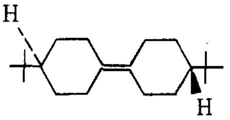
8 (trans, trans)



9 (cis, cis)



10 (syn)

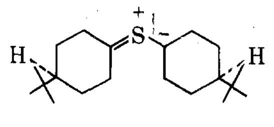


11 (anti)

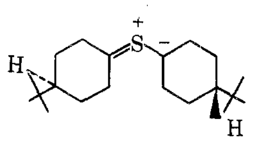
Pyrolysis of **6** under similar conditions gave in quantitative yield also a *single* thiirane, mp 224–228° dec, with a single *tert*-butyl absorption at δ 0.90 in the ^1H NMR spectrum ($CDCl_3$). ^{13}C NMR spectroscopy confirmed reflection symmetry of the cyclohexyl rings. The spectroscopic data establish the product as **8** or **9** but allow no distinction between the two. A choice between these structural possibilities was made on the basis of chemical reactivity considerations. In refluxing xylene with tri-*n*-butylphosphine **7** and **8** or **9** gave (after chromatography and recrystallization) in 90 and 70% yields, respectively, the isomeric olefins **10** and **11**, mp 137–138.5 and 183–183.5°, respectively. Compound **7** reacted much more slowly (roughly factor 100) than **8** or **9** although both reactions were clean and quantitative before work-up. Desulfurization of thiiranes by phosphorous compounds involves initial attack at sulfur followed by or concomitant with release of the alkene.[11] Steric requirements in the transition state are expected to be greater than in the ground state and reaction will be slowed at an axial relative to an equatorial position on a cyclohexyl ring owing to increased 1,3-diaxial repulsions.[12] In **7** two sets of such interactions are present, in **8** there are four such interactions, and in **9** none. The rate differences are in accord with structure **9**, which appears to be the thermodynamically less favored isomer owing to nonbonded repulsions between the axial hydrogens of the two rings, which are forced to face each other.

It has been firmly established that in general the Δ^3-1,3,4-thiadiazoline ring system loses nitrogen readily on thermolysis producing a reactive thiocarbonyl ylide intermediate.[2a] The fact that **4** and **5** afford the *same* thiirane **7** indicates the formation of a common thiocarbonyl ylide **12**, *conrotatory* ring closure of which produces **7**. This implies that the terminal carbons of the thiocarbonyl ylide segment of **12** are effectively sp^2 hybridized. The two possible conrotatory motions for ring closure of **12** are enantiomeric.

Pyrolysis of **6** produces both enantiomers of **13** (**12** with the thiocarbonyl ylide segment completely planar is meso); the two possible directions for conrotatory ring closure are diastereomeric and lead, respectively, to **8** or **9**. The exclusive formation of **9** provides an extreme example of the fairly general tendency of exothermic carbon–carbon bond forming reactions to afford the more strained isomer,[13] in this case through predictable axial–axial ring closure.[14]



12



13

Acknowledgement. We are indebted to Dr. M. P. Doyle and W. Mungall of Hope College, Holland, Mich., and to that institution for making it possible for J.K.K. to participate in an undergraduate exchange program with this university.

References and Notes

(1) Thione ylides: E. M. Burgess and H. R. Penton, Jr., *J. Org. Chem.*, **39**, 2885 (1974).

(2) Thiocarbonyl ylides and their applications: (a) J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, **37**, 4045 (1972); (b) R. M. Kellogg and W. L. Prins, *ibid.*, **39**, 2366 (1974); (c) T. Beetz and R. M. Kellogg, *J. Am. Chem. Soc.*, **95**, 7925 (1973); (d) P. Raynolds, S. Zonnebelt, S. Bakker, and R. M. Kellogg, *ibid.*, **96**, 3146 (1974); (e) A. G. Schultz, *J. Org. Chem.*, **39**, 3185 (1974); (f) A. G. Schultz and M. B. DeTar, *J. Am. Chem. Soc.*, **96**, 296 (1974); (g) W. J. Middleton, *J. Org. Chem.*, **31**, 3731 (1966); (h) S. Mitamura, M. Takaku, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **47**, 3152 (1974). See also (i) S. Tamagaki, K. Sakaki, and S. Oae, *ibid.*, **47**, 3084 (1974); (j) J. P. Synder, *J. Am. Chem. Soc.*, **96**, 5005 (1974); (k) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, **95**, 7301 (1973); (l) R. Hoffmann, H. Fujimoto, J. R. Swenson, and C.-C. Wan, *ibid.*, **95**, 7644 (1973).

(3) R. M. Kellogg and J. K. Kaiser, *J. Org. Chem.*, following paper in this issue; in press.

(4) For brevity no perspective drawings are given. Some of the stereochemical points may not be obvious unless models are used.

(5) Compound **5** was isolated earlier[2a] and its reactions were briefly investigated. Reinvestigation and improvement of experimental methodology led to the obtainment of all stereoisomers.

(6) ^{13}C NMR and other pertinent data will be reported in detail in a full publication.

(7) Satisfactory elemental analyses were obtained for all new compounds reported here.

(8) M. Franck-Neumann and M. Sedrati, *Org. Magn. Reson.*, **5**, 217 (1973).

(9) Identified by well-established precedent: (a) J. W. Emsly, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance", Vol. 2, Pergamon Press, Oxford, 1966, p 703; (b) P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966).

(10) (a) K. Kondo and A. Negishi, *Tetrahedron*, **27**, 4821 (1971); (b) B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky, *J. Am. Chem. Soc.*, **91**, 3839 (1969).

(11) D. B. Denney and M. J. Boskin, *J. Am. Chem. Soc.*, **82**, 4736 (1960).

(12) This is an extrapolation of a well-known argument to explain rate differences in SN2 reactions of cis and trans-substituted cyclohexane derivatives. See, for example, (a) E. L. Eliel, E. W. Della, and M. Rogic, *J. Org. Chem.*, **30**, 855 (1965); (b) A. R. Katritzky, P. G. Lehman, and B. B. Shapiro, *J. Chem. Soc. B.*, 1308 (1971); (c) E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.*, **83**, 2351 (1961); (d) E. A. S. Cavell, N. B. Chapman, and M. D. Johnson, *J. Chem. Soc.*, 1413 (1960); (e) R. C. Cookson, *Chem. Ind. (London)*, 337 (1953).

(13) (a) M. Schlosser, *Bull. Soc. Chim. Fr.*, 455 (1971); (b) R. Hoffmann, C. C. Levin, and R. A. Moss, *J. Am. Chem. Soc.*, **95**, 629 (1973).

(14) See, for analogy, M. Chérest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).

Department of Organic Chemistry
University of Groningen
Zernikelaan, Groningen,
The Netherlands

Richard M. Kellogg*
Mieke Noteboom
Judy K. Kaiser

Received April 23, 1975