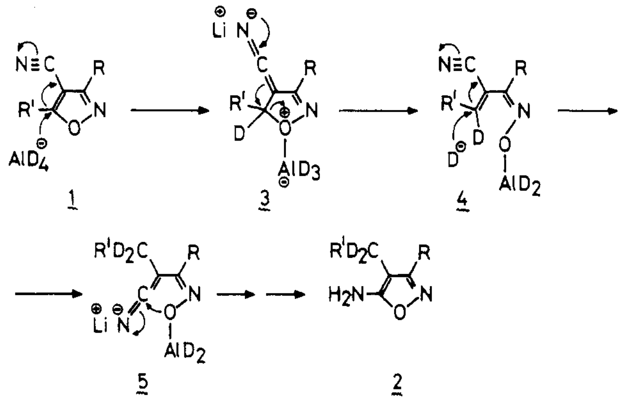
Table II. Reduction of 4-Cyanoisoxazoles 1a-c with Lithium Aluminum Hydride

product	mp, °C	mol form[a]	MS (70 eV), *m/e* (M^+, rel intensity)	IR (Nujol) ν (cm^{-1})	^1H NMR ($CDCl_3$, 60 Hz) δ, *J* (Hz)
2a[b]	84-85 (hexane-ether)	$C_6H_{10}N_2O$	126 (88)	3400, 3250, 1640	1.05 (t, 3 H, *J* = 7.1, 4-CH_2CH_3e, 2.05 (s, 3 H, 3-CH_3), 2.25 (q, 2 H, *J* = 7.1, 4-CH_2CH_3), 5.60 (br s, 2 H, NH_2)
2b	87-88 (hexane-ether)	$C_6H_8D_2N_2O$	128 (71)	3400, 3250, 2200, 2120, 1640	1.05 (s, 3 H, 4-CD_2CH_3e, 2.10 (s, 3 H, 3-CH_3), 4.70 (br s, 2 H, NH_2)
2c	58-59 (benzene)	$C_{11}H_{12}N_2O$	188 (18)	3350, 3200, 1650	1.00 (t, 3 H, *J* = 7.6, 4-$CH_2\mathbf{CH_3}$), 2.30 (q, 2 H, *J* = 7.6, 4-$\mathbf{CH_2}CH_3$), 5.20 (br s, 2 H, NH_2), 7.40 (m, 5 H, 3-C_6H_5)
2d	60-61 (benzene)	$C_{11}H_{10}D_2N_2O$	190 (10)	3450, 3200, 2250, 2140, 1650	1.00 (s, 3 H, 4-CD_2CH_3), 5.10 (br s, 2 H, NH_2), 7.50 (m, 5 H, 3-C_6H_5)
2e	88-89 (hexane-benzene)	$C_{16}H_{14}N_2O$	250 (42)	3350, 3200, 1630	3.60 (s, 2 H, 4-$\mathbf{CH_2}C_6H_5$), 7.20 (m, 5 H, 4-$CH_2\mathbf{C_6H_5}$), 7.50 (m, 5 H, 3-C_6H_5), 7.80 (br s, 2 H, NH_2)

[a] Satisfactory analytical data (C ± 0.19%, H ± 0.17%, N ± 0.18%). [b] ^{13}C NMR ($CDCl_3$) δ 9.07 (CH_3 attached to methylene group), 12.65 (CH_3 attached to C-3), 13.46 (CH_2), 92.60 (C-4), 159.66 (C-3), 163.95 (C-5).

Scheme I



the scope of this process. We report here an apparently general method for the regiospecific synthesis of 5-aminoisoxazoles[8] by reduction of 4-cyanoisoxazoles with lithium aluminum hydride. Furthermore, the mechanism of the reaction has been elucidated by incorporation of deuterium in the resulting 5-aminoisoxazoles when the reduction is carried out with lithium aluminum deuteride.

Result and Discussion

3,5-Disubstituted-4-cyanoisoxazoles **1a-c** react with $LiAlH_4$ or $LiAlD_4$ to give 3,4-disubstituted-5-aminoisoxazoles **2a-e** in 45-75% yields (Table I). Incorporation of deuterium in the methylene group attached at C-4 of **2b,d** clearly shows that the methylene carbon comes from the original C-5 carbon atom of **1a,b**.

From the deuteration experiments the mechanism of the reaction appears to occur by initial attack of hydride at C-5 and formation of the intermediate 3 (Scheme I) which is common for all the reductions of 4-functionalized 3,5-disubstituted isoxazoles with complex metal hydride.[2] The second hydride attack at C-5 may occur with preliminary Lewis acid catalyzed ring cleavage and formation of an α,β-unsaturated nitrile intermediate 4 followed by intramolecular addition of the nitrile salt intermediate 5 which cyclizes to the respective 5-aminoisoxazole.

Experimental Section

All reactions were carried out under nitrogen atmosphere. Melting points are uncorrected. 4-Cyanoisoxazoles were prepared by established procedures.[9] ^1H NMR spectra were recorded on a Varian A-60 analytical spectrometer. ^{13}C NMR spectra were determined with a Varian FT-80 instrument. Chemical shifts are reported in part per million relative to Me_4Si as the internal standard by using $CDCl_3$ as solvent. Infrared spectra were recorded for Nujol mulls, using a Pye-Unicam SP-1100 spectrophotometer. Solvents and reagents were purified by conventional methods. Electron ionization mass spectra were obtained on a Hewlett-Packard 5946-A.

5-Amino-4-ethyl-3-methylisoxazole (2a). General Procedure. (4-Cyano-3,5-dimethylisoxazole[9a] (**1a**; 6.1 g, 0.05 mol) in ether (100 mL) is added to a suspension of lithium aluminum hydride (2 g, 0.05 mol) in 50 mL of ether. The mixture is stirred at 0 °C for 6 h and then hydrolyzed with a saturated solution of ammonium chloride. The ethereal layer is separated and dried with magnesium sulfate. Evaporation of the solvent leaves a solid, which is chromatographed on silica gel with dichloromethane; yield 3.46 g (55%) of **2a**; mp 84-85 °C (hexane-ether). Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 56.99; H, 7.94; N, 22.12.

Physical constants and spectral and analytical data for compounds **2a-e** are summarized in Table II.

Registry No. 1a, 31301-46-9; **1b**, 24400-67-7; **1c**, 54535-49-8; **2a**, 91084-67-2; **2b**, 91084-68-3; **2c**, 91084-69-4; **2d**, 91084-70-7; **2e**, 91084-71-8; $LiAlH_4$, 16853-85-3; $LiAlD_4$, 14128-54-2.

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[8] For references of known methods for synthesis of 5-aminoisoxazoles, see: (a) Yamada, S.; Kowaki, C. *J. Pharm. Soc. Jpn.* **1951**, *71*, 1356. (b) Lopez, L.; Barrans, J. *C. R. Hebd. Seances Akad. Sci., Ser. C.* **1966**, *263*(7), 557. (c) Harsanyi, K.; Takacs, K.; Horvath, K. *Chem. Ber.* **1974**, *107*(8), 2563. (d) Colau, R.; Viel, C. *Bull. Soc. Chim. Fr.* **1980**, 163.

[9] (a) Kochetkov, N. K.; Sokolov, S. D.; Luboshnikova, V. M. *Zh. Obshch. Khim.* **1962**, *32*, 1778. (b) Renzi, G.; Dal Piaz, V.; Pinzauti, S. *Gazz. Chim. Ital.* **1969**, *98*, 753. (c) Quilico, A.; Fusco, R. *Rend. R, Ist. Lomb. Sci. Lett.* **1936**, *69*, 439.

NMR Studies of Geometric Isomers of 3-Dehydro-β-ionone[†]

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Recently a considerable amount of effort has been directed toward studies of structural properties of retinal and

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[†] Taken from the Senior Honors Thesis of A.T.N., University of Hawaii.

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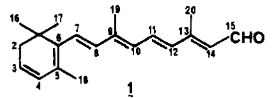
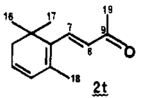
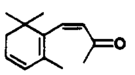
their lower homologues in relation to structural studies of the visual pigment rhodopsin.[1] For example, NMR methods have been used extensively to examine conformational properties of isomers of retinal and lower homologues of β-ionone, the C_{15}-aldehyde and the C_{18}-ketone.[2] In contrast, there has been virtually no effort directed toward studies of compounds in the vitamin A_2 series (3-dehydroretinal, 1) even though its 11-cis isomer is also a naturally occurring chromophore in the visual pigments known as the porphyropsins.[3]



1



2t



2c

Successful synthesis of six 7-trans geometric isomers of 3-dehydroretinal was reported by Isler and co-workers almost 20 years ago.[4] The isolation of a hindered 7-cis isomer has recently been reported.[5] These isomers were found to be less stable than those of retinal. Their lower stability and availability probably contributed to the apparent lack of interest in these compounds.

The photochemical studies recently conducted in our laboratory[5,6] have led to mixtures containing isomers with the hindered 7-cis geometry.[6] In this paper we report properties of the isolated geometric isomers of 3-dehydro-β-ionone **2t** and **2c**.

Experimental Section

Materials. *trans*-3-Dehydro-β-ionone was prepared according to the method of Henbest[7] by reaction of β-ionone sequentially with *N*-bromosuccinimide and *N,N*-dimethylaniline. The crude product was purified by vacuum distillation. Before usage, the compound was further purified by flash column chromatography on silica gel (10% ether in hexane as solvent). *cis*-3-Dehydro-β-ionone was previously only detected in a mixture. It has now been isolated from a photomixture, obtained in a manner described before.[6] A maximum of ~40% of the cis isomer was attainable although to minimize secondary photoproducts irradiation was usually terminated slightly before maximal conversion to the cis isomer. The cis isomer was found to be highly air- and heat-sensitive and unstable upon prolonged contact with silica gel. The only practical method of separation was flash chromatography on silica gel (10% ether in hexane as solvent). Even with this method, the isolated yield was about 10%. ***trans-2***:[6] ^{1}H NMR ($CDCl_3$) δ 1.08 (CH_3-1,1), 1.91 (CH_3-5), 2.12 (H-2), 2.32 (CH_3-9), 5.88 (H-3,4), 6.22 (H-8), 7.26 (H-7); $J_{7,8}$ = 16.5, $J_{2,3}$ = 2.1 Hz. ^{13}C NMR (see below); UV Figure 1; IR (neat) 980 (trans alkene). ***cis-2***: ^{1}H NMR ($CDCl_3$) δ 1.05 (CH_3-1,1), 1.62 (CH_3-5), 2.13 (H-2), 2.25 (CH_3-9), 5.84 (H-3,4), 6.12 (H-8), 6.57 (H-7); $J_{7,8}$ = 12.4; $J_{2,3}$ = 1.9 Hz; ^{13}C NMR (see below); UV Figure 1; IR (neat) 730 (cis alkene).

General Methods. All NMR studies, except those specified below, were conducted on an IBM-NR-80 spectrometer. Except for the dynamic NMR experiments, the probe temperature was maintained at 20 °C. All sample tubes were 5 mm. Samples were deoxygenated and sealed under vacuum after cycles of freeze–pump–thaw.

For ^{1}H NMR spectra, all free induction decay (FID) curves were accumulated in 4K and processed after zero-filled to 16K and resolution enhanced by using Gaussian multiplication. For ^{13}C spectra, FID's were accumulated at 16K and processed as such.

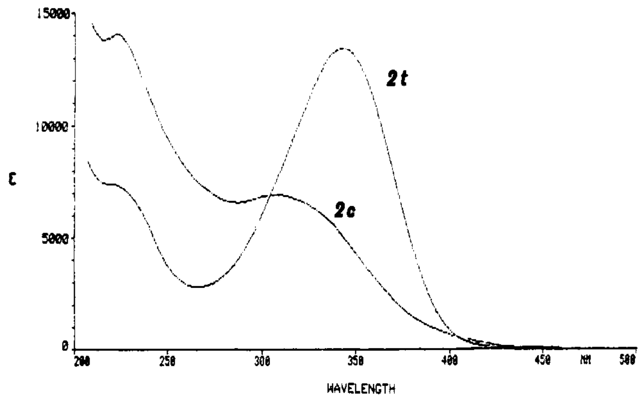


Figure 1. UV–vis absorption spectra (hexane) of *trans*- and *cis*-3-dehydro-β-ionone (**2c** is 2.5 times of actual scale).

Off-resonance decoupling ^{13}C spectra were recorded on a Nicolet NM 300 (300 MHz) spectrometer. FID data were accumulated in 16K and processed after zero-filling to 32K. NOE data were acquired under conditions identical with those described earlier.[8]

Several standard programs supplied by IBM Instruments were used: PANIC (Parameter Adjustment in NMR Iteration Calculation) for simulation of spectra and Pseudo-INET for differentiation of carbons substituted with even or odd number of hydrogens.

Results and Discussion

3-Dehydro-β-ionone and related compounds are common aroma constituents of plants, which are probably precursors to aromatic and bicyclic analogues.[9] We have shown that the air-sensitive cis isomer of 3-dehydro-β-ionone can be isolated from the photomixture by flash chromatography. In contrast to *cis*-β-ionone, it showed no tendency to undergo electrocyclization to the α-pyran form.[10]

^{1}H NMR. The ^{1}H NMR spectra of the two isomers of **2** were well resolved and readily assignable (Table I). They were temperature independent when acetone-d_6 or chloroform-*d* was used as solvent. In toluene-d_8, while the CH_3 signals of both isomers showed small temperature dependence, the *gem*-dimethyl groups of the cis isomer exhibited variations characteristic of a dynamic behavior involving a two-site exchange. In fact the results are quite similar to those observed in compounds in the parent retinal series[8,11] with the sharp high-field methyl singlet first broadening at temperatures below −30 °C and eventually splitting into two singlets (−60 °C). At 80 MHz, the coalescence temperature was found to be −50.0 °C. The chemical shift difference ($\Delta\delta$) of the dimethyl groups did not reach a constant value, apparently changing as a result of varying degree of specific interaction of the carbonyl group with the aromatic solvent at different temperatures.[12] By extrapolation, a value of 6.1 Hz was obtained for the $\Delta\delta$ of the two methyl groups which led to a $\Delta G_c^\ddagger$ value of 11.7 kcal/mol for the two-site exchange process.[11,13]

This value is comparable to the range of $\Delta G_c^\ddagger$ values (11–14 kcal/mol) reported for the ring-chain restricted rotation process in 7-cis isomers of retinal and homo-

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[1] For example, see: Birge, R. R. *Annu. Rev. Biophys. Bioeng.* **1981**, *10*, 315.

[2] See, e.g.: Liu, R. S. H.; Asato, A. E. *Tetrahedron* **1984**, *40*, 1931.

[3] Wald, G. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1953**, *12*, 606.

[4] Schwieter, U.; Saucy, G.; Montavan, M.; Planta, C. v.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1962**, *45*, 517.

[5] Liu, R. S. H.; Asato, A. E.; Denny, M. *J. Am. Chem. Soc.* **1983**, *105*, 4829.

[6] Ramamurthy, V.; Liu, R. S. H. *Tetrahedron Lett.* **1973**, 441.

[7] Henbest, H. B. *J. Chem. Soc.* **1951**, 1074.

[8] Liu, R. S. H., Zingoni, J. Kini, A.; Trammell, M.; Chu, D.; Asato, A. E.; Bopp, T. T. *J. Org. Chem.* **1983**, *48*, 4817.

[9] See, e.g.: Ohloff, G. *Prog. Chem. Org. Natl. Prod.* **1978**, *35*, 431.

[10] Marvell, E. N.; Caple, G.; Gosink, T. A.; Zimmer, G. *J. Am. Chem. Soc.* **1966**, *88*, 619.

[11] Ramamurthy, V., Bopp, T. T.; Liu, R. S. H. *Tetrahedron Lett.* **1972**, 3915.

[12] Patel, D. *Nature (London)* **1969**, *221*, 825.

[13] Jackman, L. M.; Cotton, F. A. In "Dynamic Nuclear Magnetic Resonance"; Academic Press: New York, 1975; p 76.

Table I. Long-Range Coupling Constants in 2t and 2c

nuclei	coupling constants,[a] Hz 2t	2c
H-7, CH_3-5	1.00	1.52
H-7, H-2	0.3	0.3
6,7-dihedral angle[b]	30–39°	39–53°

[a] Verified by simulation of spectra. [b] See text for discussion.

Table II. NOE in 2t and 2c

compd	irradiation	enhancement, % H-7	H-8
2t	CH_3-1,1	21	15
	CH_3-5	10	20
	CH_3-9	14	11
2c	CH_3-1,1	17	6
	CH_3-5,9	5	3

Table III. ^{13}C Chemical Shifts (ppm) of Isomers of 2[a]

carbon	2t	2c	carbon	2t	2c
1	33.8	34.0	7	141.5	140.0
2	39.7	39.2	8	130.2	131.3
3	128.0	126.7	9	198.1	200.9
4	129.4	128.6	16, 17	26.2	26.7
5	132.5	128.9	18	20.0	19.5
6	135.8	136.3	19	27.0	29.0

[a] Solvent, $CDCl_3$; internal standard, $CDCl_3$ at 77.0 ppm.

logues.[8] The additional double bond, which makes the ring more planar, apparently has a negligible effect on the barrier height of this process.

For the trans isomer in toluene-d_8, broadening of the dimethyl signal was observed at −95 °C. However the limited temperature range of the solvent made attempts to detect frozen rotational isomers (even at 300 MHz) unsuccessful.

Coupling constants (long range as well as three-bond) have been determined, and further confirmed by spectral simulation (Table I and figures in supplementary material section). The fact that similar long-range coupling was not observed in β-ionone suggests that the measured H-2 and H-7 coupling is via the π-system with the two interacting atoms separated by seven bonds!

The long-range coupling constant values between H-7 and CH_3-5 when fitted to the empirical equation[14] below gave a ring-chain dihedral angle of 35 ± 5° for the trans

$$J_{H,H'} = A \sin^2 \phi \sin^2 \phi' + B$$

where $A = 5\text{–}8$ Hz, ϕ = ring-chain dihedral angle,

$$B = 0.3 \text{ Hz}, \phi' = 60°$$

isomer and 46 ± 7° for the cis isomer. The much blue-shifted UV absorption spectrum of **2c** is consistent with the twisted conformation.

We have also determined the nuclear Overhauser effect (NOE) between hydrogens on the ring and those on the chain. The results (Table II) are in agreement with a twisted conformation with the molecule undergoing rapid rotational equilibration during the period of spin polarization. Quantitative assessment under the circumstance becomes less meaningful.

^{13}C NMR. The carbon chemical shifts of the two isomers of 3-dehydro-β-ionone are listed in Table III. The assignments were aided by a gated decoupling technique[15] which distinguished carbons 1, 2, 5, 6, and 9 (quaternary and methylene) from carbons 3, 4, 7, 8, 16, 17, 18, and 19 (methine and methyl). Carbons 1, 2, 7, 9 and 16,17 were readily assigned on the basis of their characteristic chemical shifts and intensity. Those of C-7 and -8 were further confirmed by off-resonance ^1H decoupling experiments. The assignment of carbons 18 and 19 were instead based on a comparison of the irradiated (at H-3 and 4) and unirradiated spectra. The quartet that sharpened during selective decoupling (removal of the three-bond coupling constant) was assigned to C-18. The chemical shifts of H-3,4 were too close to allow selective decoupling between these hydrogens and the corresponding carbons. The present assignment should be considered tentative, on the basis of the assumption of a bigger two-bond coupling between H-2 and C-3 than the three-bond coupling between H-2 and C-4.

As in the case of β-ionone, the assignment of C-5 and -6 presented difficulty. The present assignment followed the relative T_1 lifetime arguments as presented by Sykes and Rowan[16] in their assignment of the corresponding carbons in β-ionone.

Acknowledgment. The work was partially supported by a grant from the U.S. Public Health Service (AM-17806). The NT-300 spectrometer used in this work was acquired through matching funds provided by NSF (CHE 8100240) and the University of Hawaii. S. Park assisted in the synthesis of **2t**.

Registry No. **2t**, 14398-35-7; **2c**, 41704-09-0.

Supplementary Material Available: Experimental and simulated ^1H NMR spectra noise and gated decoupled ^{13}C NMR spectra, and selectively decoupled ^{13}C NMR spectra (4 pages). Ordering information is given on any current masthead page.

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(14) Honig, B.; Hudson, B.; Sykes, B. D.; Karplus, M. *Proc. Nat. Acad. Sci., U.S.A.* 1971, *68*, 1289.

(15) LeCocq, C.; Lallemand, J. Y. *J. Chem. Soc., Chem. Commun.* 1981, 150.

(16) Rowan, R., III; Sykes, B. D. *J. Am. Chem. Soc.* 1974, *96*, 7000.