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12-*S*-*CIS* CONFORMATIONALLY LOCKED RETINOIDS: THERMAL AND PHOTOCHEMICAL INTERCONVERSIONS LEADING TO NEW GEOMETRIC ISOMERS

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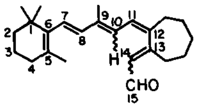
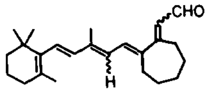
Summary: For 12-*s*-*cis* locked retinal analogues, thermal equilibria are established between 11-*cis*,13-*cis*-**1c** and 13-*cis*-**2c** and between 9-*cis*,11-*cis*,13-*cis*-**1d** and 9-*cis*,13-*cis*-**2d**; a photoisomerization occurs to transform **2c** to *all*-*trans*-**2a** and **2d** to 9-*cis*-**2b**.

That various geometrically isomeric retinoids occupy positions of central importance in a variety of biological systems make such molecules and their various analogues frequent targets of synthetic efforts. Additionally, the pivotal role played by *cis*-*trans* isomerizations of retinoids in vision[1] and energy transduction[2] has resulted in many investigations of molecular mechanisms pertaining to retinoid transformations.[3] As a part of a continuing series of investigations,[4] we recently reported the synthesis of several 12-*s*-*cis* conformationally locked retinoid analogues possessing 7-*trans*-11-*cis* linkages (**1a**-**1d**).[4c,d] In this Letter, we wish to report the preparation and characterization of the four 7-*trans*-11-*trans* isomers of this series, **2a**-**2d**, by a series of highly selective thermal and photochemical processes.



1 (7E, 11Z)

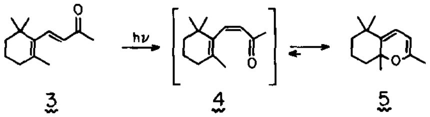


2 (7E, 11E)

a, $\Delta^9 = \Delta^{13} = E$
b, $\Delta^9 = Z$; $\Delta^{13} = E$
c, $\Delta^9 = E$; $\Delta^{13} = Z$
d, $\Delta^9 = \Delta^{13} = Z$

(E = *trans*; Z = *cis*)

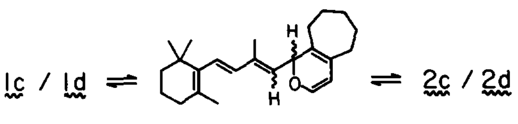
The occurrence of electrocyclizations in dienones was first demonstrated when the photolysis product of *trans*-β-ionone (**3**) was shown to be the α-pyran **5**,[5] which was believed to be formed from the intermediate *cis*-β-ionone (**4**), and when it was subsequently demonstrated that



3 **4** **5**

5 was in thermal equilibrium with small amounts of **4**.[6] In cases where the γ double bond is part of an open chain, it is possible that successive six electron electrocyclization and retroelectrocyclization in the same disrotatory sense would result in isomerization of the γ double bond and this has been invoked to account for geometric isomerizations of dienones[7] and retinals.[4,8] Accordingly, we sought to utilize these thermal processes to prepare the 13-*cis*-**2c** and 9-*cis*,13-*cis*-**2d** retinals from the known 11-*cis*,13-*cis*-**1c** and 9-*cis*,11-*cis*,13-*cis*-**1d**

retinals, respectively, via the intermediacy of α-pyrans of the type **6**. To this end, we therlyzed **1c** (refluxing hexanes, argon, dark^9)^{10} and found that an equilibrium mixture of 47% **1c** and 53% **2c**^{11} was formed (within ~1 h) and that the composition of this mixture remained unchanged through 8 hs heating. The same equilibrium mixture of **1c** and **2c** was formed by heating **2c** under identical conditions. Similarly, thermolysis of **1d** under identical conditions



6

resulted in an equilibrium mixture of 38% **1d** and 62% **2d** and this same equilibrium mixture was also obtainable in the reverse sense by thermolysis of **2d**. In all previously reported examples of transformations of retinals by reversible six electron electrocyclizations, the "more hindered" retinal (i.e., those with more *cis* double bonds) was essentially irreversibly transformed to the "less hindered" retinal.^{4ab,8} The time course of the thermal interconversions **1c** ⇌ **2c** and **1d** ⇌ **2d** are presented in Figures 1 and 2, respectively. The reactions were followed by analytical HPLC (Waters Radial Compression Module -100, 5μ Silica Radial-PAK Cartridge, 5% ethyl acetate/Skellysolve B; 0.5 mL/min) and the peak areas adjusted for molar

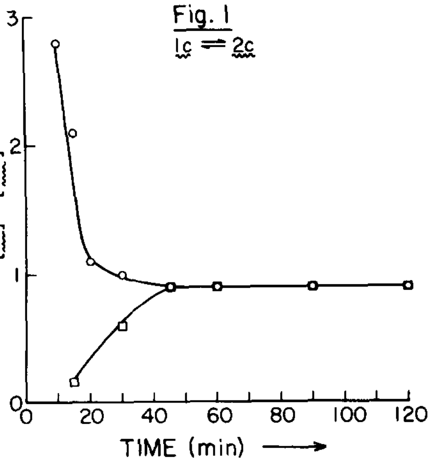


Fig. 1
1c ⇌ 2c

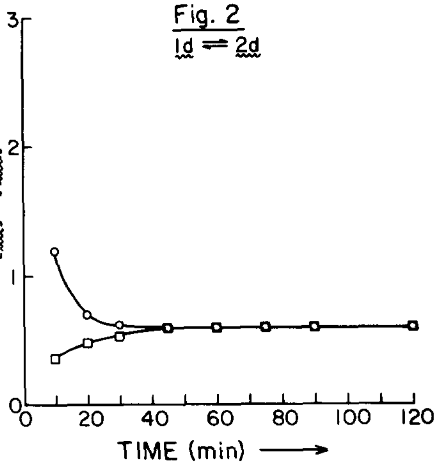


Fig. 2
1d ⇌ 2d

absorptivity at 300 nm. K$_{eq}$ values (69 °C) of 1.1 and 1.7 were calculated for the 11-*cis*,13-*cis* ⇌ 13-*cis* and 9-*cis*,11-*cis*,13-*cis* ⇌ 9-*cis*,13-*cis* interconversions, respectively. Parent retinals which possess the 11-*cis*,13-*cis*-geometry have been suggested to exist in the corresponding 12-*s*-*cis* conformations.^{4b} Thus, the 12-*s*-*cis*-locked 11-*cis*,13-*cis*- and 9-*cis*,11-*cis*,13-*cis*-retinals, **1c** and **1d**, should be relatively unperturbed energetically compared to the parent retinals of the same geometry. However, the 12-*s*-*cis* conformation is disfavored in the parent 13-*cis*- and 9*cis*,13-*cis*-retinals, and, accordingly, the 12-*s*-*cis*-locked 13-*cis*- and 9-*cis*,13-*cis* retinals, **2c** and **2d**, would be of a relatively higher energy than the corresponding parent retinals. Thus, while in the parent series retinals of 11-*cis*,13-*cis* geometry are considerably less stable than those of 11-*trans*,13-*cis* geometry, resulting in the quantitative thermal conversion of the former to the latter, in the 12-*s*-*cis*-locked series, compounds of the two geometries are of comparable energy resulting in a thermal equilibrium situation.

The presence of light (fluorescent room lights or a 100-watt tungsten bulb) during the course of the above thermolysis reactions results in the formation of an additional isomer in each case. The isomer derived from the **1c** ⇄ **2c** system was identified as the *all*-*trans*-retinal **2a** and that derived from the **1d** ⇄ **2d** system as the 9-*cis*-retinal **2b**. If light is completely excluded during the course of the thermolyses, no trace of these isomers could be detected, clearly indicating that they are not products of the thermal manifold.[9] When a hexane solution of the 13-*cis*-isomer **2c** was exposed to a 100-watt tungsten light source at -10 °C, it isomerized to give a mixture of **2c** and **2a**, no other isomer being detectable. Photolysis of **2d** under similar conditions resulted in a mixture of only **2d** and **2b**. In both cases, photolysis was carried out to >15% conversion. The remarkable affinity for photoisomerization about the 13-double bond exhibited by **2c** and **2d** is readily explicable in terms of the elegant application by Liu[12] of the Dellinger-Kasha model to the regioselective photoisomerization of retinoids. This proposal contends that the relative amounts of primary photo-products is largely dependent on the ease of rotation about equivalently substituted double bonds in the excited singlet state, which in turn is dependent on the volume of displacement accompanying such rotation. In **2c** and **2d**, rotation about the 13-double bond is by far the mode of least spatial demand and is consequently heavily favored. The bias towards photoisomerization of the 13-double bond exhibited by the parent retinals[13] is further reinforced in the 12-*s*-*cis*-locked retinals by the introduction of the 12,20-tetramethylene bridge which increases the spatial demand for twisting about the 9- and 11-double bonds.

We have utilized reversible six electron electrocyclizations characteristic of 11-*cis*,13-*cis*-retinals to effect thermal isomerization about the 11-double bond and the photochemical lability of the 13-double bond in 13-*cis*-retinals to effect isomerization about this bond. These reactions further illustrate the multifarious transformations accessible in the retinoid series and, in the following communication, we discuss the novel absorption spectra of the new 12-*s*-*cis* locked retinoids.

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(9) During initial studies, thermolyses of **1c** and **1d** carried out under ordinary laboratory light conditions resulted in Δ^{13} *cis* to *trans* isomerization as well. This unusual light sensitivity (an unexpected complexity not observed for the analogous isomers of the parent retinals discussed in Reference 4b) led to some confusion and complicated our earlier efforts to convert **1c** and **1d** to **2c** and **2d**, respectively.

(10) Spectrophotometric grade hexanes was freshly distilled from $LiAlH_4$ under argon. All glassware and magnetic stir bars used in the reactions were washed with $Na_2S_2O_3$ solution to remove any impurities which might induce geometric isomerization.

(11) All new compounds were characterized by ^{1}H-NMR, UV and high resolution mass spectroscopy.

^{1}H-NMR Data for **2a-d** and **1a-d**[a,b]

	H_7	H_8	H_{10}	H_{11}	H_{14}	H_{15}	$2(CH_3)_{16,17}$	$(CH_3)_{18}$	$(CH_3)_{19}$
1a:	6.19	6.05	6.18	6.46	5.96	10.11	1.02	1.70	1.95
	(16.4)	(16.4)	(11.7)	(11.7)	(8.0)	(8.0)			
2a:	6.30	6.17	6.29	6.80	6.18	10.04	1.04	1.74	2.00
	(15.8)	(15.8)	(12.0)	(12.0)	(8.2)	(8.2)			
1b:	6.21	6.64	6.08	6.55	5.97	10.12	1.05	1.76	1.93
	(16.0)	(16.0)	(11.9)	(11.9)	(8.1)	(8.1)			
2b:	6.23	6.66	6.20	6.87	6.15	10.04	1.04	1.74	2.04
	(16.2)	(16.2)	(11.8)	(11.8)	(8.2)	(8.2)			
1c:	6.17	6.00	5.95	6.57	5.99	9.51	1.01	1.68	1.94
	(16.1)	(16.1)	(11.7)	(11.7)	(8.2)	(8.2)			
2c:	6.31	6.17	6.29	6.47	5.98	9.64	1.04	1.74	1.95
	(16.4)	(16.4)	(11.7)	(11.7)	(8.2)	(8.2)			
1d:	6.19	6.62	5.86	6.65	6.00	9.51	1.04	1.75	1.89
	(15.8)	(15.8)	(12.0)	(12.0)	(8.2)	(8.2)			
2d:	6.28	6.58	6.20	6.54	5.95	9.60	1.02	1.71	2.04
	(15.8)	(15.8)	(12.3)	(12.3)	(7.6)	(7.6)			

[a] Chemical shift data in δ.

[b] Methyl groups appear as singlets and all other protons listed appear as doublets; coupling constants in Hz are in parentheses.

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