kcal/mol) and 1,4-dibromonaphthalene ($E_T \approx 66$ kcal/mol). Solutions of thioketones (0.05 M) were irradiated in the presence of the above sensitizers (0.001 M). Excitation of the sensitizer was effected by making use of a CS-7.60 Corning filter. Product yields were determined as before. Sensitization studies for thioketones 1–10 could not be carried out due to lack of filters to effect selective excitation.

A triplet quenching study was conducted by using alloocimine ($E_T \approx 47$ kcal/mol) as a triplet quencher of thioketones. This quenches the triplets of dialkyl thioketones and, less efficiently, that of aryl alkyl thioketone. However, owing to the lower triplet energy of diaryl thioketones alloocimene is found to be a poor quencher for these triplets. A typical experiment in the case of dialkyl and aryl alkyl thioketones is as follows. Four samples of 0.02 M solutions of thioketone with varying concentrations of the quencher (0.1–0.25 M) were irradiated (450-W medium-pressure mercury lamp with Corning glass filter CS-3.68). The amount of thioketone reacted was monitored by its visible absorption. In all the dialkyl thioketones (11–15) investigated, a linear Stern–Volmer plot was obtained. Quenching was observed in the case aryl alkyl thioketones but required high concentrations due to the poor quenching rate.

Control Experiments. (a) Stability of Thioketones in the Dark. Bicyclo[2.2.1]heptyl thioketones 11–15 kept in dark in organic solvents in an aerated atmosphere for over 1 week were found to be stable. Similarly, bubbling oxygen through these solutions in the dark for over 10 days did not bring about any reaction.

Aryl alkyl thioketones 7–10 were also stable to air and oxygen in the dark. However, thiopivalophenone polymerized in the dark at times, and the reasons for this are not clear. Rigorously purified thiopivalophenone was found to be indenfinitely stable.

Diaryl thioketones (1, 3, and 4) were stable compounds and could be stored. While (2, 5, and 6) were unstable and found to decompose over a period of 2–3 days in dark. Slow dark reaction for thioketones (1–6) was observed in chloroform, cyclohexane, benzene, carbon tetrachloride, and acetonitrile.

All the thioketones investigated revealed poor stability in dioxane and diglyme where rapid decolorization in dark occur.

(b) Stability of Thioketones in Nitrogen Atmosphere upon Irradiation. All thioketones 1–15 investigated did not undergo any noticeable change upon irradiation for 1 week with a 500-W tungsten lamp in a nitrogen atmosphere in organic solvents. However, excitation into the $\pi\pi^*$ band by using a 450-W medium-pressure mercury lamp resulted in decolorization; products of such photoreaction were not characterized. All these reactions were much slower compared to the oxidation.

(c) Stability of Sulfines to Singlet Oxygen Oxidation. Sulfines of 7–15 prepared independently were exposed to a 500-W tungsten lamp in the presence of methylene blue. But all these were found to be stable even after 2 days of irradiation in an oxygen atmosphere.

Acknowledgment. The Department of Science and Technology and the Department of Atomic Energy Commission, Government of India, are thanked for financial support. Dr. P. Balaram and Prof. R. Gleiter are thanked for the kind use of the UV–visible spectrophotometer and for UVPES data, respectively.

Registry No. 1, 958-80-5; 2, 1141-07-7; 3, 1141-08-8; 4, 1450-32-4; 5, 3705-95-1; 5 *S*-oxide, 33240-29-8; 6, 2484-99-3; 6 *S*-oxide, 78132-56-6; 7, 40920-09-0; 7 *S*-oxide, 78132-53-3; 8, 78132-52-2; 8 *S*-oxide, 78132-55-5; 9, 82234-47-7; 9 *S*-oxide, 83816-83-5; 10, 41464-62-4; 10 *S*-oxide, 78132-54-4; 11, 51849-44-6; 12, 33312-98-0; 12 *S*-oxide, 83816-84-6; 13, 875-06-9; 13 *S*-oxide, 50404-36-9; 14, 7519-74-6; 14 *S*-oxide, 50404-35-8; 15, 81049-33-4; 15 *S*-oxide, 83816-85-7; triphenyl phosphite ozonide, 21294-88-2.

Configurationally Locked Retinoids: 13-*cis*-δ-Lactones of 12-Carboxyretinol and 12-(Hydroxymethyl)retinoic Acid

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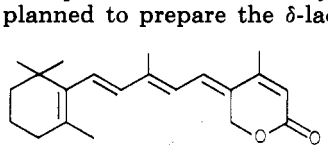
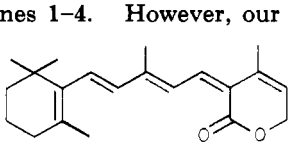
The synthesis of the δ-lactones of 13-*cis*-12-(hydroxymethyl)retinoic acid, 13-*cis*-12-carboxyretinol, 11-*cis*,13-*cis*-12-(hydroxymethyl)retinoic acid, and 11-*cis*,13-*cis*-12-carboxyretinol (1–4, respectively) from the half-esters 13-*cis*-12-carbomethoxyretinoic acid (8), methyl 13-*cis*-12-carboxyretinoate (9), 11-*cis*,13-*cis*-12-carbomethoxyretinoic acid (11), and methyl 11-*cis*,13-*cis*-12-carboxyretinoate (12) is described. The half-esters 8, 9, and 11 were prepared by methanolic saponification of 13-*cis*-12-carboxyretinoic anhydride (7); the half-ester 12 was obtained from partial methylation of 11-*cis*,13-*cis*-12-carboxyretinoic acid. The retinoids prepared were characterized primarily on the basis of their ^1H and ^{13}C NMR parameters. The relative propensity for interconversion between 13-cis and 11-cis,13-cis configurations in these systems is discussed.

As part of our interest in cyclic 13-*cis*-retinoids,[1] we had planned to prepare the δ-lactones 1–4. However, our observation that although 11-*cis*,13-*cis*-12-carboxyretinoic acid (5) was stable to isomerization, 11-*cis*,13-*cis*-12-carboxyretinoic anhydride (6) reverted to the 13-cis anhydride 7 in the dark[1] raised some doubts as to the feasibility of our goal.



1



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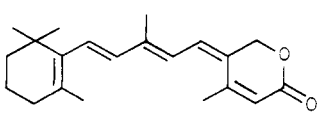

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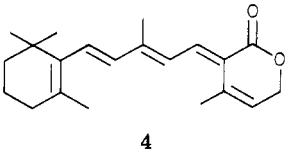
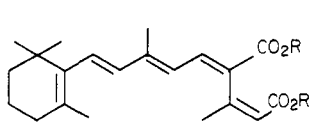


4

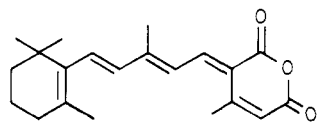
In earlier studies we had observed that treatment of 7 with methanolic base led to the production of half-esters.[1] Since selective reduction of these half-esters afforded a potential route to some of the δ-lactones 1–4, we undertook an investigation of the methanolic saponification of 7 and the reduction of the products obtained.

(1) Lewin, A. H.; Whaley, M. G.; Parker, S. R.; Carroll, F. I.; Moreland, C. G. *J. Org. Chem.* **1982**, *47*, 1799–1807.

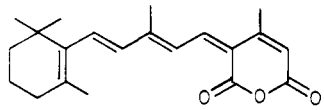
0022-3263/83/1948-0222$01.50/0



5, R = H
5E, R = CH_3



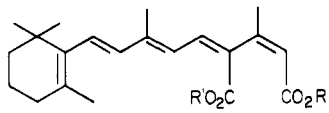
6



7

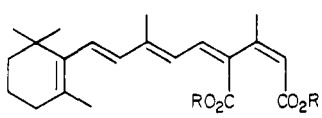
Results and Discussion

Treatment of the anhydride **7** with methanolic potassium hydroxide produced a mixture of two new retinoids in an approximately 10:1 ratio. These were expected to be monomethyl esters of 13-*cis*-12-carboxyretinoic acid (**8**, **9**). Purification of the major component by column

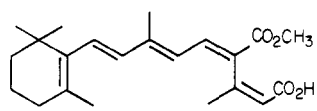


8, R = H; R′ = CH_3
9, R = CH_3; R′ = H

chromatography did indeed give a retinoid monomethyl ester, but its ^1H and ^{13}C NMR spectra resembled those of 11-*cis*,13-*cis*-12-carboxyretinoic acid (**5**) and its dimethyl ester **5E**.[1] Thus, although the 25.6-ppm resonance for the 13a-methyl in the ^{13}C NMR spectrum of this monomethyl ester is consistent with both 13-*cis*- and 11-*cis*,13-*cis*-12-carboxyretinoic acid and the analogous dimethyl esters (**10** and **5**, respectively), the chemical shifts of H-10 and H-11 in the ^1H NMR spectrum are inconsistent with a 13-cis structure (e.g., by comparison with **10**[1]). Reduction of this monomethyl ester with lithium aluminum hydride, followed by water removal, gave a lactone whose ^1H NMR spectrum exhibited singlet signals at 4.78 and 5.79 ppm for the 12a-methylene and H-14, respectively, pointing to reduction having taken place at the 12a-position. In other words, this is the δ-lactone of 12-(hydroxymethyl)retinoic acid. Since the carbomethoxy group would be reduced in preference to the carboxy group in a half-ester/half-acid, it follows that the structure of the monomethyl ester is 11-*cis*,13-*cis*-12-carbomethoxyretinoic acid (**11**), and that



10, R = H
10E, R = CH_3



11

of the lactone is 11-*cis*,13-*cis*-12-(hydroxymethyl)retinoic acid δ-lactone (**3**). It thus appeared that the saponification of the anhydride **7** was taking place with concomitant isomerization of the 11,12 double bond. Whereas facile photoisomerization of the anhydride **7** to its 11-cis isomer **6** had been observed,[1] these reactions, like all the work described in this report, were carried out under dim red lights, precluding photoisomerization. When the product mixture from the saponification of **7** was immediately reduced without purification and the product subjected to water removal, two lactones were formed which were both different from **3**. Spectral examination after chromatographic separation showed both products to lack the C-13a signals at ca. 25 ppm which are so characteristic of the

Table I. ^{13}C NMR Spectral Data (ppm) of Retinoids[a]

compd	carbon no. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	1a	5a	9a	13a	12a
1	34.8	40.2	19.7	33.5	130.8	138.2	129.9	138.0	138.0	125.2	124.6	142.1	151.6	117.1	151.6	29.1	21.8	12.3	18.0	67.4[b]
2[c]	34.8	40.2	19.7	33.7	131.5	138.4	131.4	138.4	138.1	129.9	134.2	143.1	134.1	119.9	76.1	29.5	22.3	12.9	19.7	
3	34.8	40.0	19.7	33.5	130.5	138.3	130.0	138.3	142.2	126.0	129.0	128.5	152.0	119.6	163.8	29.1	21.8	12.0	24.5	64.7
4	34.7	40.1	19.7	33.5	130.7	138.4	130.8	138.4	145.6	126.4	132.7	123.1	133.5	123.7	66.8	29.1	21.8	12.2	22.2	166.4
11	35.0	40.4	19.9	33.7	131.0	138.3	131.7	137.7	145.4	125.4	134.1	131.6	152.4	120.8	166.4	29.2	22.0	13.1	25.6	
12	34.8	40.1	19.7	33.5	130.5	138.3	130.5	138.1	144.1	125.5	133.2	132.8	152.4	120.5	165.4	29.2	21.9	12.7	25.4	166.0
13	34.7	40.1	19.7	33.5	131.5	138.1	130.9	138.2	144.3	126.4	135.7	130.5	132.4	130.6	60.2	29.1	21.7	12.7	23.6	167.6

[a] At 25.034 MHz in dioxane-d_8 unless otherwise noted. [b] In CD_3CN. [c] Recorded in $CDCl_3$; chemical shifts corrected to dioxane-d_8 by addition of +0.6 ppm.

Table II. Proton NMR Spectral Data (ppm) of Retinoids[a]

compd	proton on carbon no.										
	7	8	10	11	14	1a	5a	9a	13a	15	12a
1	6.37	6.21	6.27	6.81	5.68	1.04	1.71	2.03	2.11		5.78
2	6.38	6.38	7.65	7.00	5.75	1.00	1.69	1.97	2.02	4.83	
3	6.38	6.21	6.63	6.73	5.79	1.03	1.72	2.00	2.30		4.78
4	6.41	6.19	6.71	7.77	5.89	1.04	1.72	2.10	2.10	4.88	
11	6.35	5.99	5.96	7.44	5.88	0.98	1.66	1.98	2.00		
12	6.38	6.12	5.98	7.45	5.90	1.02	1.67	2.00	2.00		
13	6.34	6.18	6.06	7.60	5.65	1.03	1.69	1.85	2.04	3.78	

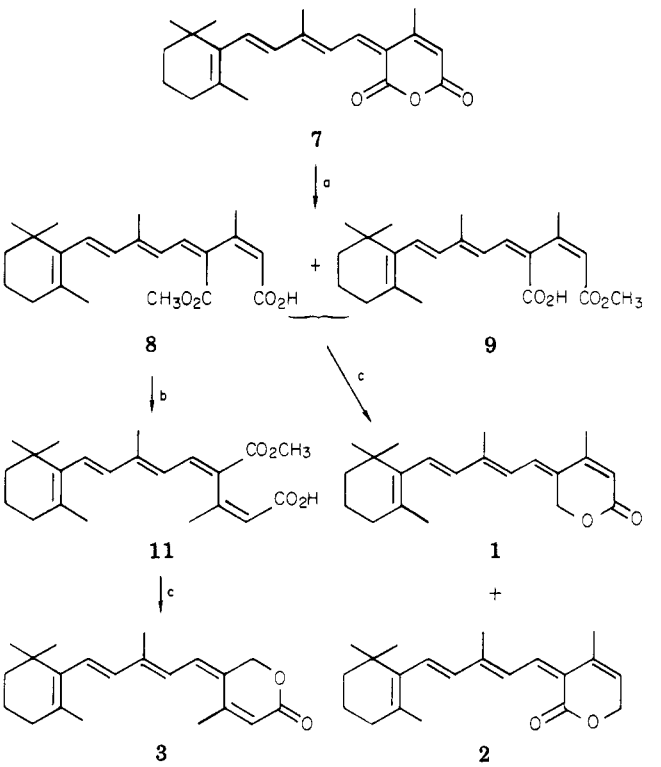
[a] At 100 MHz in dioxane-d_8.

11-cis,13-cis geometry, displaying instead signals at 18.0 and 19.7 ppm, respectively, suggestive of a cyclic 13-cis structure such as **7** (Table I). The ^{1}H NMR spectra (Table II) serve to pinpoint the position of the carbonyl group. Thus, the chemical shifts of H-10 and H-11 are upfield in the major product relative to their positions in the minor product and in model compounds such as **7** and are similar to those in **3**. Taken together with the singlet nature of the H-14 signal at 5.68, the absence of a carbonyl group at C-12a for the major product is suggested, and its structure is therefore 13-*cis*-12-(hydroxymethyl)retinoic acid δ-lactone (**1**). That the structure of the minor product is 13-*cis*-12-carboxyretinol δ-lactone (**2**) is confirmed by the H-14 triplet at 5.66 ppm, due to coupling with the methylene hydrogens at C-15.

On the basis of these structures, it appears that the methanolic saponification of 13-*cis*-12-carboxyretinoic anhydride (**7**) proceeds to give mainly 13-*cis*-12-carbomethoxyretinoic acid (**8**) with methyl 13-*cis*-12-carboxyretinoate (**9**) as a byproduct. However, this product mixture is not stable and, upon attempted purification, leads to the 11-cis,13-cis half-ester **11**. In fact, when the course of the reaction was followed by high-pressure liquid chromatography (HPLC), it was found that immediately after addition of the base, the product mixture consisted of only two components in approximately a 10:1 ratio. After 30 min, a third component, coincident with 11-*cis*,13-*cis*-12-carbomethoxyretinoic acid (**11**), appeared at the expense of the major component of the initial product mixture. At the end of 2 h **11** was the predominant product. Since potassium ion is known to lead to isomerization in retinoid systems,[2] the reaction was carried out by using sodium hydroxide; identical results were obtained. The initial product mixture could be isolated by quenching and workup immediately after disappearance of the starting anhydride **7** (<5 min). It could be kept as an oil almost without change at −70 °C for about 1 week. At room temperature the half-ester **11** appeared within 1 day; in methanol solution the product composition changed within a few hours, and this was accelerated by the addition of base. It therefore appears that the 13-cis half-esters **8** and **9** are the primary saponification products of the anhydride **7**. The major product **8** isomerizes rapidly to the 11-cis,13-cis half-ester **11** (Scheme I).

Similar results had been obtained when methylation of 13-*cis*-12-carboxyretinoic acid (**10**) was attempted. Thus, treatment of **10** with methanolic hydrochloric acid led to isomerization,[1] but analogous treatment of 11-*cis*,13-*cis*-12-carboxyretinoic acid (**5**) gave a new monomethyl ester, whose ^{1}H NMR was very similar to those of **11**, **5**, and **5E**. It therefore followed that the structure of this monomethyl ester was methyl 11-*cis*,13-*cis*-12-carboxyretinoate (**12**). This was confirmed by reduction with lithium aluminum

Scheme I[a]



[a] (a) KOH/MeOH; (b) column chromatography; (c) $LiAlH_4$, $-H_2O$.

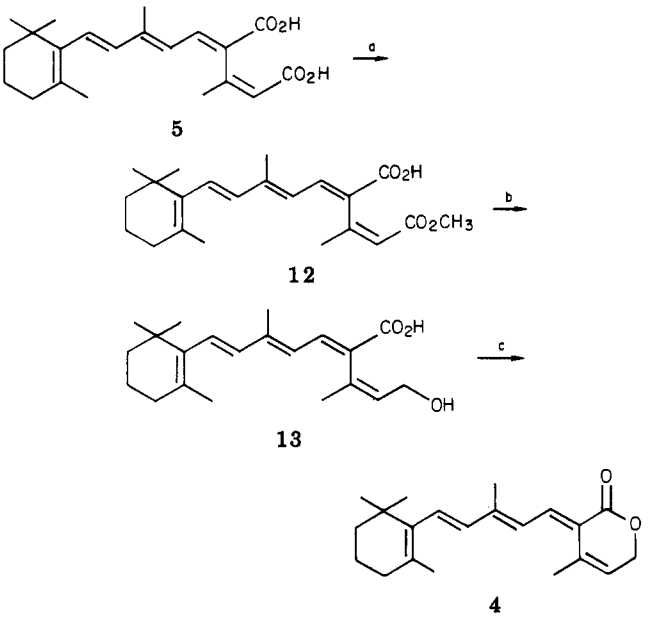
hydride, which gave a hydroxy acid **13**, the ^{1}H NMR of which exhibited a triplet at 5.66 ppm for H-14; the balance of the vinyl region of the spectrum was essentially superimposable with the spectra of **5**, **5E**, and **12**. Dehydration of **13** gave a lactone, the NMR parameters of which were perfectly consistent with the assigned structure, 11-*cis*,13-*cis*-12-carboxyretinol δ-lactone (**4**, Scheme II).

With the preparation of this lactone our goal of preparing retinoids in which the cis stereochemistry of the 13,14 double bond would be maintained in a cyclic structure was attained. The lactones **1**–**4** were all stable retinoids and were, in fact, resistant to isomerization under conditions which caused isomerization of the 13-*cis* half-ester **8** to its 11-cis,13-cis analogue **11**.

Having in hand the 11-cis,13-cis half-esters (**11** and **12**) and lactones (**3** and **4**), we could easily verify the lack of isomerization of the other 13-cis half-ester **9** (minor product) in spite of the small amount present. Specifically, the 11-cis,13-cis half-ester **12** was not detected even after leaving the product mixture **8** and **9** in basic methanol solution for long time periods, nor was the lactone **4** ever detected among the reduction–dehydration products. Control experiments showed that both **12** and **4** would have survived the reaction conditions had they been

(2) French Patent 1 320 153.

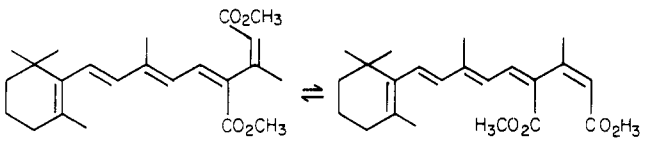
Scheme II[a]



[a] (a) 3% HCl/MeOH, (b) $LiAlH_4$/THF, (c) $-H_2O$.

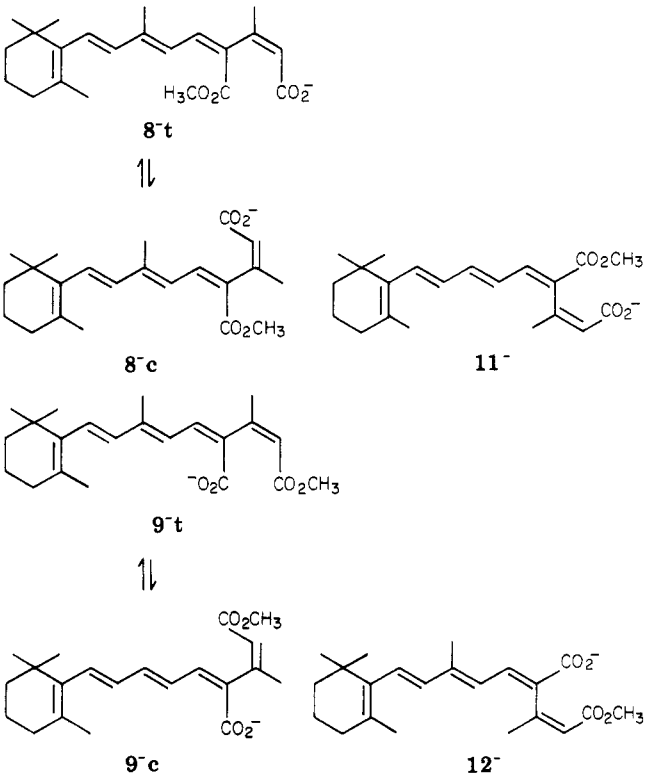
formed. It, therefore, follows that although the major primary product, 13-*cis*-12-carbomethoxyretinoic acid (**8**), isomerizes readily to the 11-cis,13-cis analogue **11**, the minor primary product, methyl 13-*cis*-12-carboxyretinoate (**9**) does not isomerize to its 11-cis,13-cis analogue **12**.

The isomerization of the 13-cis half-ester **8** to the 11-cis,13-cis half-ester **11** is not surprising. We had found that the 11-cis,13-cis configuration represented an energy minimum relative to the trans,13-cis or 11-cis configurations of 12-carboxyretinoic acid dimethyl esters and had explained this observation on the basis of conformational analysis of the retinoids in question.[1] Specifically, we had concluded, in agreement with others,[3] that the 11-cis,13-cis diester **5E** was planar in the C-7 to C-12a region, including the 12a-carboxyl group, but that the 13,14 double bond was twisted out of that plane. We had also demonstrated that the 13-cis diester **10E** existed as a dynamic equilibrium mixture of the conformations **10Ec** and **10Et** in which the



10Ec **10Et**

carbomethoxy group was in and out of conjugation in the respective conformations, and the 13,14 double bond was out of and in conjugation, respectively.[4] The conformations of the diacids **5A** and **10** have not been investigated, but the near identity of their ^1H and ^{13}C NMR spectra to those of the diesters **5E** and **10E** suggests that the same conformational situation probably obtains. The NMR spectra of the 13-cis half-esters **8** and **9** could not be studied because the compounds were not available in pure form; **8** was not stable to the purification conditions, and **9** was formed in such small amounts that its isolation in pure form did not seem worthwhile. It would appear likely that if the conformations of the diacids resemble those of the diesters, then those of the half-esters should be similar as well. Since the isomerization is accelerated in basic medium, it is tempting to examine the relative stabilities of the carboxylate anions in question: 8^- vs. 11^- and 9^- vs. 12^-.



The carboxylate anion cannot derive stabilization by delocalization in any event so any loss of conjugation due to lack of coplanarity in 8^- and 11^- would be irrelevant. The 11-cis,13-cis isomer may be somewhat more stable due to the extended form of the conjugated trienoic ester moiety of C-7 to C-12a. Thus, in this set (8^- and 11^-) there is a driving force for rearrangement. In the second isomer pair (9^- and 12^-) the loss of coplanarity at C-12 is very serious since it is not compensated for by conjugation with the C-12a group. Therefore, in spite of the steric strain, the conformer **9-t** is probably at lower or equal energy with both the conformer **9-c** and the 11-cis,13-cis isomer 12^-. Consequently, **9** does not isomerize to **12**.

The lack of isomerization of the lactones possessing 11-cis stereochemistry (**3**, **4**) to the 13-cis lactones (**1**, **2**) is of interest. Since in such cyclic systems the 1,3 interactions between the 12a- and 15-carbon are unavoidable, the determining factor for relative stability should be conjugation. Presumably the preference for extended conjugation accounts for the spontaneous isomerization of the 11-cis,13-cis anhydride **6** to the 13-cis anhydride **7**; the analogous situation might have been expected for the lactone pair **3** and **1**. However, for the lactones the energy for isomerization of the 11,12 double bond must be substantially higher than for the anhydrides **6** and **7** because of the absence of the 12-carboxyl group. Thus, although the energy of **1** may indeed be lower than that of **3**, spontaneous isomerization in the dark is precluded by the high energy barrier to isomerization. For the second lactone pair, **4** and **2**, the balance between having an extended polyene chain with a *cis*-carboxyl group (as in **1**) vs. having a *trans*-carboxyl group with a cis double bond in the polyene may not give an energy minimum for either species. Consequently, there would be no driving force for isomerization in these lactones. Taken together with the fact that isomerization would require deconjugation of both

(3) Robeson, C. D.; Cawley, J. D.; Weister, L.; Stern, M. H.; Eddinger, C. C.; Chechak, A. J. *J. Am. Chem. Soc.* **1955**, *77*, 4111–4119.
(4) Lewin, A. H.; Carroll, F. I.; Moreland, C. G. *J. Am. Chem. Soc.* **1981**, *103*, 6527–6529.

Table III. HPLC Retention Times for Retinoids

no.	retinoid name	column[a]	eluant[a]	retention time, min
1	13-*cis*-12-(hydroxymethyl)retinoic acid δ-lactone	B	C	11.0
2	13-*cis*-12-carboxyretinol δ-lactone	B	C	6.7
3	11-*cis*,13-*cis*-12-(hydroxymethyl)retinoic acid δ-lactone	B	C	13.5
4	11-*cis*,13-*cis*-12-carboxyretinoic acid δ-lactone	B	C	4.0
8	13-*cis*-12-carbomethoxyretinoic acid	A	D	8.0
9	methyl 13-*cis*-12-carboxyretinoate	A	D	6.5
11	11-*cis*,13-*cis*-12-carbomethoxyretinoic acid	A	D	9.0
12	methyl 11-*cis*,13-*cis*-12-carboxyretinoate	A	D	4.0

[a] A, Radial Pak A; B, Radial Pak B; C, 10% Et_2O/90% hexane; D, 0.2% NH_4OAc/60% CH_3CN/40% H_2O.

the polyene and the carboxyl group, this may account for the observed stability of **2** and **4** to isomerization.

In summary, it is noteworthy that although 11-*cis*,13-*cis*-12-carboxyretinoic anhydride (**6**) isomerized rapidly in the dark to 13-*cis*-12-carboxyretinoic anhydride (**7**) and 13-*cis*-12-carbomethoxyretinoic acid (**8**) isomerized readily to 11-*cis*,13-*cis*-12-carbomethoxyretinoic acid (**11**), the target δ-lactones **1**–**4** were stable to isomerization.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary tube apparatus or on a Koffler hot stage, and they are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Model 267 grating spectrophotometer, ultraviolet spectra were recorded on a Cary 14 spectrophotometer, and mass spectra were obtained on an AEI MS-902 spectrometer. Proton NMR spectra were recorded on a Varian HA-100 spectrometer and ^{13}C NMR spectra were determined on a JEOL JNM-PS-100 NMR instrument. ^1H NMR and ^{13}C NMR data are summarized in Tables I and II.

Analytical chromatography was carried out by using commercial silica gel F-254 for TLC and a Waters Associates high-pressure liquid chromatograph consisting of two constant-flow pumps (M6000A) controlled electronically by a solvent programmer (Model 660), a septumless nonstop-flow high-pressure injector (Model U6-K), and a variable-wavelength UV detector (Model 450). The columns used were Waters Associates 3.9 mm × 30 cm μ-Porasil, μ-Bondapak C_{18}, and Radial Pak A and B cartridges in a Waters Associates radial compression module (Model 100).

Preparative separations were accomplished by using silica gel prepacked columns for medium-pressure liquid chromatography and two 10 mm × 25 cm Partisil 10 columns (packed at RTI) in series or a 4 mm × 25 cm column (packed at RTI) for high-pressure chromatography.

All laboratory operations involving retinoids and related polyene systems were performed under dim red lights and in an inert atmosphere.

11-*cis*,13-*cis*-12-Carbomethoxyretinoic Acid (11). To a slurry of 200 mg (0.6 mmol) 13-*cis*-12-carboxyretinoic anhydride (**7**) in 10 mL of MeOH was added 3.1 mL (3 mmol) of 1 N KOH in MeOH. Immediate dissolution of the solid and a color change took place. TLC (silica gel; acetone–hexane, 1:1) showed the anhydride to be completely consumed. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. After drying and evaporation, the organic phase yielded 142 mg of a yellow powder, mp 129–135 °C. Chromatography of 70 mg of the powder on a size-A prepacked silica gel column, by eluting with 25% acetone–hexane at 2 mL/min and collecting 0.5-mL fractions, gave 23 mg of relatively pure material with ^1H NMR and ^{13}C NMR spectra consistent with a monomethyl ester of 11-*cis*,13-*cis*-12-carboxyretinoic acid. Mass spectral analysis gave the following: calcd for $C_{22}H_{30}O_4$ m/e 358.2143, found m/e 358.2139.

11-*cis*,13-*cis*-12-(Hydroxymethyl)retinoic Acid δ-Lactone (3). To a stirred suspension of 4.0 g (12.2 mmol) of 13-*cis*-12-carboxyretinoic anhydride (**7**) in 120 mL of MeOH at 0 °C was slowly added 48 mL of 1 N KOH in MeOH, and the reaction mixture was stirred for 2 h. It was then quenched with H_2O and extracted with Et_2O. The aqueous phase was cooled to 0 °C, quenched with saturated aqueous NH_4Cl, and extracted with Et_2O. These ethereal layers were back-washed with brine, dried over Na_2SO_4, and evaporated to give 4.02 g of an oil which was shown by HPLC to consist primarily of **11**. It was dissolved in 10 mL of THF (freshly distilled from $LiAlH_4$) and added slowly to a cold (−15 °C) slurry of 1.06 g (30 mmol) of $LiAlH_4$ in 140 mL of THF. After stirring at −15 °C for 15 min, the reaction was quenched with saturated aqueous NH_4Cl, diluted with H_2O, acidified to pH 5 with 10% H_2SO_4, and extracted with EtOAc. The residue, after evaporation of the EtOAc, was subjected to dehydration by azeotroping it five times with cyclohexane at room temperature. TLC indicated two nonpolar components and one polar component. Separation on a cleanup column (silica gel, 2:1 EtOAc/hexane) gave a small amount (488 mg) of a mixture of the nonpolar components **1** and **2**. The majority of the material was the polar component (2.1 g); this hydroxy acid was refluxed with cyclohexane with water removal by a Dean–Stark trap for 1 h. HPLC and TLC analyses indicated mainly one component which was purified by crystallization from EtOAc. The pure compound was shown to be the lactone **3**: mp 165–169 °C; IR (KBr) 1700 cm^{-1}; UV (EtOH) λ_{max} 365 nm (ε 33 225); mass spectrum, calcd for $C_{21}H_{28}O$ m/e 312.2089, found m/e 312.2086.

13-*cis*-12-(Hydroxymethyl)retinoic Acid δ-Lactone (1) and 13-*cis*-12-Carboxyretinol δ-Lactone (2). To a stirred suspension of 4.0 g (12.2 mmol) of 13-*cis*-12-carboxyretinoic anhydride (**7**) in 120 mL of MeOH at 0 °C was slowly added 48 mL of 1 N KOH in MeOH. The solution, which had turned almost colorless, was stirred at room temperature for 30 min. At the end of this time, it was quenched with saturated aqueous NH_4Cl at 0 °C, extracted with Et_2O, and back-washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to give ca. 5 g of an oil which was dissolved in 30 mL of THF (freshly distilled from $LiAlH_4$) and very slowly added to a stirred slurry of 1.31 g (32.5 mmol) of $LiAlH_4$ in 140 mL of THF at −15 °C. Stirring was continued at −15 °C for 15 min, at the end of which the reaction was quenched with saturated aqueous NH_4Cl, diluted with H_2O, and acidified to pH 5 with 10% H_2SO_4. The mixture was then extracted with EtOAc, and the combined organic extracts were evaporated. The residue was subjected to dehydration by dissolution in cyclohexane and evaporation at room temperature (five times). Since TLC still showed the presence of polar material (hydroxy acids), the cyclohexane dehydration was repeated at 60 °C. HPLC analysis of the residue showed two components to be present; these were separated by medium-pressure liquid chromatography using silica gel prepacked columns and eluting with 20–50% Et_2O/hexane. The fastest eluting component was 13-*cis*-12-carboxyretinol δ-lactone (**2**): IR (KBr) 1710 cm^{-1}; UV (EtOH) λ_{max} 367 nm (ε 18 257); mass spectrum, calcd for $C_{21}H_{28}O_2$ m/e 312.2089, found m/e 312.2086. The slower eluting fraction was predominantly 13-*cis*-12-(hydroxymethyl)retinoic acid δ-lactone (**1**) contaminated with traces of **2**. Crystallization from Et_2O–hexane gave a pale yellow solid: mp 101–103 °C; IR (KBr) 1700 cm^{-1}; UV (EtOH) λ_{max} 368 nm (ε 28 500); mass spectrum, calcd for $C_{21}H_{28}O_2$ m/e 312.2089, found m/e 312.2086.

Methyl 11-*cis*,13-*cis*-12-Carboxyretinoate (12). A solution of 1.50 g (0.004 mol) of 11-*cis*,13-*cis*-12-carboxyretinoic acid (**5**) in 3% methanolic HCl was stirred at room temperature for 6 h. The solvent was removed in vacuo, and the residue was dissolved in Et_2O, washed with H_2O and brine, and dried (Na_2SO_4). The crude ester (1.49 g) was purified by elution on a medium-pressure silica gel column (Merck, size B) by using 1% MeOH in 2:1 hexane–EtOAc to yield 650 mg (36%) of a solid: mp 130–133 °C; IR (KBr) 1675, 1720 cm^{-1}; UV (MeOH) λ_{max} 327 nm (ε 33 240);

mass spectrum, calcd for $C_{22}H_{30}O_4$ m/e 358.215, found m/e 358.215.

11-*cis*,13-*cis*-12-Carboxyretinol (13). To a cold (0 °C) slurry of 228 mg (6.0 mmol) of $LiAlH_4$ in 18 mL of THF was slowly added a solution of 260 mg (0.75 mmol) of methyl 11-*cis*,13-*cis*-12-carboxyretinoate (12) in 2 mL of THF. After being stirred for 0.5 h, the reaction mixture was quenched with a saturated solution of NH_4Cl, diluted with H_2O, and extracted with Et_2O. The organic phase was washed with H_2O and brine and dried (Na_2SO_4). The crude mixture (222 mg) was eluted on a medium-pressure silica gel column (Merck, size B) by using 0.25% MeOH and 33% Et_2O in hexanes to give a retinoid diol (80 mg). Continued elution of the column gave 11-*cis*,13-*cis*-12-carboxyretinol (13): 71 mg (29%); IR (KBr) 1725 cm^{-1}; UV (MeOH) λ_{max} 327 nm (ϵ 26 800); mass spectrum, calcd for $C_{21}H_{30}O_3$ m/e 330.219, found m/e 330.219.

11-*cis*,13-*cis*-12-Carboxyretinol δ-Lactone (4). To a cold (−15 °C) slurry of 118 mg (3.12 mmol) of $LiAlH_4$ in 50 mL of THF was slowly added a solution of 560 mg (1.56 mmol) of methyl 11-*cis*,13-*cis*-12-carboxyretinoate (12) in 10 mL of THF. After being stirred for 5 min, the reaction mixture was quenched with a saturated solution of NH_4Cl, diluted with H_2O, and extracted with Et_2O. The organic phase was washed with H_2O and brine and dried (Na_2SO_4). The crude hydroxy acid 13 (490 mg) was refluxed in 25 mL of cyclohexane by using a Dean–Stark water separator for 6 h, and the solvent was then removed in vacuo. The product was purified by elution on a medium-pressure silica gel column (Merck, size B) by using 40% Et_2O in hexanes to yield 185 mg (38%) of a gum whose spectra showed it to be 11-*cis*,13-*cis*-12-carboxyretinol δ lactone (4): IR (KBr) 1710 cm^{-1}; UV (MeOH) λ_{max} 365 nm (ϵ 20 530); mass spectrum, calcd for $C_{21}H_{28}O_2$ m/e 312.209, found m/e 312.209.

Reaction of 13-*cis*-12-Carboxyretinoic Anhydride (7) with Methanolic Potassium Hydroxide. To a 1-mL Reacti-Vial containing 1 mg (0.003 mmol) of 13-*cis*-12-carboxyretinoic anhydride (7) were added 100 μL of MeOH and 3 μL (0.003 mmol) of KOH/MeOH. The reaction was monitored by HPLC. After 0.5 h, the major product was 13-*cis*-12-carbomethoxyretinoic acid (8), accompanied by trace amounts of methyl 13-*cis*-12-carboxyretinoate (9). Heating of the isolated product mixture for 2 h gave mainly 11-*cis*,13-*cis*-12-carbomethoxyretinoic acid (11) with minor amounts of 8 and 9. The identical mixture was obtained by heating the reaction mixture (without isolation) for 2 h. Identical results were obtained by using NaOH. None of the isomeric methyl 11-*cis*,13-*cis*-12-carboxyretinoic acid (12) was detected in any stage, although it would have been detectable by HPLC had it been present.

HPLC Analysis. The best separations were achieved by using Radial Pak cartridges, although stainless steel columns gave similar results. The half-esters were analyzed by using Radial Pak A with 60% CH_3CN/40% H_2O/0.25% NH_4OAc (2 mL/min) as the eluant; detection was at 350 nm. The lactones were analyzed on Radial Pak B with 2 mL/min of 1:9 Et_2O/hexane; detection was at 350 nm. The retention data are shown in Table III. The solvents were from Burdick and Jackson, and they were degassed prior to use.

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Codeine Analogues. Synthesis of 4a-Aryldecahydroisoquinolines Containing Nitrogen Ring Functionality and of Octahydro-1*H*-indeno[1,2,3-*ef*]isoquinolines. A Total Synthesis of Codeine

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In an extension of earlier work in the benzomorphan series to the C-ring-functionalized 4a-aryldecahydroisoquinolines, the nitrogen ring was activated by partial reduction of an amide to give an enamine, and the enamine and its cis and trans iminium salts were treated with nucleophiles. Introduction of C-1 substituents as prescribed in the benzomorphan series, including the cyano, acetimino, acetyl, and aminomethyl moieties, followed by attempted B-ring closure led instead to ring closure at C-6. Closure of the B ring requires substituents at C-1 to have the β configuration. Preparation of the compounds described above afforded the more stable α isomers, and alternative cyclization at C-6 generally proved more facile than epimerization at C-1. Closure of the B ring was attained via the C-1 β-carboxaldehyde, leading to an intermediate which has been converted to codeine. Thus we report a formal total synthesis of codeine and the first synthesis of 6,6′-bridged 4a-aryldecahydroisoquinolines. The latter compounds, octahydro-1*H*-indeno[1,2,3-*ef*]isoquinolines, represent a novel class of structural analogues of codeine.

Previous reports from this laboratory have described the elaboration of β-aryl α-methylene lactams (1) to C-ring-functionalized 4a-aryldecahydroisoquinolines (4),[1,2] analogues of codeine containing the A, C, and N (nitrogen) rings (Scheme I). Extension of work in the phenyl and *m*-methoxyphenyl series to the 2,3-dimethoxyphenyl series has recently allowed preparation of 5,2′-oxygen-bridged[3] and 6,2′-oxygen-bridged 4a-aryldecahydroisoquinolines,[4] the octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines (3), and the octahydro-1*H*-[1]benzopyrano[4,3,2-*ef*]isoquinolines (5). We now extend to the 4a-aryldecahydroisoquinolines our benzomorphan (2) work[5] involving nitrogen ring

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