formation of tachysterol$_3$ (**4**). In the membrane, irradiation at a longer wavelength results in an increase in **4**, while the reverse holds true in solution. It is known from solution photolyses that lumisterol$_3$ (**5**) is formed photochemically from precholecalciferol by cyclization in the reverse stereochemical sense (9β hydrogen, 10α methyl),[12a] while *cEc* tachysterol$_3$[1c] is formed by a photochemical $Z \rightarrow E$ isomerization of the C_{6-7} double bond of *cZc* (**2**).

First addressing the environmental aspect of these differences: we envisage a model for the membrane–7-dehydrocholesterol (**1**) system in which the steroid is located along the straight hydrocarbon chains with the C_3 hydroxyl group aimed toward the aqueous interface. Much data on microviscosity,[13] cation, anion, and neutral molecule permeability, and ion channel formation agree with this picture.[14] Both vitamin D$_3$ (**3**) and tachysterol$_3$ (**4**) possess rather elongated molecular shapes which are drastically different from those of the planar and compact steroidal shape of **1** and **2**. In fact, some evidence exists that vitamin D$_3$–lipid multibilayers form *disordered* systems.[8] The membrane effect in the present study is explicable on the basis of initial ring opening of the diene **1** $\rightarrow$ **2** yielding previtamin D$_3$ (**2**) locked in the relatively restricted hydrophobic environment of the lipid multibilayer. The A ring of **2** initially lies above the plane of the C–D rings. Conversion into the alternative helical conformation (A ring below the C–D rings) which is the one leading to lumisterol$_3$ (**5**) may be achieved by torsion about the C_{5-6} bond preserving the cisoid structure of **2** (either conformation may yield **3**). This cisoid conformation in fluid solution is known to be a low energy form which rapidly equilibrates even at -100 °C between the two helical trienes.[15] In hexane solution, which we consider the isotropic counterpart of the membrane, unrestricted rotation of **2** is allowed and subsequent isomerization to **4** and **3** is favored. After photolysis the membrane remains ordered as determined by EPR, but this is not surprising because of the relatively large amount of 7-dehydrocholesterol remaining in the membrane.

A clue to the variations in products vs wavelength in the membrane relative to hexane solution is provided by comparison of the ultraviolet spectrum of **1** in the two media. The hexane spectrum is sharply defined and relatively narrow; in contrast, the membranous spectra are comparatively broader with greater absorbancy at longer wavelength. The epidermal system may absorb more strongly at wavelengths at ~300 nm relative to isotropic hydrocarbon solution.[16]

A final point deals with the nature of the electronic transition involved in the observed photochemistry. The absorption of **1** between 250 and 310 nm [λ_{max} 281 nm (ϵ 12 000)] corresponds to a $\pi \rightarrow \pi^*$ transition. Photochemistry involving $n \rightarrow \pi^*$ transitions, for example with ketones in the lipid micelles[17a,b] or vesicles,[17c] leads to photoattachment to the lipid due to biradicaloid intermediates. To probe the possible photoattachment of **1** to the membrane, [3α-^{3}H]-7-dehydrocholesterol was synthesized (specific activity, 1.4 Ci/mmol).[18] Labeled samples of **1** were introduced into the membranes listed in Table I and these were photolyzed in the standard way. The lipid part was separated by thin layer chromatography and rechromatographed on silica gel to a constant DPM. Essentially all of the tritium remained in the steroid portion.[18] This result agrees with no covalent bonding to the lipid bilayer and corresponds to concerted electrocyclizations of the dienes and trienes with essentially no biradicaloid component. There was no indication of bis steroid formation[19] or photofragmentation.

We conclude that photoformation of vitamin D$_3$ (**3**) in hydrated lipid multibilayers is a relevant model for in vivo photosynthesis and the conformational restraints imposed by the lipid geometry inhibits the biogenetically unimportant channel leading to tachysterol$_3$ (**4**).

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Longitudinal Restrictions of the Binding Site of Opsin As Measured with Retinal Isomers and Analogues

Sir:

Of the 12 presently known geometric isomers of retinal, 9 (11-cis, 9-cis,[1,2] 9,13-dicis,[2] 7-cis, 7,9-dicis, 7,13-dicis, 7,9,13-tricis,[3] 7,11-dicis,[4] and 9,11-dicis[5]) are known to form rhodopsin or its isomers when incubated with cattle opsin, one (11,13-dicis[1]) gives ambiguous results, and two (the all-trans and 13-cis isomers) are known with certainty not to form stable

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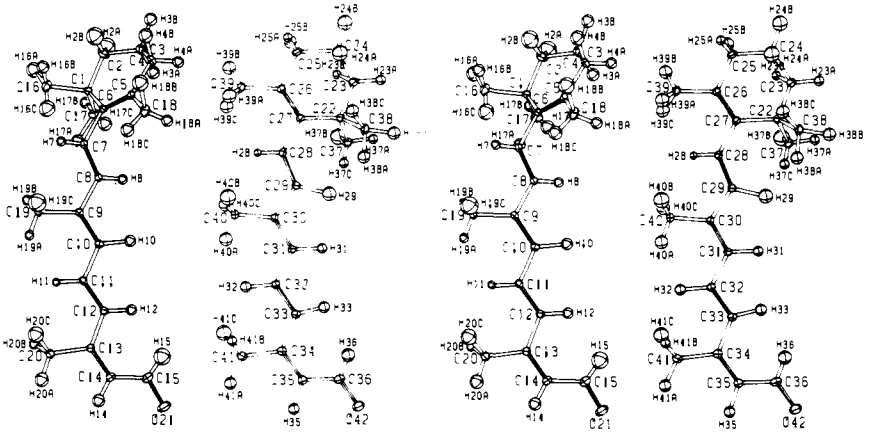

Figure 1. Stereoview of 13-*cis*-retinal[11] showing the 6-*s*-cis and 6-*s*-trans conformers which coexist in the crystal structure (5% probability ellipsoids are shown). The two conformers are shown with the orientations of the C(11)–C(12) and the C(32)–C(33) bonds the same to facilitate comparison. The C(5)–C(6)–C(7)–C(8) and C(26)–C(27)–C(28)–C(29) torsion angles are +65 and +175°, respectively.

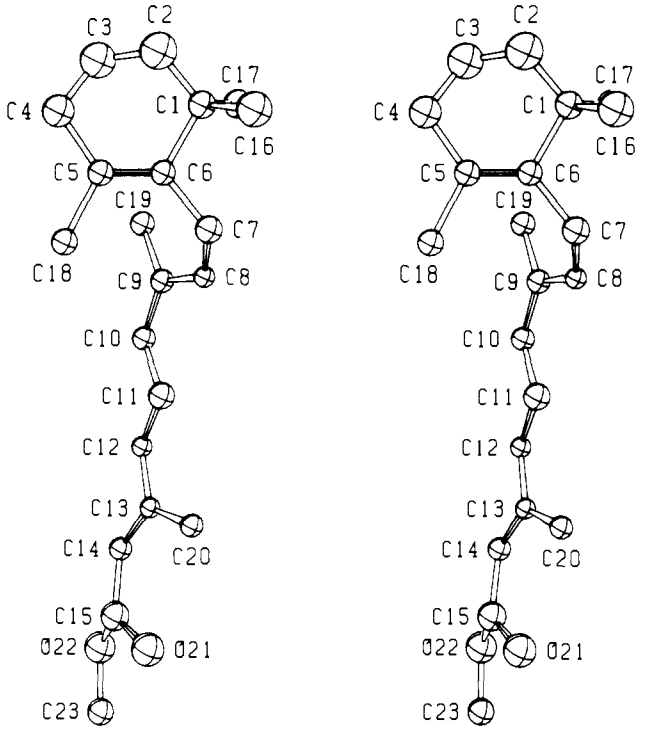

Figure 2. Stereoview of methyl 7,9-*cis*^{2}-retinoate[12] using 20% probability ellipsoids. C(5), C(6), and C(7) define the plane of the drawing. The C(5)–C(6)–C(7)–C(8) torsion angle is −53°.

pigment analogues. After having established the importance of the trimethylcyclohexenyl ring in the interaction with the hydrophobic pocket of opsin,[6] Matsumoto and Yoshizawa[7] subsequently proposed the existence of a longitudinal restriction to the binding site of opsin. Although the idea appears to be sound, their approach was extremely rudimentary. We now present a refined model which attempts to define both a lower and an upper limit to the longitudinal restriction.

Matsumoto and Yoshizawa[7] assumed that all retinal isomers are planar and that all their bond lengths and bond angles are identical. With these somewhat inaccurate assumptions, the problem was reduced to an exercise in drawing hexagons. The all-trans isomer was shown to have the longest distance between the center of the ring [C(O)] and C(15). A group of four isomers, one of which is 13-cis, have a somewhat shorter C(O)–C(15) distance. The three remaining groups of isomers have even shorter C(O)–C(15) distances and all readily form pigments. Therefore, they reasoned that the negative results of the all-trans and the 13-cis isomers occurred because their chain lengths are longer than the farthest stretchable distance between the hydrophobic pocket and the lysine residue. This plausible explanation, however, was accompanied by their erroneous prediction that both 7,9-*cis*^{2}- and 9,11-*cis*^{2}-retinal (the latter only synthesized recently[5]), being members of the 13-cis group, would not combine with opsin to form pigments.

Matsumoto and Yoshizawa realized, however, that their erroneous conclusion was probably the result of assuming an incorrect molecular shape. This difficulty is removed in the current approach. The C(O)–C(15) distances of the most stable conformations in solids have been measured in crystallographic studies of retinal isomers and their derivatives. Additionally, the corresponding distances in other low-energy conformers have also been calculated by simply rotating the most flexible single bonds.

The crystal structures of *all-trans*- and 11-*cis*-retinals[8,9] (and of *all-trans*-β-ionylidene-γ-crotonic acid, the C_{17} acid[10]) have been reported. A program at the University of Hawaii has been initiated to determine the crystal structures of all other retinal isomers. Thus far, the structures of 13-*cis*-retinal[11] and methyl 7,9-*cis*^{2}-retinoate[12] (the retinal of the latter is an oil) have been determined. Their stereoviews are shown in Figures 1 and 2.

An analysis of the crystallographic data for 11-*cis*-retinal[9] indicates that its C(O)–C(15) distance is 9.8 Å. However, the molecule is known to be very flexible about its C(12)–C(13) single bond. The insert to Figure 3a shows the change in total energy of 11-*cis*-retinal upon rotation of the C(12)–C(13) bond.[13] The figure suggests that the molecule should exist primarily in the twisted 12-*s*-cis form (which agrees with the crystallographic results); however, in solution and at room temperature, the 12-*s*-cis and 12-*s*-trans conformers appear to be in equilibrium with significant amounts of both present.[14a] A rotation of 30–130°, which results in the interconversion of the two conformers, can easily take place, leading to corresponding changes in the C(O)–C(15) distance. The arrows show (Figure 3a) that the distance will remain between 9.6 and 10.9 Å. The limits to the longitudinal restriction of the binding site of opsin are likely to fall within this region.

We now consider the results of *all-trans*- and 13-*cis*-retinal and the C_{17} aldehyde,[15] all of which fail to give pigments, and 7,9-*cis*^{2}-retinal,[3] which gives a pigment analogue at a slow rate. An analysis of the crystallographic data for *all-trans*-retinal[8] indicates that its C(O)–C(15) distance is 12.3 Å, which is clearly outside the binding zone. The polyene chain of the molecule exists with all of the single bonds from C(7) to C(15) in the *s*-trans conformation;[14] however, the C(6)–C(7) bond

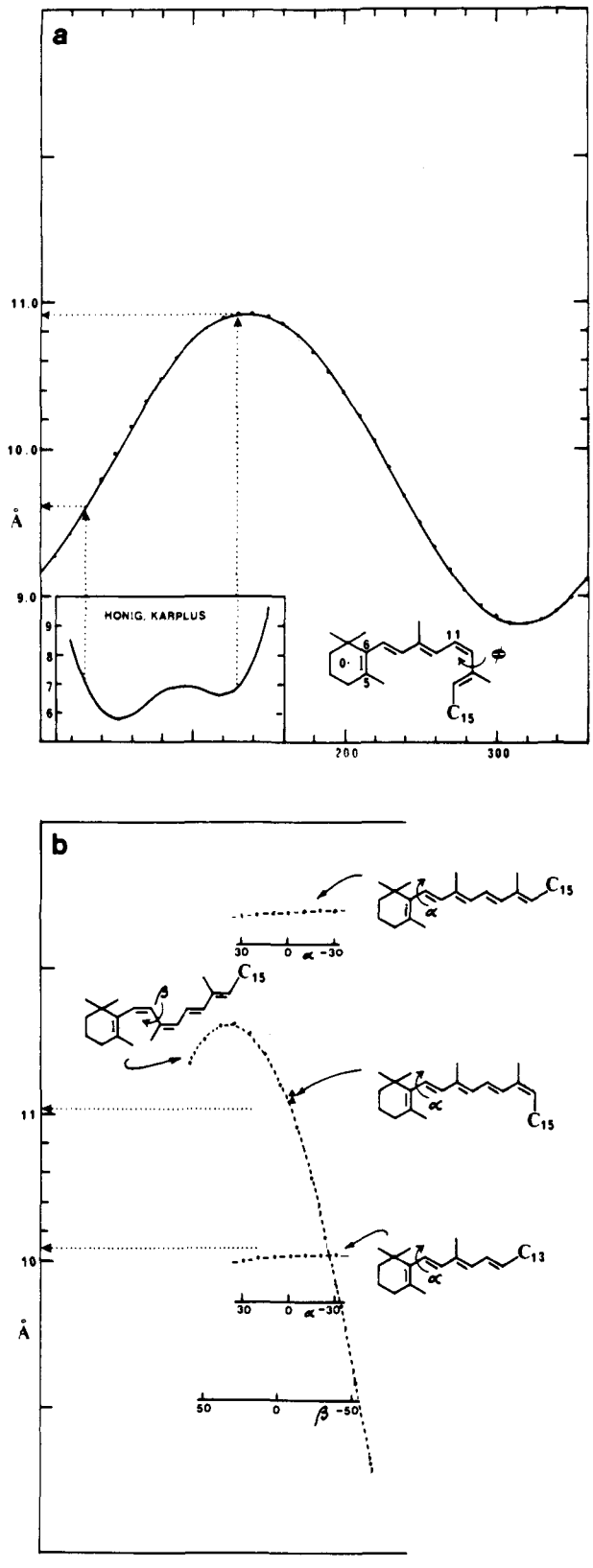

Figure 3. (a) The 9.6–10.9-Å critical distance for binding as determined from the low-energy conformations of 11-*cis*-retinal. The lower insert is the calculated result of the change in total energy of 11-*cis*-retinal as a result of twisting the C(12)–C(13) single bond.[13] (b) The critical distances of *all-trans*-retinal (top), 13-*cis*-retinal (middle), and the C_{17} aldehyde (bottom) as a result of twisting the C(6)–C(7) bond (α). (The critical distances in the two 13-*cis*-retinal conformers are the values found from the crystallographic data and are indicated by ▲.) The dashed curve represents the change of the C(O)–C(15) distance in the 7,9-dicis isomer (left) as a result of rotating the C(8)–C(9) single bond (β), while keeping the ring-chain orientation (α) the same as that found in the crystal.

is relatively flexible.[16] Nevertheless, rotation about this bond *does not* significantly affect the critical distance. The top of Figure 3b shows that a rotation of the torsion angle α by ±30° from the value (−58°) found in the crystal changes the critical distance by only ~0.1 Å. The 13-cis isomer, which has critical distances of 11.2 Å for both the 6-*s*-cis and 6-*s*-trans conformers (these coexist in the crystal structure), does not form a pigment with opsin. Most interesting is the negative result of the C_{17} aldehyde, which has a critical distance slightly in excess of 10.0 Å [based on the crystallographic data in ref 10 or the crystallographic data for *all-trans*-retinal, but truncated at the C(13)–C(14) bond]. This allows the lower limit of the binding site of opsin to be raised to ~10.1 Å. Furthermore, this result is consistent with the idea that 12-*s*-trans is indeed the preferred conformation in the pigment.[17]

We now consider the result of the 7,9-dicis isomer. In close agreement with Matsumoto and Yoshizawa, the C(O)–C(15) distance determined from the crystallographic data[12] is 11.1 Å, which is indeed close to that of the 13-cis isomer. However, the molecule need not remain in the 8-*s*-trans conformation; in fact, the crystal structure indicates that the polyene chain at carbons 7–10 is twisted 27° from planarity (β = +153°). A further rotation about the C(8)–C(9) bond (between 10 and 30°) greatly shortens the C(O)–C(15) distance so that it now falls within the 10.1–10.9-Å binding zone (Figure 3b). Therefore, it is not surprising that 7,9-*cis*[2]-retinal forms a pigment analogue with opsin, albeit at a reduced rate.

We believe the above represents the beginning of a quantitative and systematic approach of using retinal analogues as meter sticks to determine the longitudinal restrictions to the binding site of opsin. It is hoped that, when the molecular dimensions of more retinal isomers and analogues are known, the active zone will be better defined, and it may be possible to learn about limits to the width of the binding site, if any.

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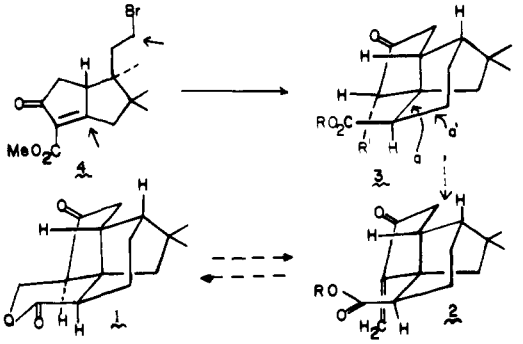
Total Synthesis of *dl*-Quadrone

Sir:

Interest in the total synthesis of the *Aspergillus terreus* derived quadrone (**1**)[1,2] arises from its novel tetracyclic ring system and from its reported antitumor properties. Though the efficacy, not to speak of the mode of action, of quadrone remains to be clarified, it is recognized that **2**, formally derivable from **1** by β elimination, is at least reminiscent, in its α-methylenecarbonyl arrangement, of a large number of known antitumor agents.[3]

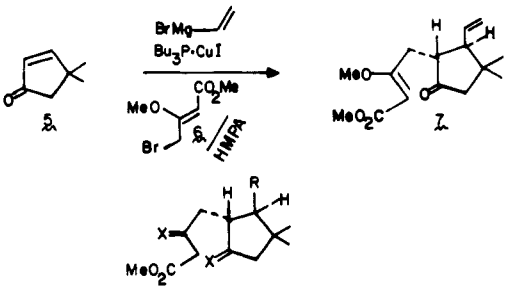
Our plan for synthesizing quadrone envisioned the reverse of the bioactivation process hypothesized above, i.e., the conversion of **2** (R = H) into **1**. Thus, systems such as **2** (R = H or alkyl) emerged, on chemical and biological considerations, as attractive subgoals. The scheme **4** → **3** → **2** → **1** (see dotted lines) presented itself as a plausible scenario. In our original formulation, we envisioned the possibility that the carbomethoxyl group in structure **4** would become a control element in structure **3** (see function R′). Regiochemical guidance for proper placement of the α-methylene group in **2** thus would be provided.[4]

The conversion of **4** → **3** can be perceived to involve, overall, the attachment of the nucleophilic CH_3-CO_2R through two of its CH bonds to two potentially electrophilic centers (see arrows in **4**), *with the added proviso that the CO_2R function must emerge in an axial disposition.* Either mode of cyclization leading from structure **4** → structure **3** (see disconnection arrows a and a′) involves the closing of a propano bridge on the convex face of a bicyclo[3.3.0]octanone system—a risky and, therefore, interesting proposition for research. Below we report the first total synthesis of *dl*-quadrone wherein all regiochemical and stereochemical issues were resolved apparently with complete and favorable specificity.



A viable synthesis of compound **4** was our first concern. Conjugate addition of vinyl magnesium bromide to enone **5**,[5] followed by trapping of the resultant metalloenolate specie with **6**,[6] afforded **7**[7] (40–55% yield). While the β,α-dialkylation of cycloalkenones, as a general concept, is well precedented,[8,9] the use of **6** as a γ-electrophilic equivalent of acetoacetate in a trapping context had not been demonstrated.[10]

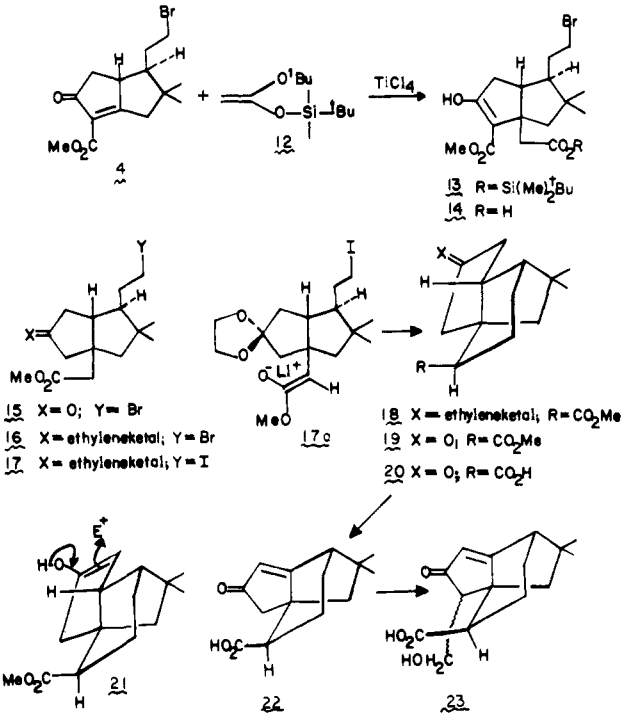
The diketal **8**, derived (ethylene glycol, *p*-TsOH, toluene, reflux) from **7**, was subjected to hydroboration (BH_3, THF, 0 °C → room temperature, 1.5 h) followed by oxidation with alkaline hydrogen peroxide to afford alcohol **9**. The latter was converted (mesyl chloride, triethylamine, ether, 0 °C → room temperature, 3 h) to **10** which, after treatment with lithium bromide in acetone (reflux, 6 h) and deketalization, gave **11**[11] in 55% overall yield from **7**. Exposure of **11** to 0.5 equiv of sodium methoxide in methanol at 0 °C provided the desired **4**,[7,11] mp 57–58 °C, in 76% yield.



8 R = vinyl, X = ethyleneketal
9 R = CH_2CH_2OH, X = ethyleneketal
10 R = CH_2CH_2OMs, X = ethyleneketal
11 R = CH_2CH_2Br, X = O → **4**

The tricyclic acid **20** was reached as follows. A Mukaiyama[12] reaction of **4** with 1-*tert*-butoxy-1-*tert*-butyldimethylsilyloxyethylene[13] (**12**) (1 equiv of **4**, 1.1 equiv of $TiCl_4$, 5 equiv of **12**, CH_2Cl_2, −78 °C, 10 min) afforded a high yield of crude **13** *in which the tert-butyl group had been cleaved.* Desilylation with $Bu_4N^+F^-$ afforded the acid, **14**[7], mp 159–161 °C, in 70% overall yield. However, for our purpose, crude diester **13** was subjected to the action of 1 M HCl in dioxane under reflux for 1 h. After esterification of the crude *monoacid*[14] with diazomethane, the keto ester **15**[7] was in hand in 63% overall yield from **4**. Ketalization (ethylene glycol, *p*-TsOH, toluene, reflux, 6 h) afforded **16**[7] which, after Finkelstein reaction (sodium iodide–acetone containing a trace of pyridine, reflux, 12 h), gave rise to **17** (87% from **15**).

Reaction of **17** with lithium hexamethyl disilazide in THF (−78° → −23 °C, ~40 min, followed by addition of 20% HMPA, followed by stirring from −23 °C → room temperature for 6.5 h) afforded a 56% yield of **18**[7] *bearing the axial*



15 X = O; Y = Br
16 X = ethyleneketal; Y = Br
17 X = ethyleneketal; Y = I
18 X = ethyleneketal; R = CO_2Me
19 X = O; R = CO_2Me
20 X = O; R = CO_2H

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