(16) Cf. W. R. Jackson and W. B. Jennings, *J. Chem. Soc. B*, 1221 (1969).
(17) No Cr–H absorption was detected in the ^{1}H NMR spectrum between 20 ppm downfield and 10 ppm upfeld; the severe line broadening may have obscured the signal. Warming to −30 °C provided a spectrum consistent with a simple mixture of 1 and 2-cyanopropane, and normal line widths. A referee pointed out that the reversal reactions (**4** → **1**) "are surprising" and suggested that a second (undetected) intermediate is responsible for the reversal. This possibility cannot be ruled out by the data in hand, but **4** is the only intermediate detected (>90% yield) and the products of reversal are obtained in >80% yield. Therefore, if a second intermediate is involved in the reversal reactions, it must be in rapid equilibrium with **4** and remain at low concentration. These points are currently under investigation.
(18) Complexes of 1,3-dienes with chromium–carbonyl units are rare, but a 1,3-butadienetetracarbonylchromium(0) has recently been characterized. Cf. I. Fischler, M. Budzwait, and E. Koerner von Gustdorf, *J. Organomet. Chem.*, **105**, 325 (1976).
(19) The isomers **7**, **8**, and **9** were shown to be stable to the acid and iodine conditions used to quench the intermediate. Presumably, rapid hydrogen shifts occur in the diene–chromium species such as **11** and **12**, with **12** being the isomer favored at equilibrium.
(20) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.
(21) Recipient of a Camille and Henry Dreyfuss Teacher-Scholar Grant, 1973–1978.

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Received May 18, 1976

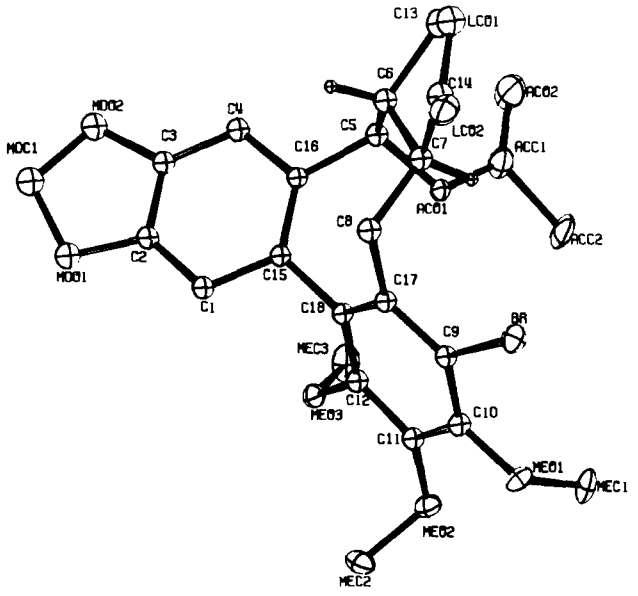
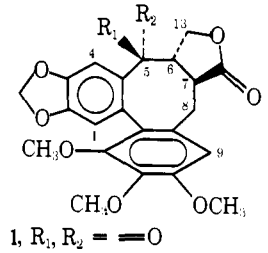


Figure 1. Computer drawing of 9-bromoisosteganacin from x-ray data. Thermal ellipsoids enclose 50% electron density, except for hydrogen positions on C-6 and C-7. These are predicted positions assuming tetrahedral geometry, C–H distances of 1.0 Å and arbitrary thermal parameters.

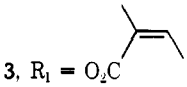
Isosteganacin

Sir:

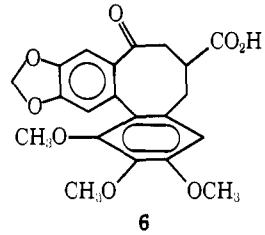
In 1974 Kupchan reported the isolation and structure elucidation of steganone (**1**) and related dibenzocyclooctadiene lignan lactones, among which steganacin (**2**) and steganangin (**3**) showed significant antileukemic activity.[1] We have recently described the first total synthesis of (±)-steganacin[2] and now report some unusual stereochemical considerations which control synthesis in this series.



1, R_1, R_2 = =O
2, R_1 = OAc; R_2 = H



3, R_1 = O_2C ; R_2 = H
4, R_1 = OH; R_2 = H
5, R_1 = H; R_2 = OH

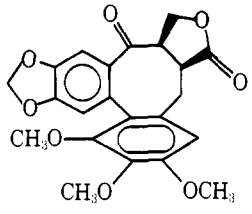


6

In our preceding communication we reported the preparation of (±)-steganone (**1**) by hydroxymethylation of the racemic keto acid **6** with HCHO in dilute base. When crude crystalline steganone (mp 223–226 °C) from this reaction was reduced with $NaBH_4$ (1:1 MeOH–CH_2Cl_2, 25 °C, 3 min) we obtained a mixture of three isomeric alcohols separable by careful preparative TLC (SiO_2, 20% cyclohexane–ether). The two major alcohols were steganol (**4**) and episteganol (**5**), as described by Kupchan, whereas the third alcohol (10–15% yield) was a new substance, mp 242–244 °C, which we named isosteganol.[3] This new isomer was not seen when the $NaBH_4$ reduction was carried out on highly purified steganone (mp 229–230 °C). Careful TLC and HPLC analyses revealed that the isosteganol *had not been produced in the $NaBH_4$ reduction step*, but was in fact a significant by-product from the initial hydroxymethylation of keto acid **6.**

Oxidation of isosteganol (Jones reagent, 25 °C, 15 min) yields the $C_{22}H_{20}O_8$ ketone isosteganone, mp 209–212.5 °C.[4] Reduction of isosteganone ($NaBH_4$, CH_2Cl_2–MeOH, 0 °C, 3 min) yields exclusively isosteganol. Pure isosteganone shows striking spectroscopic differences from steganone. Whereas the latter shows the 1667 cm^{-1} $\nu_{C=O}$ stretch and δ 7.53 NMR singlet (deshielded ortho proton) characteristic of such an aryl ketone, isosteganone shows a 1707 cm^{-1} ketone carbonyl stretch and has no proton NMR signal downfield of δ 6.71. These data imply that the ketone carbonyl of isosteganone is not coplanar with the adjacent aromatic ring.

Treatment of isosteganone with either sodium acetate (EtOH, reflux, 3 h) or by heating in a soft glass tube (230 °C, 3 min) led to quantitative formation of steganone. We conclude that the difference between iso and normal series could arise (1) from cis vs. trans γ-lactone ring junctions (**7** vs. **1**), or (2) from hindered rotation about the biaryl bond (**8** vs. **1**), or (3) possibly from both sources (**9** vs. **1**). Models of ketolactones **7, 8,** or **9** all show the ketone carbonyl out of the plane of the methylenedioxyphenyl ring.



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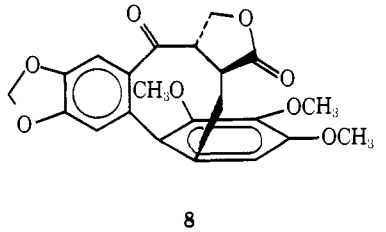

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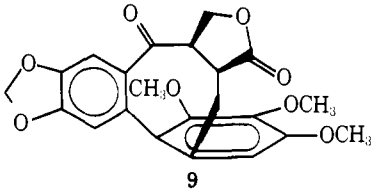
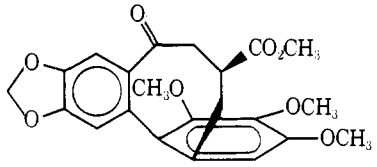


9

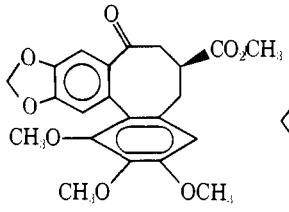
Evidence on these alternatives was derived from esterification of keto acid **6** (3% HCl in MeOH, reflux 6 h) to yield oily keto ester **10** [ir 1728, 1653 cm^{-1}].[5] Chromatography (SiO_2, 20% hexane in ether) resolved **10** into two distinctly different crystalline $C_{22}H_{22}O_8$ keto esters (ca. 1:1), the more

polar (**10a,** mp 132–133.5 °C) showing NMR (100 MHz, $CDCl_3$, δ) 7.50 (s, 1 H), 6.60 (s, 1 H), 6.53 (s, 1 H), 6.02 (br d, J = 2 Hz, 2 H), 3.90 (s, 6 H), 3.67 (s, 3 H), 3.55 (s, 3 H), 3.0–2.2 (m, 5 H), the less polar (**10b,** mp 131–133 °C) with NMR (100 MHz, $CDCl_3$, δ) 7.66 (s, 1 H), 6.64 (s, 1 H), 6.45 (s, 1 H), 6.04 (br d, J = 2 Hz, 2 H), 3.91 (s, 3 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 3.56 (s, 3 H), 3.3–2.3 (m, 5 H). Melting of either ester converts it rapidly into the 1:1 mixture of both, consistent with thermal equilibration by rotation about the biaryl bond. Heating of **10a** in 1:1 chloroform–heptane gave reversible first-order kinetics with $\Delta H^{\ddagger}$ = 22.1 kcal/mol, $\Delta S^{\ddagger}$ = 0.0 eu, and K_{eq} = 0.85 at 100 °C.[6]

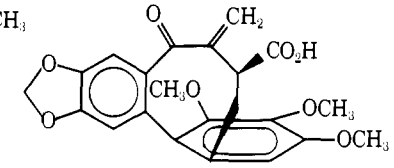
Separate conversion of each diastereomeric keto ester **10** to the corresponding keto lactone was achieved with HCHO in 1 N NaOH (25 °C, aqueous THF). The less polar keto ester **10b** gave steganone as the only neutral product, whereas the more polar **10a** produced only isosteganol, presumably via a cross-Cannizzaro reduction of the ketonic intermediate. With Kupchan's x-ray studies these results define the less polar keto ester as having stereochemistry **10b,** whereas the more polar is **10a.**



10a



10b

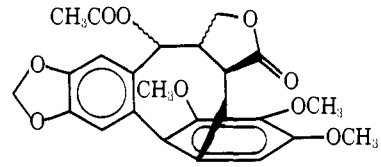


11

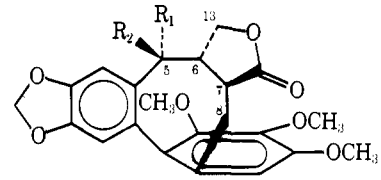
Although **10a** and **10b** are largely equilibrated in several hours at 80 °C by biaryl rotation, this simple mechanism does not explain the observed conversion of isosteganone to steganone. If it did, then isosteganol and its derivatives should also undergo thermal isomerization to the normal series. They do not! For example, acetylation of isosteganol (Ac_2O, C_5H_5N, 50 °C, 6 h) generates isosteganacin (mp 230–231 °C, NMR δ 1.69 (s 3 H, $COCH_3$); ir ($CHCl_3$) 1768, 1738 cm^{-1}) which is *unaltered at 240 °C for 60 min.* We conclude that the γ-lactone so locks the molecule that biaryl rotation is precluded for isosteganacin, whereas isosteganone must exhibit a special process to overcome this restriction. It is likely that this consists of reversible β-elimination to an α-methylene keto acid (**11**) in which biaryl rotation is again possible.[7]

Isosteganacin must have gross structure **12,** with both lactone and C-5 stereochemistry still in doubt. Bromination of **12** ($C_5H_5NHBr_3$, $CHCl_3$, 25 °C, 18 h) cleanly produced 9-bromoisosteganacin, mp 244–245 °C, NMR δ 1.68 ($COCH_3$).

9-Bromoisosteganacin crystallizes in the triclinic space group $P\bar{1}$ with cell constants a = 11.087 ± 0.003, b = 10.096 ± 0.004, c = 12.389 ± 0.003 Å, α = 92.218 ± 0.002°, β = 93.687 ± 0.002°; γ = 123.045 ± 0.002°. Intensity data were collected using an automated four-circle diffractometer and monochromatic Mo Kα radiation. An initial solution was obtained using the direct methods program MULTAN III and the 300 largest normalized structure factors E. The atomic positions obtained for the 25 located atoms were refined and used to phase a difference Fourier calculation with which the remaining atomic positions were obtained. The model was refined to convergence using 1987 independent reflections with $F > 3\sigma$ and $2\theta < 40°$. In the final refinement, only the 12 nonring atoms were refined assuming anisotropic thermal motion, leading to conventional and weighted R factors of 6.78 and 9.66%, respectively. No attempt was made to locate the hydrogen atoms in this structure. As Figure 1 reveals, isosteganacin has structure **13,** and therefore isosteganone must be **14.**



12



13, R_1 = OAc; R_2 = H
14, R_1, R_2 = =O

The crystal structure clearly explains the high-field NMR signals for the acetate methyls (anisotropic ring shielding) and $J_{5,6} \approx 0$ in **13** (dihedral angle ~90°). Dreiding models of **14** show the ketone nearly 90° out of the methylenedioxyphenyl plane. This explains both the unusual spectroscopic features of **14** and its facile cross-Cannizzaro reduction. Finally, the stereospecificity of both the Cannizzaro and $NaBH_4$ reductions is well accommodated by preferred approach of the hydride donors from the side anti to both the C-13 CH_2 and the bulky trimethoxyphenyl ring.

Preliminary studies with isosteganacin and steganacin indicate that in the concentration range of 1–10 μM, these compounds inhibit the in vitro polymerization of chicken brain tubulin into microtubules. Such effects on microtubule assembly may account for the reported antineoplastic activity of steganacin.[8,9]

Acknowledgment. Partial support of this work by Grant CA 11326 from the National Cancer Institute, the United States Public Health Service, and by a faculty grant from the Hoffmann-LaRoche Co., is gratefully acknowledged. L.S.L. and C.K. thank the University of Rochester for Sherman Clark Fellowships. We thank Dr. Bruce Spivack for assistance with the x-ray work.

Supplementary Material Available: Tables of bond lengths, bond angles, atomic position and thermal parameters, and observed and calculated structure factors (18 pages). Ordering information is given on any current masthead page.

References and Notes

(1) S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, and R. F. Bryan, *J. Am. Chem. Soc.*, **95,** 1335 (1973).
(2) A. S. Kende and L. S. Liebeskind, *J. Am. Chem. Soc.*, **98,** 267 (1976).
(3) Isosteganol: NMR (100 MHz, $CDCl_3$, δ) 6.66 (s, 1 H), 6.63 (s, 1 H), 6.58 (s, 1 H), 6.01 (d, J = 3 Hz, 2 H), 4.76 (s, 1 H; in very pure samples this absorption shows up as a doublet with J = 8 Hz, indicating coupling to the hydroxyl proton), 4.3 (m, 2 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.67 (s, 3 H), 3.17 (d, J = 13 Hz, 1 H), 2.47 (m, 3 H).
(4) Isosteganone: NMR (100 MHz, $CDCl_3$, δ) 6.71 (s, 1 H), 6.63 (s, 1 H), 6.56 (s, 1 H), 6.06 (s, 2 H), 4.4 (m, 2 H), 3.87 (s, 6 H), 3.61 (m, 1 H), 3.51 (s, 3 H), 3.29 (d, J = 13 Hz, 1 H), 2.50 (m, 2 H).
(5) Keto ester: NMR (100 MHz, $CDCl_3$, δ) 7.65, 7.50 (two s, 1 H), 6.64, 6.60, 6.51, 6.45 (four s, 2 H), 6.03 (br s, 2 H), 3.90, 3.83 (two s, 6 H), 3.69, 3.67 (two s, 3 H), 3.55 (s, 3 H), 2.8 (m, 5 H). Spectroscopic data rule out the formation of a Ψ-ester.
(6) These parameters are consistent with those found in similar systems: cf. K. Mislow, S. Hyden, and H. Schaefer, *J. Am. Chem. Soc.*, **84,** 1449 (1962).
(7) Isosteganone is stable in C_6H_6 at reflux. Steganone undergoes rapid exchange of one H by D in NaOAc–CH_3OD at reflux, consistent with the pro-

posed β-elimination mechanism.

(8) S. B. Horwitz and P. B. Schiff, Albert Einstein College of Medicine, personal communication.

(9) Note Added in Proof. A recent total synthesis of racemic steganone via isosteganone has been achieved by L. R. Hughes and R. A. Raphael, *Tetrahedron Lett.*, 1543 (1976). Professor Raphael has kindly informed us that the spectroscopic and chemical properties of their isosteganone, as well as their independent x-ray structure determination of isosteganol, are in full accord with our results.

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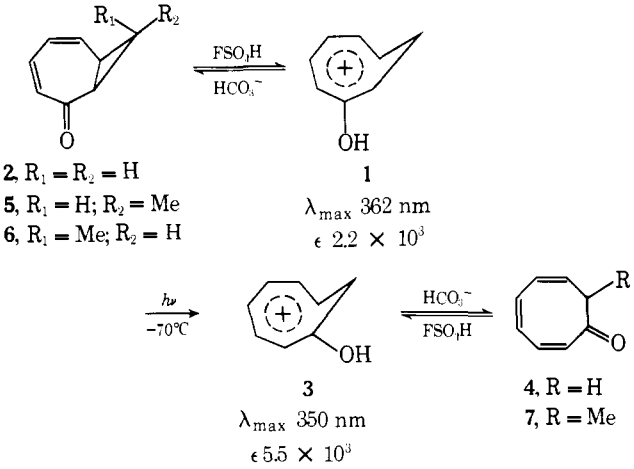
Received May 5, 1976

Circumambulatory Rearrangements of Homotropylium Cations: Photoisomerization of 2-Hydroxyhomotropylium Cations[1]

Sir:

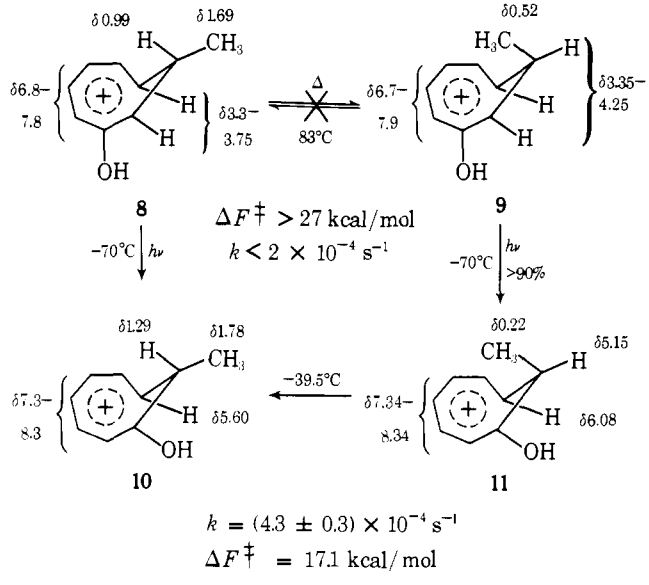
While the thermally induced circumambulations of a cyclopropyl around the periphery of the five-membered ring of a bicyclo[3.1.0]hexenyl cation are well known,[2] comparable peregrinations have not been detected with homotropylium cations.[3] Previous attempts to detect such a degenerate rearrangement of homotropylium cations have been restricted to the ground-state manifold;[3] however, there is good reason to expect on the basis of a consideration of least motion[4] and orbital symmetry[5] that such a reaction would be more likely to occur in the first excited state. To this end we have examined the photochemistry of some labeled homotropylium cations and report here our results with the 2-hydroxy systems.[6]

The 2-hydroxyhomotropylium cation (**1**), generated by the protonation of **2** in FSO_3H,[7] was irradiated at −70 °C with light of wavelength greater than 360 nm.[8] Only one product could be detected by ^1H NMR and this was shown to be **3** on the basis of its spectrum.[9] Cyclooctatrienone (**4**) was recovered on neutralization of the acid solution of the photoproduct. Under the conditions of the photoisomerization, **3** was both thermally and photochemically stable.



In order to label the methylene carbon of **1**, the methyl-substituted cations were prepared by the protonation of the corresponding homotropones **5** and **6**. Contrary to a previous report,[10] the addition of diazoethane to tropone gives not only **7** but also substantial amounts of **6** and a smaller proportion of **5**. Separation of these isomers was difficult, but by a combination of column and thick-layer chromatography, samples of **6** containing some 10–20% of **5** were obtained. The exo isomer **5** was prepared using a comparable procedure to thay recently described.[11]

Dissolution of **5** and **6** in FSO_3H gave cations **8** and **9**, respectively, each of which exhibited a ^1H NMR spectrum completely consistent with the assigned structures. The acid solutions of **8** and **9** were stable up to 80 °C. At this temperature each underwent a general decomposition without there being any evidence for the interconversion of **8** and **9**.



Irradiation of a FSO_3H solution of **8** (−70 °C, λ > 360 nm) caused it to isomerize to give **10.** The product was identified as **10** on the basis of the similarity of its ^1H NMR spectrum to that of **3** and by the independent production of this cation by the protonation of **7** in FSO_3H. The stereochemistry at C(8) was evidenced by the chemical shifts of the C(8) proton and methyl resonances.

A mixture of **8** and **9** in FSO_3H at −70 °C was photochemically converted to **10** and a further cation. This new cation, which exhibited a ^1H NMR spectrum completely consistent with that expected for **11,** was thermally unstable and rearranged quantitatively to give **10** in a first-order process (at −39.5 °C, $k = 4.3 \times 10^{-4}$ s^{-1}, $\Delta F^{\ddagger} = 17.1$ kcal/mol). Such a rearrangement is not unexpected in view of the low barrier reported for the interconversion of the 8-*exo*- and 8-*endo*-deuterio-1-methoxyhomotropylium cations[12] and the known preference for C(8) substituents to adopt the exo position in homotropylium cations.[13] The thermal conversion of **11** to **10** also occurred under the irradiation conditions ($t_{1/2} \simeq 10$ h at −70 °C); however, correcting for this thermal rearrangement, the photoisomerization of **9** to **11** was found to proceed with greater than 90% stereoselectivity.

The conversions of **8** and **9** to **10** and **11,** respectively, show that these photoisomerizations involve a basic skeletal rearrangement in which C(8) and its attendant substituents migrate around the "seven-membered" ring.[14] Formally such a rearrangement can be thought of as involving a photoinduced [1,6]-sigmatropic shift of a bicyclo[5.1.0]octadienyl resonance form of **8** and **9.** If orbital symmetry were to be obeyed, such a reaction should proceed with inversion of configuration at C(8), leading to an overall retention of stereochemistry at the migrating center. This is indeed the steric result observed; however, it should be pointed out that this is also the stereochemistry expected for the least motion pathway. While it is difficult to gauge the relative importance of least motion and orbital symmetry in this type of cyclopropyl circumambulation, it would seem that the former factor is important and should be taken into account in these reactions.[15]

As can be seen from a comparison of the barriers to ring inversion of **9** ($\Delta F^{\ddagger} > 27$ kcal/mol) and **11** ($\Delta F^{\ddagger} = 17.1$ kcal/mol), the ground-state properties of the 1- and 2-hy-