m/e 226 (M^+), 211, 185, 143, (base), 115 and 91. Anal. Calcd for $C_{17}H_{22}$: C, 90.21; H, 9.79. Found: C, 90.14; H, 9.64.

Triplet-Sensitized Irradiation of 1-(3,3-Dimethyl-2-phenylcyclopropen-1-yl)-5-hexene (34). A solution containing 200 mg of **34** and 20 mg of thioxanthenone in 200 mL of benzene was irradiated with a 450-W Hanovia lamp equipped with a Uranium glass filter sleeve for 2 h. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography using hexane as the eluent. The major fraction contained 135 mg (69%) of a clear oil whose structure was assigned as 2,2-dimethyl-3-phenyltricyclo[4.3.0.$0^{1,3}$]nonane (**35**) on the basis of its spectral properties: NMR ($CDCl_3$, 360 MHz) δ 0.78 (s, 3 H), 1.06 (dt, 1 H, J = 12.5 and 2.7 Hz), 1.22 (s, 3 H), 1.32 (dt, 1 H, J = 13.2 and 2.7 Hz), 1.44 (dd, 1 H, J = 11.1 and 2.5 Hz), 1.45–1.78 (m, 5 H), 1.85–1.93 (m, 1 H), 2.15 (dd, 1 H, J = 11.1 and 4.8 Hz), 2.27 (m, 1 H) and 7.13–7.32 (m, 5 H); IR (neat) 3060–2860, 1750, 1605, 1500, 1445, 1390, 1375, 925, 810, 760 and 700 cm^{-1}; UV (95% ethanol) 222 nm (ϵ 7050); MS, m/e 226 (M^+), 211 (base), 183, 91 and 77; HRMS calcd for $C_{17}H_{22}$ 226.1722, found 226.1718.

Quantum Yield Determinations. Quantum yields were determined by using a "merry-go-round" apparatus[75] equipped with a 450-W Hanovia lamp housed in a quartz well at the center of the carriage. Samples in 13-mm Pyrex test tubes were degassed to 5×10^{-3} mm in 5 freeze–thaw cycles and then sealed. Benzophenone–benzhydrol actinometry was used for quantum yield determinations. An actinometer yield of 0.69 was used when the concentration of benzophenone and benzhydrol in benzene was 0.1 M.[76] For the sensitized runs a filter solution of potassium dichromate in aqueous potassium carbonate was circulated through the well and the entire unit allowed to run for 1 h prior to use.[77] A Uranium glass filter sleeve and Corning 7-54 filters were also used in conjunction with the filter solution. The concentrations were adjusted so that the sensitizer absorbed more than 98% of the light. The conversions were run to 25% or less. The mass balance in these runs was generally better than 98%.

Acknowledgment. We are grateful to the National Science Foundation for financial support.

Supplementary Material Available: Experimental details for the preparation of 4-bromo-1,1-dideuterio-1-phenylbutane (3 pages). Ordering information is given on any current masthead page.

(75) Moses, F. G.; Liu, R. S. H.; Monroe, B. M. *Mol. Photochem.* **1969**, *1*, 245.

(76) Moore, W. M.; Ketchum, M. *J. Am. Chem. Soc.* **1962**, *84*, 1368.
(77) Wagner, P. J.; Nakahira, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 3668.

Stereochemical Equilibrium in Benzoctalones[1]

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Stereochemical equilibrations have been carried out at 25 °C on a series of benzoctalones having the ketone function adjacent to the epimerizable ring-juncture positions and either hydrogen or methyl at the ring-juncture position β to the ketone; trans/cis ratios are presented and discussed. The introduction of the angular methyl group invariably shifted equilibria in the direction of the cis epimer, by ca. 1.2–2.1 kcal/mol in the anthracenoid compounds and by 0.6–1.4 kcal/mol in the phenanthrenoids. Anthracenoid systems always had trans/cis ratios greater than unity, whether methylated or not, and produced consistently higher proportions of trans epimer than corresponding phenanthrenoid systems. The latter, when angularly methylated, invariably favored the cis epimers at equilibrium. The only system favoring the cis epimer in both the angularly methylated and unmethylated forms was the phenanthrenoid having the ketone within the bay region, probably due to steric interactions there that destabilize the trans epimers.

In seeking experimental data on stereochemical equilibrium in unsymmetrical octahydrophenanthrenes,[2] we became aware that what was then available in the literature was quite fragmentary. We therefore undertook a systematic study to generate accurate experimental data on trans–cis equilibrium for several entire families of benzoctalins—both octahydrophenanthrenes and octahydroanthracenes, both unsubstituted and angularly methylated. Beyond our own specific data requirements, we felt that this stereochemical aspect of benzoctalins must reflect very closely the situation in the octalins[3] and represented an incompletely studied simple perturbation of the decalin system.

Steric and conformational effects in the decalins have long been of basic interest, and the interactions governing the trans–cis equilibrium in decalin are well studied and understood.[4] An abundance of data has also accumulated

(1) Taken in part from the Ph.D. Thesis of D.J.L., Rutgers University, 1987.

(2) (a) Thompson, H. W.; Melillo, D. G. *J. Am. Chem. Soc.* **1970**, *92*, 3218. (b) Thompson, H. W.; McPherson, E.; Lences, B. L. *J. Org. Chem.* **1976**, *41*, 2903. (c) Thompson, H. W.; McPherson, E. *Ibid.* **1977**, *42*, 3350.

(3) (a) Taylor, D. A. H. *Chem. Ind. (London)* **1954**, 250. (b) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1955**, *77*, 2505. (c) Turner, R. B.; Meador, W. R.; Winkler, R. E. *Ibid.* **1957**, *79*, 4122. (d) Hussey, A. S.; Sauvage, J.-F.; Baker, R. H. *J. Org. Chem.* **1961**, *26*, 256. (e) Bucourt, R. *Bull. Soc. Chim. Fr.* **1963**, 1262. (f) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341. (g) Schappell, F. G.; Pines, H. *Ibid.* **1966**, *31*, 1735. (h) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1968**, *90*, 5773. (i) Weitkamp, A. W. *Adv. Catal.* **1968**, *18*, 1. (j) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (k) Valente, C.; Eadon, G. *Ibid.* **1984**, *49*, 44. (l) Price, J. D.; Johnson, R. P. *Tetrahedron Lett.* **1985**, *26*, 2499.

(4) For example, see: Hanack, M. *Conformation Theory*; Academic: New York, 1965. Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley-Interscience: New York, 1965.

0022-3263/88/1953-4201$01.50/0 © 1988 American Chemical Society

Table I. Estimated and Measured Stability Data for Trans vs Cis Epimers in Some Simple Decalin System

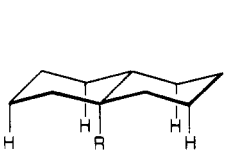
compound	gauche or 1,3-diaxial interactions, cis[a]/trans	trans/cis ratio at equilibrium[b]	$-\Delta G°$ in kcal/mol (temp, °K)
decalin (1)	3/0	99/1[c]	2.6 (298)[c]
1-decalone (2)	1/0	95/5[d]	1.7 (298)
9-methyldecalin (3)	5/4	64/36[e]	0.38 (338)[e]
10-methyl-1-decalone (4)	3/3	59/41[f]	0.24 (338)
9-methyldecalin (3)	5/4	57/43[g]	0.29 (523)[g]
9-methyl-1-decalone (5)	3/4	41/59[h]	−0.38 (523)

[a] For the all-chair cis conformer with the smaller number of unfavorable interactions. [b] For temperatures, see next column. [c] $\Delta H°_{586}$ and $\Delta S°_{597}$, derived experimentally in ref 7a, were used here to estimate $\Delta G°_{298}$, from which this trans/cis ratio was calculated. [d] Equilibrium established experimentally at 298 K, this study. [e] $\Delta H°_{584}$ and $\Delta S°_{584}$, derived experimentally in ref 7b, were used here to estimate $\Delta G°_{338}$, from which this trans/cis ratio was calculated. [f] Equilibrium established experimentally at 338 K in ref 8a. [g] $\Delta H°_{584}$ and $\Delta S°_{584}$, derived experimentally in ref 7b, were used here to estimate $\Delta G°_{523}$, from which this trans/cis ratio was calculated. [h] Equilibrium established experimentally at 523 K in ref 8b.

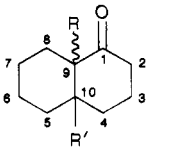
regarding the effect on this stereochemical equilibrium of many simple modifications of the decalin structure, e.g., the introduction of angular groups at the ring juncture and the replacement of ring carbons by heteroatoms or carbonyl functions.[4,5] However most of this data was random, and no systematic studies seemed to exist of the interactions of two or more such perturbations.

Both the Lewis acid catalysts used in some hydrocarbon equilibrations[6] and the conditions most often cited for stereochemical equilibration of decalin systems, hydrogenation catalysts at temperatures in excess of 250 °C,[7] are rather drastic. However, ketones like 1-decalone (**2**) can be equilibrated at room temperature with relatively mild acid or base,[5b] and because some of the data we sought actually involved keto compounds,[2a] we decided to adopt this modification to the system and examine a series of benzoctalones. How much the ketone function itself would perturb the equilibria was, of course, a serious question, which we hoped to answer at least in part with our data.

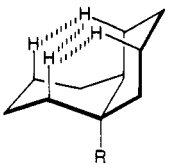
Among the several effects of introducing a ketone group adjacent to the ring juncture in decalin,[5b] the most easily estimated is that of stabilizing specific epimers and conformers by removing an axial hydrogen from steric interactions. *trans*-Decalin (**1t**), with no gauche butane or 1,3-diaxial interactions, should be affected relatively little in this regard. However, on the concave face of *cis*-decalin (**1c**), this process removes two of the three serious steric H–H interactions in one of the conformations, making the cis epimer less unfavorable for 1-decalone (**2c**) than for decalin (**1c**, see Table I). For 10-methyl-1-decalone (**4**), the same effect operates on the concave face of the cis epimer (**4c** vs **3c**), but is counterbalanced by removal of a 1,3-diaxial Me–H interaction on the methylated face in



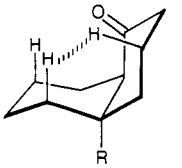
1t: R = H
3t: R = Me



2: R = R′ = H
4: R = H; R′ = Me
5: R = Me; R′ = H



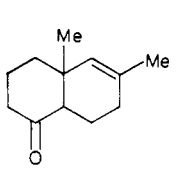
1c: R = H
3c: R = Me



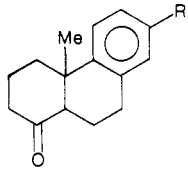
2c: R = H
4c: R = Me

the trans epimer (cf. **3t**). Thus this sort of simple "first-order" analysis suggests that introduction of a carbonyl group into methyldecalin stabilizes the cis epimer more than it does the trans and that trans and cis should be of comparable stability in 10-methyl-1-decalone (**4**), in good qualitative agreement with experimental data (Table I). The cases of 9-methyl-1-decalone (**5**) vs 10-methyl-1-decalone (**4**) demonstrate clearly that ketone groups cannot be sited around such systems at random without counting the cost but that simple analyses may sometimes account well qualitatively for the positions of equilibria. Similar simple analyses, as well as computer analyses that take into account bond angle and other changes, can be carried out for the introduction of double bonds into decalin,[5b,e,g] but even the latter become less reliable as perturbations accumulate[9] (e.g. octalones), particularly when trans and cis epimers are energetically similar.

The question of the usefulness of a benzoctalin as a model for an octalin, i.e. of the real effect on equilibria of extending such a molecule by "benzo-annelation", was nearly impossible to answer when we began our study because of the lack of published experimental data. In anthracene derivatives, where the molecule is linear so that the extension does not impinge stereochemically on the rest of the system, the effect should be slight. For phenanthrene derivatives, it is easily imaginable that crowding within the bay region might affect equilibria, probably to destabilize trans epimers. However for making direct comparisons the only reliable data we knew of involved compounds **6**[10] and **7**,[11] suggesting a change in $\Delta G°$ of less than 0.5 kcal/mol.



6: (18–19% trans/81–82% cis)



7: R = H, OMe, $CHMe_2$ (~30% trans/~70% cis)

Combinations of a carbonyl, an angular methyl, and a benzo ring at the various appropriate sites on the decalin

(5) For example, see: (a) Crabb, T. A.; Newton, R. F. *Tetrahedron Lett.* **1971**, 3361. (b) Allinger, N. L.; Lane, G. A.; Wang, G. L. *J. Org. Chem.* **1974**, *39*, 704. (c) Dolmazon, R.; Gelin, S. *Ibid.* **1984**, *49*, 4003. (d) Gras, J.-L.; Bertrand, M. *Tetrahedron Lett.* **1979**, 4549.

(6) (a) Zubenko, V. G.; Vorob'yeva, N. S.; Zemskova, Z. K.; Pekhk, T. I.; Petrov, A. A. *Neftekhimiya* **1981**, *21*, 323; *Chem. Abstr.* **1981**, *95*, 149806*m*. (b) Bansal, R. C.; Browne, C. E.; Eisenbraun, E. J.; Thomson, J. S. *J. Org. Chem.* **1988**, *53*, 452.

(7) (a) Allinger, N. L.; Coke, J. L. *J. Am. Chem. Soc.* **1959**, *81*, 4080. (b) Allinger, N. .; Coke, J. L. *J. Org. Chem.* **1961**, *26*, 2096. (c) Hönig, H.; Allinger, N. L. *Ibid.* **1985**, *50*, 4630.

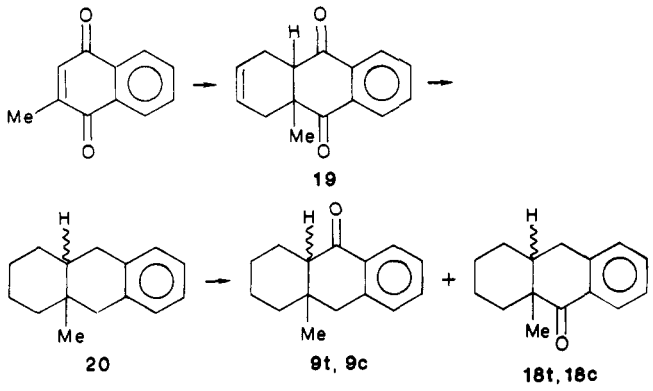
(8) (a) Rao, B.; Weiler, L. *Tetrahedron Lett.* **1971**, 927. Balf, R. J.; Rao, B.; Weiler, L. *Can. J. Chem.* **1971**, *49*, 3135. (b) Ross, A.; Smith, P. A. S.; Dreiding, A. *J. Org. Chem.* **1955**, *20*, 905.

(9) Goldsmith, D. J.; Bowen, J. P.; Qamhiyeh, E.; Still, W. C. *J. Org. Chem.* **1987**, *52*, 951.

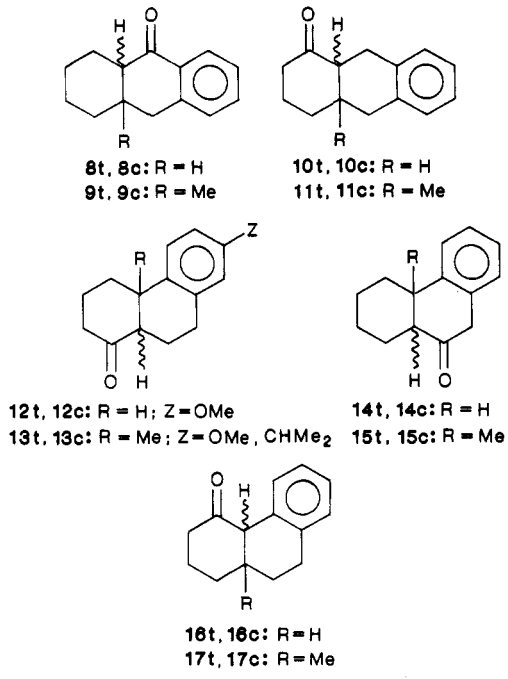
(10) Van der Gen, A.; Wiedhaup, K.; Swoboda, J. J.; Dunathan, H. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 2656.

(11) (a) Ziegler, F. E.; Kloek, J. A. *Tetrahedron Lett.* **1974**, 315; *Tetrahedron* **1977**, *33*, 373. (b) Huffman, J. W.; Harris, P. G. *J. Org. Chem.* **1977**, *42*, 2357. (c) Gonzalez-Sierra, M.; Leader, H. N.; McChesney, J. D. *Ibid.* **1985**, *50*, 4450. (d) Brinkmeyer, R. S. *Tetrahedron Lett.* **1979**, 207. (e) For an erroneous stereochemical assignment, see: Banerjee, A. J.; Garcia, W. F. *Synth. Commun.* **1980**, *10*, 693.

Scheme I



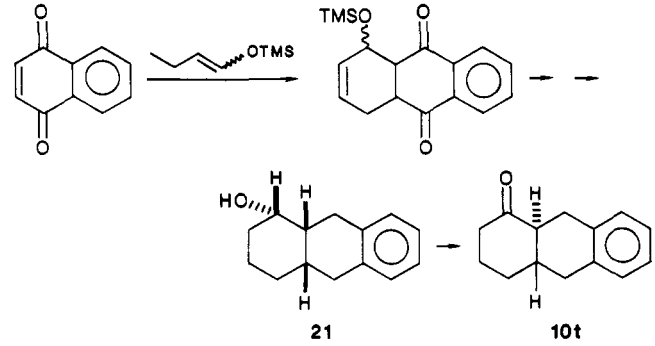
skeleton lead to the two anthracenoid systems (8–11) and the three phenanthrenoid systems (12–17) we chose to study.



Results and Discussion

Anthracenoid Set (8–11). For these eight compounds, no equilibration data existed, and only **8t** and **8c** had previously been reported. Compound **8t**, first synthesized about 50 years ago, had been assigned stereochemistry only on the basis of its greater thermodynamic stability and some doubtful chemical proof.[12a,b] We prepared **8t** by the original route, involving acylation of benzene with cyclohexanedicarboxylic anhydride, and we have confirmed the previous stereochemical assignment by ^{1}H NMR spectroscopy. Although the pure (+)-cis epimer of 1,2,3,4,4a,9a-hexahydro-9(10*H*)-anthracenone (**8c**) has been prepared (mp 79–81 °C),[13a] the racemate has been reported

Scheme II



only in impure form (mp 79–85 °C[12a] and 86–88 °C[12c]) and mentioned once without data as a synthetic intermediate.[13b] By manipulating incompletely equilibrated mixtures of **8t** and **8c**, we obtained this material as a sharply melting crystalline solid (101–102 °C) whose ^{1}H NMR spectrum confirmed its stereochemistry and the absence of **8t**.

The angularly substituted hexahydro-9(10*H*)-anthracenone **9** was approached by several unsuccessful routes, which gave us material methylated α rather than β to the ketone (**18**).[13a,14] Finally, the brute-force procedure outlined in Scheme I provided **9t** and **9c**, as well as the previously obtained **18t** and **18c** and other byproducts, all separable by HPLC and identified by GC–MS and NMR. The relative amounts of **9** and of **18** produced by the oxidation of **20** were consistent with more difficult oxidation adjacent to the angular methyl. Also consistent with the structures assigned, **9t** and **9c** were interconvertible with base, while **18t** and **18c** were not. Stereochemical assignments to the liquid epimers **9t** and **9c**, as well as to other methylated epimeric pairs in this work, were made on the basis of the relative widths and of the chemical shifts of the methyl singlets in the NMR spectra.

Numerous individual examples,[10,15a] as well as a comprehensive study of forty steroids,[15b] have shown that in angularly methylated decalin skeletons there is an excellent correlation, for trans and cis epimeric pairs, between ring-juncture stereochemistry and the relative widths, in the NMR spectra, of the methyl singlets measured at half-height. This correlation derives from four-bond "*W*-type" coupling, which is maximized when the methyl and the ring hydrogen(s) with which it is coupled are in a trans diaxial relationship. A trans ring juncture allows three such interactions, resulting in greater broadening of the methyl signal than in the case of a cis ring juncture, which allows only one.

The chemical shift correlation is more complex but is equally documentable. In decalins and certain other fused bicyclic systems, the relative chemical shifts for angular methyl groups may be directly correlated with ring-juncture stereochemistry. This derives partly from a chemical shift difference, which appears to be inherent to such systems even in the absence of any polar or unsaturated substituents, in which the singlet for a methyl group at a cis juncture is found ca. 0.13 ppm downfield relative to the corresponding trans case.[15a] This shift, like that of equatorial vs axial hydrogens in cyclohexane, presumably has its origin in the magnetic anisotropy of the bond framework of the rings. In correlations worked out extensively for steroids, these peak positions are found to be

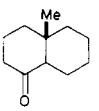
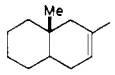
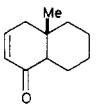
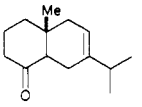
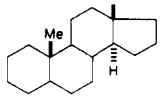
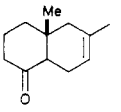
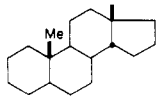
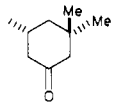
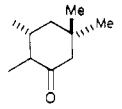
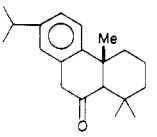
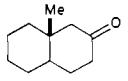
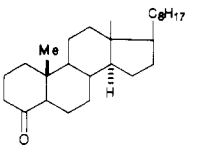
(12) (a) Cook, J. W.; Hewett, C. L.; Lawrence, C. A. *J. Chem. Soc.* **1936**, 71. (b) Cook, J. W.; McGinnis, N. A.; Mitchell, S. *Ibid.* **1944**, 286. (c) Arbuzov, Y. A.; Bolesov, I. G.; Bregadze, V. I.; Kolosov, M. N.; Shemyakin, M. M.; El'perina, E. A. *Izv. Akad. Nauk S.S.S.R., Ser. Khim.* **1964**, 310; *Chem. Abstr* **1964**, *60*, 11959*d*. (d) Scribner, J. D.; Miller, J. A. *J. Chem. Soc.* **1965**, 5377. (e) Snatzke, G.; Ho, P. C. *Tetrahedron* **1971**, *27*, 3645. (f) Zwinselman, J. J.; Van den Heuvel, C. G.; Nibbering, N. M. M. *Adv. Mass Spectrom.* **1980**, *8A*, 808. (g) Essiz, M.; Guillaumet, G.; Brunet, J.-J.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 240.

(13) (a) Hagishita, S.; Kuriyama, K. *Bull. Soc. Chem. Jpn.* **1982**, *55*, 3216. (b) Trahanovsky, W. S.; Swenson, K. E. *J. Org. Chem.* **1981**, *46*, 2984.

(14) Lutz, R. E.; Taylor, R. J. *J. Am. Chem. Soc.* **1933**, *55*, 1168.

(15) (a) Robinson, M. J. T. *Tetrahedron Lett.* **1965**, 1685. (b) Williamson, K. L.; Howell, T., Spencer, T. A. *J. Am. Chem. Soc.* **1966**, *88*, 325.

Table II. Correlation of Chemical Shifts with Stereochemistry for Angular Methyl Groups in Systems Related to 9-Methyldecalin

compound	δ cis	δ trans	Δδ	ref	compound	δ cis	δ trans	Δδ	ref
	0.96	0.83	0.13	15a		1.02	0.77	0.25	8a
	0.87	0.77	0.10	10		1.00	0.92	0.08	17b
	3.05	2.85	0.20	15b		1.05	0.71	0.34	17c
	0.925	0.792	0.133	16a		1.06	0.76	0.30	10
	0.900	0.767	0.133	16a	**6** **13**, Z = H **13**, Z = OMe	1.07 1.35 1.30	0.83 1.03 1.00	0.24 0.32 0.30	10 11b–d 11a
	1.05[a]	0.88[b]	0.17	15a	**15**	1.12	1.00	0.12	18
	1.05[a]	0.86[b]	0.19	15a		1.56	1.14–1.17	0.4	19
	0.97	0.79	0.18	17a		1.113	0.745	0.368	16a

[a] Equatorial. [b] Axial.

Table III. Chemical Shifts and Widths at Half-Height for Angular Methyl Groups in the NMR Spectra of Benzoctalones

compd	δ cis	δ trans	Δδ	$\omega_{1/2}$, Hz cis	$\omega_{1/2}$, Hz trans	$\Delta\omega_{1/2}$
9	1.01	0.84	0.17	1.39	2.00	0.61
11	1.10	0.80	0.30	1.57	2.08	0.51
13[a]	1.30[b]	0.99[b]	0.31	1.09	1.38	0.29
15	1.13	1.04	0.09	0.96	1.68	0.72
17	1.09	0.83	0.26	0.90	1.41	0.51

[a] These values were determined from a spectrum run on a sample of **13**, R = OMe, prepared and stereochemically equilibrated by Mr. (now Dr.) Gerard E. Linkowski during 1969–70. [b] Cf. Table II and ref 11a.

influenced predictably and additively by nearby polar groups and unsaturation.[16] For our cases, in which the angular methyl is placed β to a ring ketone, as in 4-keto-steroids, 10-methyl-1-decalone (**4**), or 9-methyl-2-decalone, the effect of the carbonyl is generally to increase this chemical shift difference by a factor of around 1.5–3, so that it is less likely to be overcome by the effects of other substituents (Table II). Thus, for simple systems lacking polar substituents near the angular methyl, this correlation, particularly in conjunction with the peak widths, may be used with great confidence for assignment of stereochemistry of epimeric pairs of angularly methylated decalins.

The hexahydro-1(2*H*)-anthracenone **10** was synthesized by the Diels–Alder route shown in Scheme II and yielded a single crystalline epimer, assigned trans stereochemistry on the basis of its NMR spectrum. This was the only ketone in our entire study that appeared as a single isomer at equilibrium and for which we were not able even to detect with certainty the other epimer.[20] The Diels–Alder reaction shown should lead to a cis adduct and, indeed,

(16) (a) Zürcher, R. F. *Helv. Chim. Acta* **1963**, *46*, 2054. (b) Cheung, H. T.; Williamson, D. G. *Tetrahedron* **1969**, *25*, 119 and references cited therein.

(17) (a) Shaffer, G. W. *J. Org. Chem.* **1973**, *38*, 2842. (b) MacKenzie, B. D.; Angelo, M. M.; Wolinsky, J. *Ibid.* **1979**, *44*, 4042. (c) Garratt, P. J.; Porter, J. R. *Ibid.* **1986**, *51*, 5450.

(18) Valko, J. T.; Wolinsky, J. *J. Org. Chem.* **1979**, *44*, 1502.

(19) Huffman, J. W.; Gibbs, J. J. *J. Org. Chem.* **1974**, *39*, 2501.

(20) (a) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056 and references cited. (b) Bilyard, K. G.; Garratt, P. J. *Tetrahedron Lett.* **1981**, *22*, 1755 and references cited.

the NMR spectrum of alcohol **21** supports the cis structure shown. However, we were unsuccessful in attempts to isolate the cis ketone **10c** by oxidation of **21** under conditions which would prevent epimerization.

The methylated compound, **11**, was prepared by hydrogenolysis of the known hexahydro-1,10-anthracenedione,[21] made from Hagemann's ester by the published route, consisting of successive benzylation, decarboxylation, cyanide addition, hydrolysis, and ring closure. The resulting mixture was separable by HPLC into the individual oily epimers **11t** and **11c**, which were assigned stereochemistry on the basis of the methyl singlets in their ^{1}H NMR spectra (Table III).

Phenanthrenoid Set (12–17). Because of their relationship to terpenoid natural products, several of the compounds in this general set were already known, although existing equilibrium data was more scarce. For a hexahydro-1(2*H*)-phenanthrenone, the 7-methoxy derivative **12** offered several advantages. Both epimers of this compound, made in connection with syntheses directed toward estrone and other 19-norsteroids, were already characterized as stable crystalline solids;[22] the existing equilibrium data, however, based only on IR measurements, seemed of very doubtful accuracy.[22f] These compounds (**12t,c**) were synthesized via the α,β-unsaturated ketone, as described in the literature, and isolated as a pair of crystalline epimers.

The angularly methylated analogue (**13**) of the above system, variously substituted at the 7-position (Z = H, OMe, $CHMe_2$), is the most often synthesized and best studied in our entire phenanthrenoid set because of its position in both the degradation and synthesis of dehydroabietic acid. The stereochemical purity of several liquid ketone preparations was a subject of early interest[23] and several groups ultimately used NMR or GC to measure accurately the position of equilibrium in these compounds.[11] We chose not to remeasure these equilibria ourselves but to accept the most consistent of the literature values.

Both epimers of the hexahydro-9(10*H*)-phenanthrenone **14** have been reported as pure materials with configurations firmly established,[24] and the position of their equilibrium has been measured within the recent era of quantitative chromatographic and NMR analysis.[18] We therefore accepted the values already reported for this equilibrium.

A route analogous to that used for **14**, Friedel–Crafts reaction of phenylacetyl chloride with methylcyclohexene, has been used to synthesize the corresponding angularly methylated ketones **15**,[18,23b,25] also of interest with respect to dehydroabietic acid. However, as no equilibrium data was reported, we have repeated this synthesis, purified the trans and enriched the cis epimer, confirmed the previous stereochemical assignments by NMR, and carried out this equilibration.

The hexahydro-4(1*H*)-phenanthrenone **16** has been reported in the literature as a model for the synthesis of morphine, with, however, only one epimer ever isolated or detected.[26] The trans stereochemistry assigned on unstated grounds to that material (and to its 5,6-dimethoxy analogue!) was rendered even more doubtful by the later opposite assignment (by NMR) to the B–C ring juncture of the more stable epimer of an 11-ketoestradiol ether.[27] We have synthesized **16** by the published route, involving conjugate addition of malonic ester to 2-phenylcyclohexenone, and we have established by means of NMR that the previously isolated epimer, which predominates by ca. three to one at equilibrium, was in fact misassigned and has cis stereochemistry, as indeed proved to be the case with one of our own compounds, which was similar to **16** and prompted our original interest in this subject.[2a]

Angular methylation of the above system was accomplished by addition of lithium dimethylcuprate to the corresponding α,β-unsaturated ketone.[26b,c,28] The less stable epimer (**17t**) of the product could not be isolated because of the very small amounts present but was readily resolved from **17c** and the various minor byproducts by GC and could be identified by mass spectrometry.

Table IV shows the measured trans/cis ratios at equilibrium for benzoctalones **8–17** and the values of $-\Delta G°$ calculated from those ratios. Also included for each

Table IV. Trans/Cis Equilibrium Ratios and Free-Energy Values for Benzoctalones 8–17

compd	t/c ratio	$-\Delta G°_{298}$, kcal/mol	$-\Delta_{Me}\Delta G°_{298}$, kcal/mol[a]
8	88/12	1.18	
9	51/49	0.02	1.16
10	(99/1)[b]	(2.7)[b]	
11	74/26	0.62	(2.1)
12	57/43	0.17	
13	(30/70)[c]	−0.51[c]	0.68
14	61/39[d]	0.26[d]	
15	37/63	−0.32	0.58
16	24/76	−0.68	
17	3/97	−2.06	1.38

[a] The change in $-\Delta G°_{298}$ produced in a given even-numbered ketone by introducing the angular methyl group. [b] An estimated value; the minor epimer was not detectable at equilibrium, and 400-MHz spectra exhibited negligible differences between pure crystalline **10t** and the equilibrated mixture. [c] The most consistent t/c ratios cited for **13** (ref 11a, R = OMe; ref 11b, R = H, $CHMe_2$) are all 33–4/66–7. However the only temperatures referred to are in ref 11b, where the equilibrations *appear* to have been carried out at or near 100 °C. Therefore the $-\Delta G°$ value here is for 373 K; if this value is used for $-\Delta G°_{298}$, calculation gives the ratio shown, ca. 30/70, which accords well with some trial measurements made in our own laboratories by Mr. (now Dr.) Gerard E. Linkowski in 1969–70. [d] Equilibrations carried out at 298 K in ref 18.

(21) (a) Ghatak, U. R.; Chakravarty, J.; Banerjee, A. K. *Tetrahedron* **1968**, *24*, 1577. (b) Ghatak, U. R.; Dasgupta, R.; Chakravarty, J. *Ibid.* **1974**, *30*, 187. (c) Ghosh, S.; Dasgupta, R.; Chakravarty, J.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 804.

(22) (a) Robinson, R.; Walker, J. *J. Chem. Soc.* **1936**, 747. (b) Bachmann, W. E.; Kushner, S.; Stevenson, A. C. *J. Am. Chem. Soc.* **1942**, *64*, 974. (c) Johnson, W. S.; Jones, A. R.; Schneider, W. P. *Ibid.* **1950**, *72*, 2395. (d) Ansell, M. F.; Brown, S. S. *Chem. Ind. (London)* **1956**, 984. (e) Birch, A. J.; Smith, H.; Thornton, R. E. *Ibid.* **1956**, 1310. (f) Birch, A. J.; Smith, H.; Thornton, R. E. *J. Chem. Soc.* **1957**, 1339. (g) Nelson, N. A.; Garland, R. B. *J. Am. Chem. Soc.* **1957**, *79*, 6313. (h) Ansell, M. F.; Brown, S. S. *J. Chem. Soc.* **1958**, 3956. (i) Ansell, M. F., Drucker, J. W. *Ibid.* **1961**, 206. (j) Balasubramanian, S. K. *Tetrahedron* **1961**, *12*, 196. (k) Nagata, W.; Terasawa, T.: Tori, K. *J. Am. Chem. Soc.* **1964**, *86*, 3746. (l) For an erroneous assignment of relative trans/cis stabilities, see: Julia, M.; Chottard, J.-C.; Basselier, J.-J. *Bull. Soc. Chim. Fr.* **1966**, 3037, and Chottard, J.-C.; Julia, M. *Ibid.* **1968**, 3700.

(23) (a) Stork, G.; Burgstahler, A. *J. Am. Chem. Soc.* **1951**, *73*, 3544. (b) Barltrop, J. A.; Rogers, N. A. J. *J. Chem. Soc.* **1958**, 2566. (c) Barltrop, J. A.; Day, A. C. *Chem. Ind. (London)* **1959**, 1450. (d) Saha, N. N.; Ganguly, B. K.; Dutta, P. C. *J. Am. Chem. Soc.* **1959**, *81*, 3670. (e) Stork, G.; Schulenberg, J. W. *Ibid.* **1962**, *84*, 284. (f) Huffman, J. W.; Stockel, R. F. *J. Org. Chem.* **1963**, *28*, 506.

(24) (a) Gutsche, C. D.; Johnson, W. S. *J. Am. Chem. Soc.* **1946**, *68*, 2239. (b) Parham, W. E.; Czuba, L. J. *Ibid.* **1968**, *90*, 4030.

(25) Parham, W. E.; Wheeler, E. L.; Dodson, R. M. *J. Am. Chem. Soc.* **1955**, *77*, 1166.

(26) (a) Ginsburg, D.; Pappo, R. *J. Chem. Soc.* **1951**, 938. (b) Koelsch, C. F. *J. Am. Chem. Soc.* **1951**, *73*, 2951. (c) Ginsburg, D.; Pappo, R. *J. Chem. Soc.* **1953**, 1524. (d) Elad, D.; Ginsburg, D. *Ibid.* **1953**, 2664. (e) Klibanski, Y.; Ginsburg, D. *Ibid.* **1957**, 1293. (f) Bien, S.; Boazi, M. *Ibid.* **1959**, 1727.

(27) Liang, C. D.; Baran, J. S.; Allinger, N. L.; Yuh, Y. *Tetrahedron* **1976**, *32*, 2067.

(28) Ponton, J.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem.* **1981**, *46*, 118.

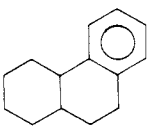
even–odd pair is the increment of $-\Delta G°$ generated by the addition of the angular methyl group. A number of generalizations and trends are evident from Table IV. Most generally, addition of an angular methyl group invariably decreases the relative stability of a trans epimer, presumably for the same reasons that it does so in decalin and decalones. The extent of the destabilization varies considerably but can be characterized in a general way as ca. 1.4 ± 0.8 kcal/mol.

Another generalization that can be drawn is that trans epimers are always favored to a greater degree in our anthracenoid than in the corresponding phenanthrenoid systems. The effect of adding an angular methyl group is sufficiently constant that this is just as true for the methylated series (odd numbers) as it is for the unmethylated series (even). In fact this effect is so pronounced that for the methylated compounds cis isomers *never* predominate at equilibrium in the anthracenoids and *always* predominate in the phenanthrenoids. This predominance of the cis epimer in the methylated phenanthrenoids is strikingly high (>32:1) in the case of the bay-region ketone **17**. When the trans-destabilizing effect of an angular methyl group is absent (even series), not only both of the anthracenoid but all except one of the phenanthrenoid systems have trans/cis ratios greater than one, so that for the entire unmethylated series the trans isomer is favored at equilibrium in every case except that of the bay-region ketone **16**.

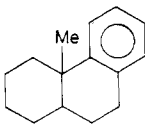
The unmethylated anthracenoids **8** and **10** have the same carbon skeleton; therefore any differences between them can be viewed as attributable to the placement of the keto group. The same is true for compounds **9** and **11**. Clearly the placement of the carbonyl group does make a difference in both of these cases, although that difference is much greater in the unmethylated anthracenoids (ca. 1.5 kcal/mol) than in the methylated ones (0.6 kcal/mol). Since we lack equilibrium data on the norketo species, we cannot further quantify those differences relative to the parent hydrocarbon. However we do have equilibrium data (Table I) on the norbenzo ketones decalone (**2**) and 10-methyldecalone (**4**) so we are able to stipulate somewhat more exactly the energetic effect of "benzo-annelation" in **2** and **4**. The effects of linear benzo-annelation at the ketone ring (**8** and **9**) vs at the nonketone ring (**10** and **11**) are consistently opposite and also consistently diminished by the presence of an angular methyl. Benzo-annelation of decalones **2** and **4** adjacent to the keto function diminishes the stability of the trans epimer by some 0.5 kcal/mol in the absence of an angular methyl group but only by about 40% of that value (0.2 kcal/mol) when an angular methyl is present (i.e., relative to 10-methyldecalone, **4**). Linear benzo-annelation of decalones **2** and **4** in the opposite direction (**10** and **11**) renders the trans epimer *more* stable by about 1.0 kcal/mol without an angular methyl and by about 40% of that amount (0.4 kcal/mol) when an angular methyl is present.

As has been done above, each phenanthrenoid in Table IV may also be viewed either as an octahydrophenanthrene in which a carbonyl is being generated or as a decalone to which a benzo ring is being appended. In this way, sets of compounds with identical precursors may yield useful comparisons. However, the pairs of compounds **12**, **14** and **13**, **15** have trans/cis ratios that are so similar—nearly within experimental error—that for this unsymmetrical octahydrophenanthrene skeleton, whether methylated or unmethylated at the tertiary benzylic position, neither of the above operations will reveal significant differences for **12** vs **14** or for **13** vs **15**.

However, for this system we do have some equilibrium data, not available when we began our study, for the norketo compounds **22** and **23**.[6,29] Relative to **22**, the



22



23

introduction of a carbonyl to give **12** or **14** increases the relative stability of the cis epimer by ca. 0.5 kcal/mol, while relative to **23**, carbonyl introduction (→**13** and **15**) has the opposite effect and stabilizes the trans epimers by ca. 0.6 kcal/mol. These effects may be compared with the analogous changes **1** → **2** and **3** → **4** in Table I, which produce, respectively, a substantial (ca. 0.9 kcal/mol) and a nearly negligible (ca. 0.15 kcal/mol) stabilization of the cis epimer.

Similarly, for 1-decalone (**2**), benzo-annelation at either C3–C4 or at C5–C6 produces nearly identical results, destabilizing the trans epimers by ca. 1.5 kcal/mol in each case. Analogous benzo-annelation of 10-methyldecalone (**4**) at either of these positions destabilizes the trans epimers by only 40% of this value, ca. 0.65 kcal/mol, almost exactly as in the unmethylated vs methylated anthracenoid compounds.

From several points of view the 4-ketophenanthrenoids **16** and **17** are the most interesting compounds in our study, those in which benzo-annelation of **2** and **4** has produced the greatest shift of equilibrium. For **16** this shift, of ca. 2.4 kcal/mol, is greater by about 50% than that produced by benzo-annelation at any other position in **2** and renders it the only unmethylated compound in our study whose equilibrium actually favors cis. For **17**, the shift in $-\Delta G°$ produced by benzo-annelation of **4** (2.3 kcal/mol) is essentially as large as that for the unmethylated case cited above, in contrast to the values seen for **9**, **11**, **13**, and **15**, where the methylated benzo-annelation shifts are all about 40% of the unmethylated cases. In actuality, for **17** the shift factors attributable to methylation (**2** → **4**) and to benzo-annelation (**2** → **16**) appear to be essentially additive, whereas for **9**, **11**, and **13** the additivity is poor. While this may suggest the presence of some factor (e.g., bay-region hindrance) operating in the pair **16**–**17** that is not present in the others, it does seem clear from the general consistency of **16** and **17** with the other even–odd pairs i.e., increased cis stability upon methylation, that this unusual bias in favor of the cis epimer is primarily a peculiarity of the unmethylated system, i.e, of the particular juxtaposition of carbonyl and benzo-ring in **16**, which then behaves more or less normally when the angular methyl is added in **17**.

The carbon skeleton of **17** is not identical with that of compounds **13** and **15** (**23**), hence direct comparisons regarding carbonyl placement cannot be made with **17**. However the skeletons of **12**, **14**, and **16** (**22**) differ only in the placement of the carbonyl group. The change in $-\Delta G°$ due to introduction of carbonyl into **22** is small and very similar for **12** and **14** (ca. 0.55 and 0.45 kcal/mol, respectively) but is about three times as large for **16** (ca. 1.4 kcal/mol). This difference between **12** and **14** on the one hand versus **16** on the other is not so large as the

(29) The equilibrations in ref 6a, carried out using an $AlBr_3$ catalyst, yielded trans/cis ratios for **22** of 77/23 at 22 °C and 69/31 at 127 °C, and for **23** of 22/78 at 127 °C and 30/70 at 317 °C. From these, trans/cis ratios at our working temperature, 25 °C, may be calculated of ca. 77/23 for **22** and 15/85 for **23**.

difference between 8 and 10; nevertheless it is obvious that carbonyl placement in the bay region of 22 is very different energetically from placement at the alternative positions in 12 and 14.

The key question, of course, is what the source of the cis stability or trans instability is in 16 and 17. Inspection of models suggests, as do the authors of ref 27, that this source is steric repulsion, within the bay region in the trans epimers, between the carbonyl oxygen and the aromatic hydrogen at C5. An alternative explanation, which cannot be disproved at present, is that this preference is inherent, for more subtle reasons, in this particular juxtaposition of sp^2 carbons within the decalin framework and would be present in the corresponding octalone, independent of the presence of the benzo-substituent.[17c] We believe the former is the more likely explanation.

Experimental Section[30]

1,2,3,4,4a,9a-Hexahydro-9(10*H*)-anthracenones (8). These compounds were prepared as described in the literature.[12a,b] The trans epimer **8t**, recrystallized from hexane and sublimed, had mp 108–109 °C (lit.[12a–e] mps within the range 109–111 °C) and gave the following spectral data: IR 1680, 1605, 750 cm^{-1}; ^1H NMR (400 MHz) δ 8.03 (1 H, dd, J = 8, 1.5 Hz), 7.45 (1 H, td, J = 8, 1.5 Hz), 7.30 (1 H, t, J = 8 Hz), 7.22 (1 H, d, J = 8 Hz), 2.89 (1 H, dd, J = 16, 4 Hz), 2.78 (1 H, dd, J = 16, 11 Hz), 2.42 (1 H, dm, J = 13 Hz), 2.13 (1 H, ddd, J = 12.5, 11.0, 3.6 Hz), 1.92 (3 H, m), 1.78 (1 H, m), 1.41–1.20 (4 H, m); ^{13}C NMR δ 199.8 (s), 143.4 (s), 133.1 (d), 132.3 (s), 128.5 (d), 127.2 (d), 126.5 (d), 51.9 (d), 40.0 (d), 37.3 (t), 34.0 (t), 25.9 (t), 25.7 (t), 25.4 (t); MS, m/e (relative intensity) 200 (100, M^+), 158 (83), 145 (75), 118 (50), 90 (46).

The cis epimer **8c** was obtained by repeatedly seeding mixtures with **8t** and removing the **8t**. Some initial cis enrichment was obtainable by rapid cold precipitation of **8** from concentrated H_2SO_4 solution.[31] Compound **8c** had mp 101–102 °C (lit. mp, see Discussion): IR 1680, 1605, 750 cm^{-1}; NMR (400 MHz) δ 8.06 (1 H, dd, J = 8, 1.5 Hz), 7.46 (1 H, td, J = 8, 1.5 Hz), 7.30 (1 H, t, J = 8 Hz), 7.23 (1 H, d, J = 8 Hz), 3.06 (1 H, dd, J = 16, 4.6 Hz), 2.97 (1 H, dd, J = 16, 5.8 Hz), 2.71 (1 H, m), 2.43 (1 H, m), 2.21 (1 H, m), 1.64 (1 H, m), 1.6–1.38 (6 H, m); MS, m/e (relative intensity) 200 (96, M^+), 158 (84), 145 (100), 118 (53), 90 (45); HRMS, $C_{14}H_{16}O$ requires 200.1201, found 200.1203.

A sample of **8t** into which deuterium had been base exchanged (mp 107.5–109 °C) showed complete loss of the ^1H NMR absorption at δ 2.13, whose coupling constants were 12.5, 11.0, and 3.6 Hz, showing that this ring-juncture proton has two diaxial couplings, consistent only with **8t**. In addition the benzylic hydrogens in **8t** at δ 2.89 and 2.78 have vicinal coupling constants of 4 and 11.3 Hz, respectively, while the corresponding values for the vicinal couplings in **8c** (δ 3.06, J = 4.6 Hz; δ 2.97, J = 5.8) are consistent only with a conformer having no diaxial couplings.

1,2,3,4,4a,9,9a,10-Octahydro-4a-methylanthracenes (20). Dione **19** was prepared as described in the literature[32] by reaction of butadiene with 2-methylnaphthoquinone and isolated in 98% yield as an oil, shown by GC to be partially isomerized (trans/cis = 1/10). The above dione (3.3 g, 14.6 mmol) was stirred with 330 mg of 5% Pd/C in 25 mL of HOAc at 65 °C under 4 atm of H_2 for 28 h. The mixture was cooled, filtered, and concentrated to yield 3.3 g of **20** as a yellow oil, shown by GC and NMR to have a trans/cis ratio of 1/2: IR 3010, 2920, 2850, 730 cm^{-1}; NMR (60 MHz) δ 7.1 (4 H, s), 3.4–1.0 (13 H, m), 0.95 (2 H, s), 0.82 (1 H, s);[13a] GC–MS (CI, CH_4) showed m/e 201 (M + H) for each epimer.

1,2,3,4,4a,9a-Hexahydro-4a-methyl-9(10*H*)-anthracenones (9). A mixture of 0.50 g (1.6 mmol, based on 65% purity) of **20** was stirred with 1.7 g (7.9 mmol) of pyridinium chlorochromate and 4 g of Celite in 30 mL of benzene at reflux for 60 h. The cooled mixture was diluted with Et_2O, filtered, and concentrated to give an amber oil; this was suspended in hexane, refiltered, and reconcentrated to give 280 mg of a light yellow oil, shown by GC–MS and NMR to contain about 53% of **9**. The remaining 47% consisted principally of **18**, along with unchanged **20** and minor amounts of **19** and ketols. The desired materials were separated as colorless oils by HPLC; ketones **18t** and **18c** were distinguishable from **9** by their methyl singlets at δ 1.07[13a] and 1.19, respectively, and by the vicinal splitting evident in their benzylic hydrogens in the region δ 3.5–2.5. Compound **9t** gave the following data: IR 1680, 1600, 720 cm^{-1}; NMR (200 MHz) δ 7.97 (1 H, dd, J = 8, 1.5 Hz), 7.45 (1 H, td, J = 8, 1.5 Hz), 7.27 (1 H, t, J = 8 Hz), 7.18 (1 H, d, J = 8 Hz), 2.99 (1 H, d, J = 16 Hz), 2.71 (1 H, d, J = 16 Hz), 2.40 (1 H, dd, J = 11, 3 Hz), 1.7–1.1 (8 H, m), 0.84 (3 H, s).

The cis epimer **9c** gave the following data: IR 1675, 1600, 720 cm^{-1}; NMR (200 MHz) δ 8.04 (1 H, dd, J = 8, 1.5 Hz), 7.50 (1 H, td, J = 8, 1.5 Hz), 7.32 (1 H, t, J = 8 Hz), 7.25 (1 H, d, J = 8 Hz), 3.33 (1 H, d, J = 17 Hz), 2.46 (1 H, d, J = 17 Hz), 2.29 (1 H, dd, J = 11, 4 Hz), 1.8–1.2 (8 H, m), 1.01 (3 H, s); HRMS, $C_{15}H_{18}O$ requires 214.1358, found 214.1359.

1,2,3,4,4a,9,9a,10-Octahydro-1-anthracenol (21). A mixture of 12.6 mL (72 mmol) of 1-[(trimethylsilyl)oxy]-1,3-butadiene and 5.5 g (35 mmol) of 1,4-naphthoquinone in 100 mL of PhMe was stirred at reflux for 16 h. The cooled mixture was concentrated to 10.8 g of amber oil, which was suspended in 100 mL of Et_2O, filtered, and reconcentrated to 8.4 g (80%) of yellow oil: IR 1700, 1690, 1595, 1255, 845 cm^{-1}; NMR (60 MHz) δ 8.2–7.5 (4 H, m), 5.95–5.75 (2 H, m), 4.45 (1 H, br t), 3.6–3.0 (3 H, m), 2.8–1.8 (1 H, m), –0.4 (9 H, s); GC–MS (CI, CH_4) m/e (relative intensity) 301 (3, M + H), 285 (52), 211 (100), 133 (72).

The above crude Diels–Alder product (1.0 g, 3.3 mmol) was stirred along with 100 mg of 5% Pd/C in 25 mL of PhMe at 25 °C under 4 atm of H_2 pressure for 20 h (H_2 uptake, 5 mmol). The mixture was filtered and concentrated to 1.0 g (100%) of yellow oil: IR 1685, 1590, 1250, 835 cm^{-1}; NMR (200 MHz) δ 8.05 (2 H, m), 7.7 (2 H, m), 4.3 (1 H, m), 3.1 (2 H, s), 2.6 (2 H, m), 2.1–1.2 (4 H, m), –0.40 (9 H, s); GC–MS, m/e (relative intensity) 302 (5, M^+), 287 (22), 142 (56), 75 (100).

The above crude diketone (1.0 g, 3.3 mmol) was stirred with 200 mg of 5% Pd/C in 25 mL of HOAc at 65 °C under 4 atm of H_2 pressure for 6.5 h (H_2 uptake, 17 mmol). The cooled mixture was filtered and concentrated to 640 mg of yellow oil, which was dissolved in 25 mL of CH_2Cl_2, washed with saturated $NaHCO_3$, and dried; GC–MS showed two isomeric components in unequal amounts, each having a molecular weight of 202. Concentration gave 500 mg (75%) of yellow oil, which crystallized on standing; recrystallization of 100 mg from 1 mL of Me_2CO at –20 °C gave 40 mg of white crystals, mp 128–129 °C: IR 3350, 3280, 750 cm^{-1}; NMR (400 MHz) δ 7.10 (4 H, m), 3.90 (1 H, dt, J = 10.5, 5 Hz), 3.02 (1 H, dd, J = 17, 6 Hz), 2.82 (2 H, d, J = 9 Hz), 2.60 (1 H, dd, J = 17, 2 Hz), 2.35 (1 H, m), 1.92 (1 H, m), 1.75 (2 H, m), 1.65–1.15 (6 H, m); MS, m/e (relative intensity) 202 (3, M^+), 184 (34), 142 (70), 141 (100), 129 (31), 128 (53), 115 (29).

***trans*-3,4,4a,9,9a,10-Hexahydro-1(2*H*)-anthracenone (10t).** A solution of 100 mg (0.50 mmol) of pure alcohol **21** in 2 mL of Me_2CO was stirred at 25 °C during dropwise addition of 0.20 mL of Jones reagent over 1 min. The usual extractive workup gave 100 mg of yellow oil, which crystallized from hexane as colorless needles, mp 98–100 °C: IR 1705, 750 cm^{-1}; NMR (400 MHz,

(30) Melting points were determined on a Thomas-Hoover Uni-Melt or on a Laboratory Devices Mel-Temp apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283 instrument, with neat liquids and KBr pellets for solids. ^1H NMR spectra were recorded on Varian T-60A, XL-200, and XL-400 spectrometers, and unless otherwise specified, with $CDCl_3$ solutions containing 1% $SiMe_4$. ^{13}C NMR spectra were run at 50 MHz on an IBM WP 200-SY instrument with $CDCl_3$ as solvent. Mass spectra (MS) were run with a Finnigan Model 3300 spectrometer coupled to a Finnigan 9500 gas chromatograph with an SE-54 capillary column. High-resolution mass spectra (HRMS) were obtained from a VG Analytical ZAB spectrometer with a direct insertion probe. The electron-impact mode was used unless otherwise specified. Gas chromatography (GC) was performed on a Hewlett-Packard Model 5880A instrument with an SE-30 methyl silicone capillary column. High-pressure liquid chromatography (HPLC) was carried out using a Varian Model 5000 instrument equipped with a Zorbax C_8 reverse-phase column and UV detector (275 nm); the mobile phase was 3:1 MeO–H_2O.

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$CDCl_3/C_6D_6$) δ 6.95 (3 H, m), 6.87 (1 H, m), 2.88 (1 H, dd, J = 17, 10 Hz), 2.86 (1 H, dd, J = 17, 7 Hz), 2.57 (1 H, dd, J = 17, 5 Hz), 2.34 (1 H, dd, J = 17, 11 Hz), 2.23 (1 H, d/quin, J = 13, 2 Hz), 1.93 (1 H, tdd, J = 14, 7.5, 1 Hz), 1.89 (1 H, m), 1.66 (1 H, d/quin, J = 10, 3 Hz), 1.55 (1 H, dm, J = 13 Hz), 1.44 (1 H, qt, J = 11, 4 Hz), 1.34 (1 H, qt, J = 13, 4), 1.04 (1 H, tdd, J = 13, 12, 4 Hz); MS, m/e (relative intensity) 200 (40, M^+), 154 (39), 141 (62), 129 (77), 128 (100), 115 (45); HRMS, $C_{14}H_{16}O$ requires 200.1201, found 200.1203.

Because we were unable to isolate or detect **10c**, while our equilibration conditions produced negligible changes in samples of **10t**, a 25-mg sample of **10t** was subjected to our equilibration conditions with Na dissolved in CD_3OD and quenching with D_2O, in order to demonstrate that proton removal was taking place. The recovered solid (22 mg, 88%) had mp 96–99 °C and its NMR spectrum (200 MHz, $CDCl_3$) showed loss of 3 H and complete loss of coupling from the above peaks at δ 2.88 and 2.86 (which in $CDCl_3$ are isochronous at δ 2.95).

3,4,4a,9,9a,10-Hexahydro-4a-methyl-1(2*H*)-anthracenones (11). A mixture of 2.7 g (12 mmol) of 3,4,4a,9a-tetrahydro-4a-methyl-1,10(2*H*,9*H*)-anthracenedione, prepared as described in the literature[21,33] was stirred with 600 mg of 5% Pd/C in 25 mL of HOAc at 85 °C under 4 atm of H_2 pressure for 7 days (H_2 uptake, 24 mmol). The cooled mixture was filtered and subjected to the usual workup, leading to 1.7 g (67%) of pale oil shown by GC to consist of 65% **11t** and 15% **11c**, along with 20% of a series of unknown byproducts; pure **11t** and **11c** were provided by HPLC. The trans epimer **11t** had mp 72–73 °C and gave the following spectral data: IR 1708, 760 cm^{-1}; NMR (400 MHz) δ 7.15 (3 H, m), 7.05 (1 H, t, J = 6 Hz), 2.96 (1 H, dd, J = 18, 12 Hz), 2.88 (1 H, d, J = 16.5 Hz), 2.80 (1 H, dd, J = 18, 5.5 Hz), 2.63 (1 H, d, J = 16.5 Hz), 2.59 (1 H, dd, J = 12, 5.5 Hz), 2.42 (2 H, m), 2.03 (1 H, m), 1.95 (1 H, m), 1.79 (2 H, m), 0.80 (3 H, s); MS, m/e (relative intensity) 214 (67, M^+), 199 (100), 181 (73), 143 (45), 141 (43), 129 (45), 128 (80), 127 (32), 115 (78), 104 (35), 91 (47); HRMS, $C_{15}H_{18}O$ requires 214.1358, found 214.1359.

The oily cis epimer **11c** gave the following data: IR 1710, 740 cm^{-1}; NMR (400 MHz) δ 7.17–7.03 (3 H, m), 6.97 (1 H, d, J = 7.5 Hz), 3.29 (1 H, dd, J = 18, 2 Hz), 2.79 (1 H, dd, J = 18, 7 Hz), 2.77 (1 H, d, J = 17 Hz), 2.54 (1 H, d, J = 7 Hz), 2.37 (2 H, m), 2.26 (1 H, d, J = 17 Hz), 2.00 (2 H, m), 1.79 (2 H, m), 1.10 (3 H, s); MS, m/e (relative intensity) 14 (75, M^+), 199 (90), 181 (75), 143 (70), 141 (46), 129 (58), 128 (100), 115 (73), 104 (78), 91 (42).

3,4,4a,9,10,10a-Hexahydro-7-methoxy-1(2*H*)-phenanthrenones (12). These materials were prepared[34] as described in the literature.[22f] The trans epimer **12t** had mp 106.5–108.5 °C (lit.[22a,f] mp 109, 111 °C): IR 1720, 1615 cm^{-1}; NMR (400 MHz) δ 7.23 (1 H, d, J = 9 Hz), 6.75 (1 H, dd, J = 9, 3 Hz), 6.66 (1 H, d, J = 3 Hz), 3.80 (3 H, s), 2.84 (2 H, m), 2.73 (1 H, td, J = 12, 3 Hz), 2.61 (1 H, dm, J = 13 Hz), 2.53–2.41 (2 H, m), 2.35 (1 H, td, J = 12, 3 Hz), 2.30–2.18 (2 H, m), 1.86 (1 H, tdd, J = 13, 5, 4 Hz), 1.77–1.61 (2 H, m).

The cis epimer **12c** had mp 69–70.5 °C (lit.[22f] mp 68–71 °C): IR 1720, 1620 cm^{-1}; NMR (400 MHz) δ 7.08 (1 H, d, J = 8.5 Hz), 6.75 (1 H, dd, J = 8.5, 3 Hz), 6.63 (1 H, d, J = 3 Hz), 3.79 (3 H, s), 3.14 (1 H, dt, J = 10, 5 Hz), 2.91 (1 H, ddd, J = 16.5, 8, 3.5 Hz), 2.81 (1 H, ddd, J = 16.5, 10.5, 6 Hz), 2.72 (1 H, dm, J = 11.5), 2.43 (1 H, ddd, J = 14.5, 11, 6 Hz), 2.36 (1 H, dm, J = 15), 2.13 (1 H, dtd, J = 13, 11, 6 Hz), 2.06–1.87 (3 H, m), 1.86–1.75 (2 H, m).

4b,5,6,7,8,8a-Hexahydro-4b-methyl-9(10*H*)-phenanthrenones (15). These compounds were prepared essentially as described in the literature[18] and isolated in 55% yield as a pale yellow distilled oil, shown by GC to contain 40% of **15t** and 50% of **15c**, along with 10% multiple unknown byproducts. Pure **15t** and partially purified **15c** were provided by HPLC. The oily trans epimer **15t** gave the following data: IR 1710, 755 cm^{-1}; NMR (400 MHz) δ 7.38 (1 H, dd, J = 8, 1.5 Hz), 7.28 (1 H, td, J = 8, 1.5 Hz), 7.22 (1 H, td, J = 8, 1.5 Hz), 7.12 (1 H, dd, J = 8, 1.5 Hz), 3.67 (1 H, d, J = 20 Hz), 3.64 (1 H, d, J = 20 Hz), 2.43 (1 H, dd, J = 12, 4 Hz), 2.32 (1 H, dm, J = 12 Hz), 1.98 (1 H, dm, J = 14 Hz), 1.88 (1 H, dm, J = 13 Hz), 1.76 (1 H, dm, J = 13.5 Hz), 1.68 (1 H, td, J = 12, 4 Hz), 1.54 (2 H, m), 1.20 (1 H, qt, J = 13, 4 Hz), 1.04 (3 H, s); GC–MS (CI, CH_4), m/e (relative intensity) 215 (62, M + H), 197 (100), 119 (28), 91 (52).

The oily cis epimer **15c** gave the following data: IR 1710, 755 cm^{-1}; NMR (400 MHz) δ 7.35 (1 H, d, J = 8 Hz), 7.28 (1 H, t, J = 8 Hz), 7.21 (1 H, dt, J = 8, 1.5 Hz), 7.03 (1 H, d, J = 8 Hz), 3.68 (1 H, d, J = 22 Hz), 3.61 (1 H, d, J = 22 Hz), 2.45 (2 H, m), 2.34 (1 H, dd, J = 12, 3.5 Hz), 1.80–1.25 (6 H, m), 1.13 (3 H, s); GC–MS (CI, CH_4), m/e (relative intensity) 215 (84, M + H), 197 (100), 119 (32), 91 (74).

The cis epimer **15c** was found to be subject to easy air–oxidation,[25] as has also been noted for **14**.[18,24a] This was much more rapid for **15c** than for **15t** and resulted in progressive contamination of samples of **15c** with yellow material, which was not isolated but whose spectral characteristics seemed consistent with diketone.[25]

2,3,10,10a-Tetrahydro-4,9(1*H*,4a*H*)-phenanthrenedione. (3-Oxo-*trans*-2-phenylcyclohexane)acetic acid, prepared as described in the literature[26] was cyclized by heating with polyphosphoric acid at 100–130 °C for 15 min, followed by addition of H_2O at 80 °C and stirring at 25 °C for 18 h before isolation, so that the product must certainly have been stereochemically equilibrated. Simple chromatograhy removed byproducts and provided the diketone as a crudely crystalline mixture. The two epimers, purified further by recrystallization were easily distinguishable by their doublets at δ 3.99 (cis, J = 5.25 Hz) and 3.91 (trans, J = 11.75), so that NMR as well as GC allowed measurement of the original trans/cis ratio, which was ca. 1/7. Thus the previous assignments of trans stereochemistry to the stabler epimer of this diketone and its analogues[26] is erroneous.

2,3,4a,9,10,10a-Hexahydro-4(1*H*)-phenanthrenones (16). These compounds were prepared by direct hydrogenolysis of the 4,9-dione as described in the literature.[26a,c] Recrystallization and HPLC were able to achieve only partial enrichment with **16t**: IR 1710, 1500, 755, 740 cm^{-1}; GC–MS, m/e (relative intensity) 200 (6, M^+), 156 (35), 141 (16), 129 (100), 128 (80), 115 (15). The NMR spectrum of **16t** in $CDCl_3$ has a 1 H (benzylic) doublet at δ 3.68, which is not optimally resolved from the corresponding doublet in **16c**; however, in $CDCl_3/C_6D_6$ these are well separated and can be used for characterization and quantitation: δ 3.89 (cis, J = 5.5 Hz) vs 3.82 (trans, J = 11.7 Hz).

The pure cis epimer **16c** was provided by recrystallization and HPLC as a white solid (lit.[26a] mp 48–49 °C): IR 1710, 1500, 740 cm^{-1}; NMR (400 MHz) δ 7.15 (3 H, m), 6.92 (1 H, dd, J = 7.5, 2 Hz), 3.72 (1 H, d, J = 5.5 Hz), 2.92 (1 H, dt, J = 17.5, 6.5 Hz), 2.82 (1 H, dt, J = 17.5, 6.5 Hz), 2.51 (1 H, m), 2.39 (2 H, m), 1.93 (3 H, m), 1.76 (3 H, m); GC–MS, m/e (relative intensity) 200 (21, M^+), 156 (24), 143 (31), 129 (100), 128 (96), 115 (33).

2,3,4a,9,10,10a-Hexahydro-10a-methyl-4(1*H*)-phenanthrenones (17). 2,3,9,10-Tetrahydro-4(1*H*)-phenanthrenone[28] was prepared as described in the literature[26d] and dissolved (50 mg, 0.25 mmol) in 1.0 mL of dry Et_2O. This solution was added dropwise with stirring at 0 °C over 2 min to a solution previously prepared by 0 °C addition over 5 min of 0.91 mL (1.0 mmol) of 1.1 M MeLi in Et_2O to a stirred mixture of 96 mg (0.50 mmol) in CuI in 7 mL of dry Et_2O. The final mixture was stirred for 45 min at 0 °C and worked up by pouring slowly into 25 mL of vigorously stirred 2 N HCl. Concentration of the dried Et_2O extracts led to 38 mg (71%) of amber oil, shown by GC–MS to consist of 72% **17**, accompanied by 17% of 1,2-addition product and 11% double-addition product. The proportion of **17t** present was too small for effective separation; however, it was resolvable from **17c** by GC, its NMR singlet at δ 0.83 was readily distinguishable and GC–MS gave the following data: m/e (relative intensity) 214 (12, M^+), 143 (78), 129 (33), 128 (100), 115 (39), 91 (22).

The oily cis epimer **17c** gave the following data: IR 1705, 750 cm^{-1}; NMR (400 MHz) δ 7.16 (3 H, m), 6.91 (1 H, d, J = 7.5 Hz), 3.34 (1 H, s), 2.97 (1 H, dt, J = 18, 7 Hz), 2.85 (1 H, dt, J = 18, 6 Hz), 2.40–2.26 (2 H, m), 2.0–1.75 (4 H, m), 1.58–1.45 (2 H, m), 1.09 (3 H, s); MS, m/e (relative intensity) 214 (18, M^+), 143 (76),

(33) In our preparation, this diketone, without specific equilibration, was obtained as a 2:1 mixture of epimers in which the NMR methyl singlet for the major one was upfield, at δ 1.06 (lit.[21b] δ 1.05), consistent with the trans epimer, while that for the minor epimer appeared at δ 1.39, consistent with cis stereochemistry; this supports the stereochemical assignment made by the authors of ref 21b.

(34) We thank Jeffrey M. Gottlieb for the preparation, isolation, and preliminary equilibration of **12t** and **12c**, carried out during 1970–71 and supported during the summer of 1970 by a grant from the NSF.

129 (48), 128 (100), 115 (38), 91 (23); HRMS, $C_{15}H_{18}O$ requires 214.1358, found 214.1358.

General Procedure for Equilibrations. Typically a sample of 10 mg (47–50 μmol) of ketone was dissolved at 25 °C in 2.0 mL of dry MeOH containing 5 μmol of NaOMe (10 mol % based on ketone) and stirred under N_2 at 25 °C. Samples of 50 μL were withdrawan periodically by syringe, quenched with HOAc, and analyzed by capillary GC. Equilibrations were generally carried out for at least twice as long as required to reach equilibrium, which was usually within 24 h. When equilibrium was reached, quantitative ^1H NMR data from larger-scale experiments could sometimes be used to supplement the GC data. Wherever possible equilibria were approached from both sides, with either pure epimers or mixtures enriched in one epimer relative to the equilibrium values.

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Synthesis and Electrochemistry of Pyrimidoquinazoline-5,10-diones. Design of Hydrolytically Stable High Potential Quinones and New Reductive Alkylation Systems

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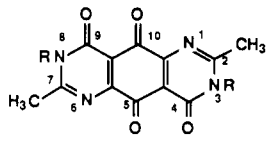
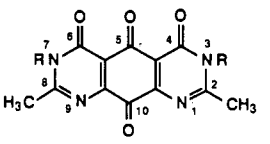
The synthesis of pyrimido[4,5-*g*]quinazoline-5,10-diones **1** and pyrimido[5,4-*g*]quinazoline-5,10-diones **2** was carried out in conjunction with the design of both hydrolytically stable high potential quinones and new purine-like reductive alkylators. These systems consist of a benzoquinone ring bearing two fused pyrimidin-4(3*H*)-one rings. The fused pyrimidinone rings serve to protect **1** and **2** from hydrolysis as well as to raise quinone redox potentials by stabilizing the hydroquinones with internal hydrogen bonds (65 mV increase per hydrogen bond). Synthesis of **1** and **2** involved pyrimidinone ring annelation to a 2,5-diamino-3-nitroterephthalic acid derivative and to a 2,4-diamino-1,5-dicarboxy-3-nitrobenzene derivative, respectively. The synthetic studies provided insights into the electronic effects of nitro and amino groups on the annelation process.

Pyrimidoquinazolines bearing 4,5-*g* and 5,4-*g* ring fusion were first prepared near the turn of the century[1] but have not received much attention since that time.[2] Our interest in quinone derivatives of these ring systems (**1** and **2**) stems from ongoing efforts to develop both new reductive alkylators and high potential quinones stable toward hydrolysis. Described here are the synthesis and electrochemistry of the pyrimido[4,5-*g*]quinazolines **1** and pyrimido[5,4-*g*]quinazolines **2** shown.



1



2

R = CH_3, a
R = H , b

Reductive alkylators based on the benzimidazole,[3] imidazo[4,5-*g*]quinazoline,[4,5] and quinazoline[6] ring systems have been designed by functionalizing the quinone derivatives of these ring systems with $-CH_2X$, where X is a leaving group. As is thought to be the case with many naturally occurring quinones,[7] these systems afford alkylating quinone methide species upon reduction to the corresponding hydroquinone species. Indeed, the imidazo[4,5-*g*]quinazoline derivatives act as active-site-directed reductive alkylators of xanthine oxidase by virtue of their purine-like structure.[5] Since many purine-utilizing enzymes tolerate drastic structural changes in their substrates,[8] the pyrimidoquinazolines may also interact with these enzymes. The synthetic studies described herein will be useful in preparing the bifunctional pyrimidoquinazoline reductive alkylators (i.e., derivatives with leaving groups substituted on the 2 and 7 methyls of **1** and on the 2 and 8 methyls of **2**).

Hydrolytic stability of the quinone derivatives **1** and **2** is crucial to both reductive alkylation and quinone-mediated oxidation studies. Reductive alkylation relies on stable quinone derivatives; only the hydroquinone derivatives should be active as an alkylator. Mechanistic studies of quinone–hydroquinone conversions mediated by various reducing substrates are ideally carried out without the accompanying reductive-addition and addition–elimination reactions typical of many quinones.[9] The studies described here indicate that the fused pyrimidine rings of **1** and **2** confer a great deal of hydrolytic stability on the benzoquinone system. Thus, the title quinones are stable in concentrated acids as well as in basic solutions. Nernst fits of E_m vs pH data provide, at a glance, the redox po-

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