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Photocyclization of Diethylstilbestrol. Isolation of a Stable, Self-Trapping Dihydrophenanthrene Intermediate

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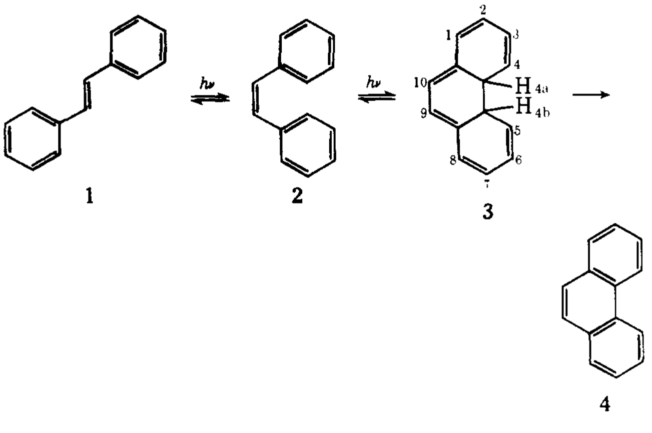
Abstract: Near-ultraviolet irradiation of the synthetic estrogen diethylstilbestrol, a stilbene derivative, resulted in the isolation of the first stable 4a,4b-dihydrophenanthrene. The stability of this DHP is the result of a double tautomerism of the initially formed dienol to a diketone structure in which the tendency to rearomatization is lost. Furthermore, the reverse ring-opening photoreaction may be prevented by the conversion of the prerequisite π,π^* character of the lowest excited singlet to an n,π^* state in the diketone. NMR and mass spectral data provided direct spectrochemical evidence for the trans configuration of the intact 4a,4b-hydrogen atoms, in agreement with orbital symmetry considerations and with recent chemical proof. Time-lapse spectrometric determinations demonstrated the overall transformation to be free of side reactions and to give quantitative conversion to the DHP without further oxidation to the phenanthrene product characteristic of stilbene photocyclizations. The mechanism involves an initial trans ⇌ cis photoisomerization, competitive photocyclization of the cis isomer, and a fast dark tautomerization of the dienol DHP to the isolable dihydrophenanthrenedione product.

Although the photooxidative cyclization of stilbenes (**1**) to phenanthrenes (**4**) is a reaction of remarkable generality and synthetic utility,[2] definitive mechanistic studies have been thwarted by the extreme instability of the proposed intermediate dihydrophenanthrenes (DHP's). These intermediates may often be detected in solution by their visible absorption in the 400–500-nm region, but have heretofore resisted isolation because of rapid oxidative hydrogen abstraction to phenanthrenes or reverse ring opening to starting stilbenes, processes which occur both thermally and photochemically.

Several ingenious, partially successful attempts to prepare stable intermediates have been reported. Muszkat and Fischer[3] photolyzed a hexamethylstilbene to obtain in situ 21% conversion to a "DHP" in which both inner hydrogens were replaced by methyl; the intermediate resisted oxidation but underwent the usual ring opening during attempts at isolation. The same authors achieved 67% conversion in solution upon monochromatic irradiation of fused *cis*-stilbene. Analogous results have been reported by Ramey and Boekelheide.[4] Blackburn et al.[5] reasoned from steric arguments that DHP's prepared from styrylnaphthalenes might have enhanced stability. Their intermediates proved relatively long lived in solution, but were not isolable. Isolation of rearranged, biphenylic, nonoxidized intermediates was described by Sargent and Timmons,[6] but these compounds lacked the true DHP structure, which is characterized by and is chiefly remarkable for the presence of "inner" hydrogens at the 4a,4b positions of the phenanthrene nucleus.



1 **2** **3** **4**

We report the isolation in high yield of a completely stable, true DHP intermediate, obtained upon irradiation of synthetic estrogenic hormone diethylstilbestrol (α,α'-diethyl-4,4′-stilbenediol, DES).[7] Stabilization of this DHP is conferred by a unique self-trapping double enol → keto tau-

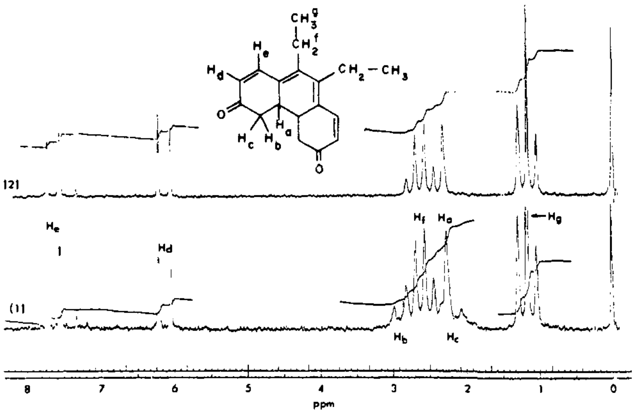


Figure 1. The 60-MHz ^{1}H NMR spectra in $CDCl_3$ of (1) photoproduct **8** and (2) its tetradeuterated derivative.

tomerism. The inner hydrogens remain intact and are accessible, as is the intermediate itself, to detailed stereochemical and mechanistic investigations.

Results and Discussion

Characterization of the DHP. In contrast to the marked instability of DHP's previously described, generation and isolation of photoproduct **8** of diethylstilbestrol **5** presented little difficulty. Irradiation at 254 nm of preparative-scale (0.5 g) solutions of DES led to formation of more than 60% DHP **8** as calculated from changes in the absorbance of diluted aliquots of the reaction mixture and from the molar extinctions of **5** and **8**. On a smaller scale, under optimum conditions employed for investigation of mechanism, conversions of up to 95% were observed. Facile separation of neutral product from phenolic starting material, followed by recrystallization, afforded a 25% overall yield of golden-yellow crystals of DHP **8**. The product is stable indefinitely at room temperature in vacuo, but darkens over several weeks on exposure to air.

Spectrochemical characterization of the ketonic DHP was unambiguous. The mass spectrum exhibited a parent peak at *m/e* 268, isomeric with diethylstilbestrol. Loss of phenolic functional groups was demonstrated by the insensitivity of the electronic spectrum of **8** to alkali and by the disappearance of the hydroxylic bands in the infrared; the ir spectrum showed, instead, an intense band at 1651 cm^{-1}, assigned to highly conjugated carbonyl.

The NMR spectrum of **8** displayed in Figure 1 permitted direct observation of the inner 4a,4b protons; their resonance appeared as a singlet at 2.27 ppm. It is remarkable that this signal is unsplit by either of the adjacent methylene protons. As shown below, this observation is valuable in confirming the stereochemical and conformational details of the DHP photoproduct. The signals corresponding to the methylene protons in the rings appear as multiplets in the 2-3-ppm region, partially obscured by the methylene quartet of the ethyl groups. The signal for the ring methylene protons shows that they are nonequivalent. This is consistent with the presence of a stable, asymmetric conformation. The highly deshielded vinyl protons appeared as a doublet pair centered at 6.1 and 7.6 ppm.

Final structural proof for **8** was obtained from the mass and NMR spectra of tetradeuterated derivative obtained by exchange of the four active protons α to the carbonyl groups by treatment with $NaOCH_3$-CH_3OD. The parent peak and most major peaks in the mass spectrum of **8**-d_4 were shifted higher by four *m/e* units. In the NMR spectrum of **8**-d_4 shown in Figure 1, the singlet at 2.27 ppm was retained. This confirms its assignment to the 4a,4b hydrogens; integration of the 2-3-ppm region demonstrated loss of four protons. The fact that the doublet at 6.1 ppm was sharpened by deuteration confirmed the assignment of the signal to the vinyl protons α to the carbonyl which have lost long-range coupling interaction.

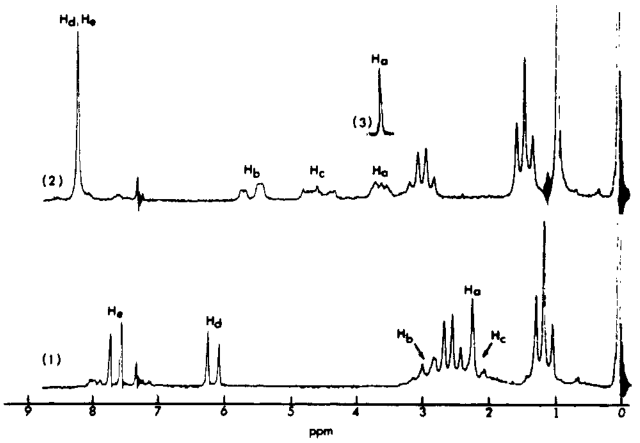


Figure 2. The 60-MHz ^{1}H NMR spectra in $CDCl_3$ of (1) photoproduct **8**, (2) same, containing 1 molar equiv of $Eu(fod)_3$, and (3, inset) the unsplit peak of the inner protons of **8**-d_4, also shifted by $Eu(fod)_3$. For assignments, see Figure 1.

Stereochemistry of Inner Hydrogens. Isolation and characterization of photoproduct **8** as the first example of stable DHP presented a unique opportunity for elucidation of the stereochemistry of the photocyclization reaction. Particularly relevant to this aspect was the stereochemistry of the inner 4a,4b hydrogens. Assuming a concerted reaction in a first excited state, the Woodward-Hoffmann orbital symmetry rules[9] predict a conrotatory cyclization with consequent trans configuration for the 4a and 4b hydrogens. Steric restraints in the formation of substituted dihydrophenanthrenes also favor trans geometry.[3,4] However, reaction from a hot ground state suggested by quantum mechanical calculations[10] would result in cis configuration.

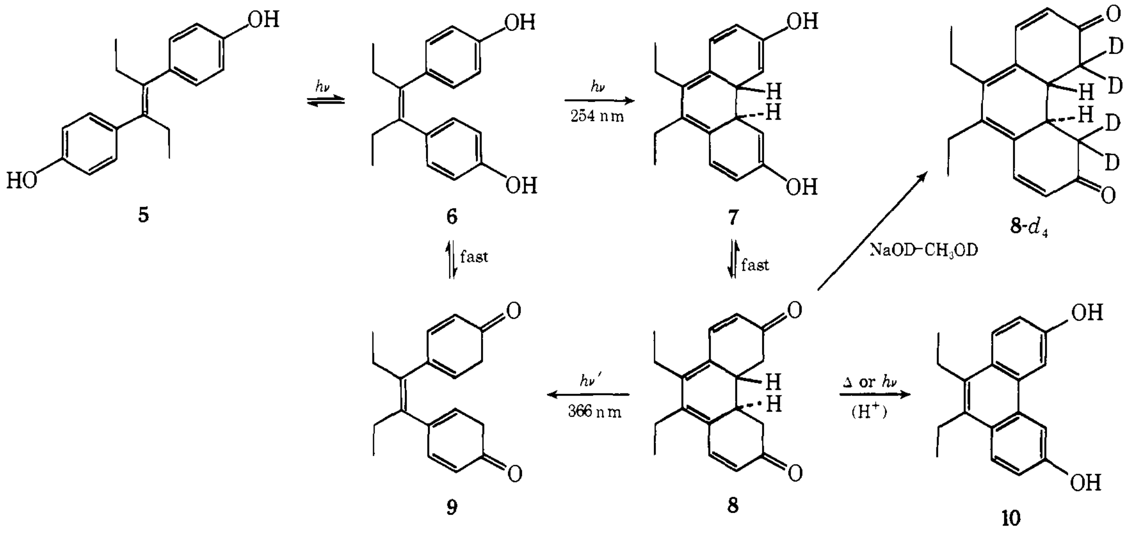
Subsequent to our original communication[7] describing the isolation of the DHP, Cuppen and Laarhoven[11] confirmed the trans configuration by ozonolysis and oxidation of **8** to afford the racemic (rather than meso) butane-1,2,3,4-tetracarboxylic acid.

Detailed examination of the NMR spectra of **8**, **8**-d_4, and their complexes with Siever's shift reagent $Eu(fod)_3$ provided a direct spectrochemical probe on the intact DHP in support of the trans orientation. As is shown in Figure 1, the signal at 2.27 ppm, assigned to the inner H's of **8**, is unsplit by either of the adjacent methylene protons. The two hydrogens of the methylene groups in the ring are themselves nonequivalent, display strong mutual coupling, and appear at approximately 2.3 and 2.9 ppm.

The NMR spectrum of the complex of **8** with $Eu(fod)_3$ displayed in Figure 2 shows the expected downfield shift for all protons. At 1:1 molar ratio, the inner hydrogens were shifted 1.4 to 3.7 ppm; in **8**-d_4 these resonances remained a well-defined singlet, but for nondeuterated **8** the singlet was now split. This demonstrates that coupling with at least one of the adjacent methylene protons was initially degenerate only because of similar chemical shifts.

Absence of coupling between the inner proton and the other adjacent methylenic hydrogen, the one responsible for the signal at 2.9 ppm, is most naturally explained by a mutual orientation involving a dihedral angle of approximately 90° (Karplus' rule[12]). Dreiding models of **8** with cis inner hydrogens clearly indicate that the molecule would have a rigid structure incompatible with this hypothesis. The mea-

Scheme I



sured angles between the inner protons and the two adjacent C-4 protons in the cis configuration were 50 and 170°. In contrast, models of *trans*-**8** indicated a strainless structure in which the outer rings were interconvertible between two conformations. Although one of the possible conformations had angles comparable with those of *cis*-DHP, the other, shown in Figure 3, gave measurements of 20 and 100°. In this conformation, the proton subtending the 100° angle would give negligible coupling. Furthermore, being oriented approximately normal to the plane of the carbonyl group, it should be deshielded. Therefore, its NMR resonance was logically assigned to the 2.9-ppm signal. The other C-4 proton lies in the carbonyl plane, consistent with the assigned 2.3-ppm shift. This value is naturally upfield of "typical" CH$_2$—C=O signals usually found around 2.5 ppm.[13]

The *trans*-DHP structure is therefore in full agreement with the highly unusual singlet resonance of the inner protons, whereas the alternative *cis*-DHP offers no consistency with the observed data.

An additional direct probe for the trans assignment is provided by the mass spectrum of **8**. Mallory et al.[14] had argued that *cis*-DHP would undergo facile exothermic elimination of molecular hydrogen. Recent mass spectral studies of stilbenes and related compounds[15,16] have also associated prominent loss of two *m/e* units from the parent peak with highly probable cis configurations for the 4a,4b hydrogens. It is therefore significant that the mass spectrum of **8** showed only a minor peak (1.3% of M$^+$) at M$^+$ − 2.[17]

Unique Stability of DHP. The mechanistic details for the phototransformation of DES, given in Scheme I, differ from those commonly accepted for photocyclization of stilbenes chiefly because of unique features associated with the presence of the phenolic hydroxyls. The initial cis–trans photoisomerization between **5** and **6** is followed by ring closure of the cis isomer to give the dihydrophenanthrenediol **7**, which immediately tautomerizes to the isolable dihydrophenanthrenedione **8**. The net stabilization due to the double ketonization of enol **7** was calculated on the basis of bond energies to be approximately 37 kcal/mol. Therefore, the equilibrium concentration of dienol **7** is expected to be extremely small, although its presence may be inferred by the observed smooth deuteration of **8** to **8**-d_4.

The stabilization afforded by the self-trapping tautomerism of dihydrophenanthrenediol **7** may be viewed thermodynamically not only from the standpoint of bond energies but also in relation to the reduced tendency of **8** towards rearomatization. The powerful drive to reestablish aromaticity had defeated all previous attempts to obtain isolable DHP's from other stilbenes. Thus, both in the solid state and in neutral solution, **8** is remarkably stable toward oxidation to phenanthrenediol **10**. Prolonged irradiation of solutions of **8** at 254 nm led only to gradual and irreversible disappearance of the DHP, without any detectible formation of **10**. On the other hand, we have observed that the **8** → **10** reaction occurs readily both thermally and photochemically in acid media, in agreement with the results of Hugelshofer et al.[18] who irradiated **5** in glacial HOAc to produce **10** without detection of DHP **8**.

When compared with other DHP's dihydrophenanthrenedione **8** is also remarkably resistant toward the reverse ring opening, with formation of *cis*-stilbenediol **6**. In the present instance, this reaction does not occur in the absence of light: solutions of **8** stored in the dark for several months exhibited no spectral changes. The **8** → **6** reaction was observed to occur photochemically only upon prolonged selective irradiation with long-wavelength ultraviolet or visible light. In contrast, the reverse reaction of typical DHP intermediates is part of a simple photoequilibrium and constitutes a chief frustration during attempts of isolation. The difference is explained naturally by the fact that the ring-opening reaction of enone **8** initially gives a nonaromatic species, the dienone **9**. As shown in Scheme I, the keto-enol tautomerism step present in the DES photocyclization determines a unique lack of identity between the forward and reverse stilbene photocyclization. Therefore, for reasons similar to those conferring resistance to oxidation, the ring-opening reaction of enone **8** lacks the driving force of immediate aromatization.

There is still another possible cause for the absence of the reverse photodecyclization characteristic of all previous photoreactive stilbenes. It has been shown repeatedly[2] that *cis*-stilbene ⇌ DHP reactions proceed through a π,π* lowest excited singlet state.[19] In fact, if the character of the S$_1$ state is changed to an n,π* type, say, by attaching nitro, amino, or acetyl substituents to the stilbene, the photocyclization no longer takes place. One can assume that in the unique case of DHP **8**, which is actually a ketone, the lowest excited singlet state is n,π*. Consequently, the lifetime of the S$_2$ (π,π*) state would be severely shortened by rapid internal conversion to S$_1$, which in turn could be efficiently depopulated by intersystem crossing. Since the formation of the π,π* singlet is presumably required for both cyclization and decyclization, its ephemeral existence in **8** explains the poor efficiency for the reverse, ring-opening **8** → **6** reaction. This possibility remains to be tested.

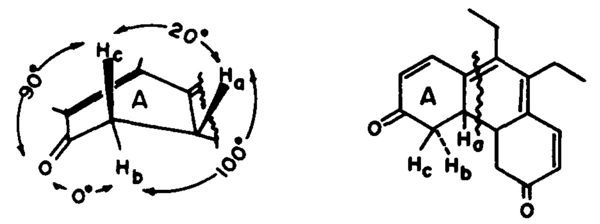


Figure 3. Conformational details derived from molecular models of DHP **8** in which the inner protons are trans.

Time-Lapse Spectrometry. The smooth, regularly incremented progression of the DES → DHP reaction and the stability of the photoproduct are well demonstrated in Figure 4, by the consecutive spectra recorded during the course of successive short irradiations of dilute (10^{-5} M) buffered solutions of DES with 9-W short-wave handlamp. The absorption of the initial reactant, *trans*-diethylstilbestrol (**5**), is shown in scan 1. During photolysis, the maximum at 240 nm decreases gradually and is displaced towards shorter wavelengths, while two other new peaks, with λ_{max} at 292 and 418 nm, appear and increase progressively. The family of curves in Figure 4 pass through a clearly defined isosbestic point at 265 nm.

There are several aspects of the photochemically induced spectral changes shown in Figure 4 which deserve consideration in view of their relevancy to the mechanism. One can notice, for instance, that after the initial 2 min of irradiation the peak at 240 nm has shifted abruptly to 230 nm; the loss of absorbance in this region is considerably greater during this period than during any of the subsequent irradiations and is accompanied by a disproportionately slight increase of absorbance at 418 nm, the long-wavelength absorption maximum for DHP **8**. Since *cis*-DES has λ_{max} in ethanol at 233 nm,[20] this first spectral change is consistent with rapid initial establishment of the cis-trans photoequilibrium for DES. Following this short "induction" period, buildup of absorbance at 418 and 292 nm is rapid and correlates well with the gradual decrease in absorbance attributable to DES in the 220-270-nm region. The isosbestic point maintained at 265 nm throughout the entire process clearly demonstrates the absence of complicating side or consecutive dark or photochemical reactions. In particular, the spectra in Figure 4 suggest that no phenanthrenediol **10** is formed during the irradiation, up to conversions exceeding 85%: there is no identifiable absorption characteristic of **10**. In acid solution, by contrast, the presence of **10** is conspicuous by the appearance of fine vibrational structure characteristic of rigid polynuclear aromatic hydrocarbons in the 250-260-nm region (see Figure 5). As expected, the occurrence of this consecutive reaction is accompanied by loss of isosbestic behavior.

The last absorption spectrum in Figure 4, curve 10, corresponds to a **5** → **8** photoconversion of 86%. In other experiments, under optimized conditions, clean transformation to **8** has exceeded 95%.

Photocyclization of Related Compounds. Tautomerization of both enolic groups appears essential for production of stable DHP's. Dimethylstilbestrol dimethyl ether (**11**) has been reported to give the corresponding phenanthrene, **13**, as the only product. We have been able to detect intermediate DHP **12** only by transient absorbance around 450 nm, observed upon irradiation of concentrated, degassed solutions of **11**. Irradiation of the monomethyl ether **14** produced a slightly less unstable intermediate. Oxidation to **17** was extensive unless oxygen was rigorously excluded from the reaction medium. When 10^{-3} M solutions were degassed through several freeze-pump-thaw cycles, sealed in

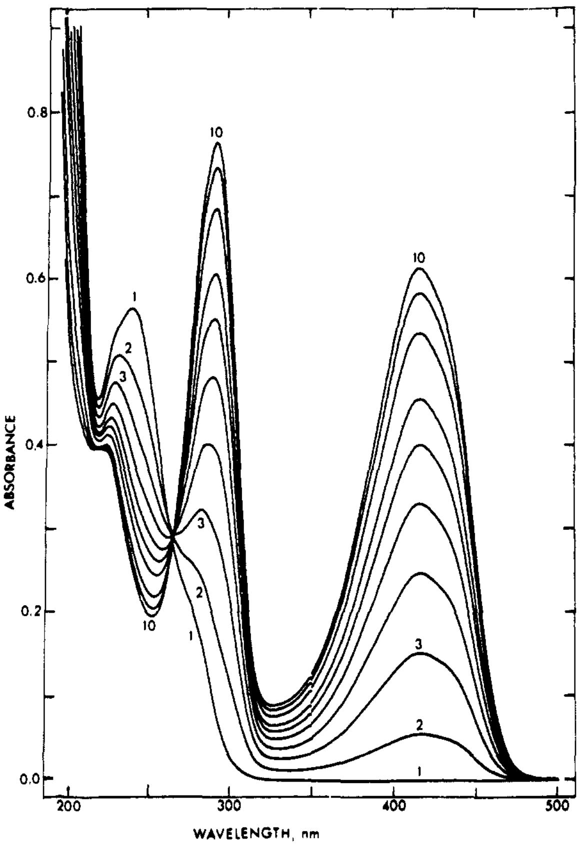


Figure 4. Sequential spectra from irradiation of 10^{-5} M solution of diethylstilbestrol in methanol-aqueous K_2HPO_4. Total irradiation times for scans 1-10 were 0, 2, 4, 6, 8, 10, 12, 16, 20, and 24 min, respectively.

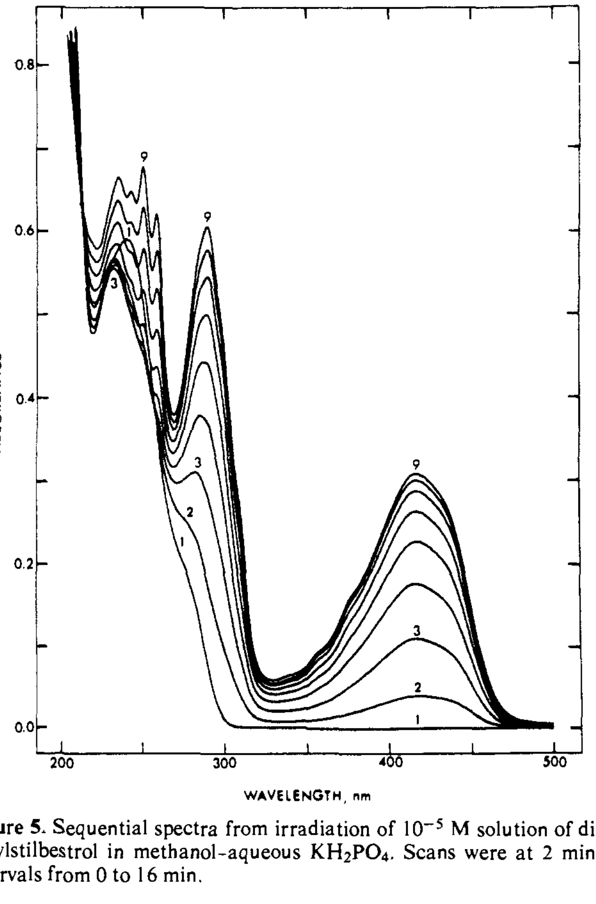
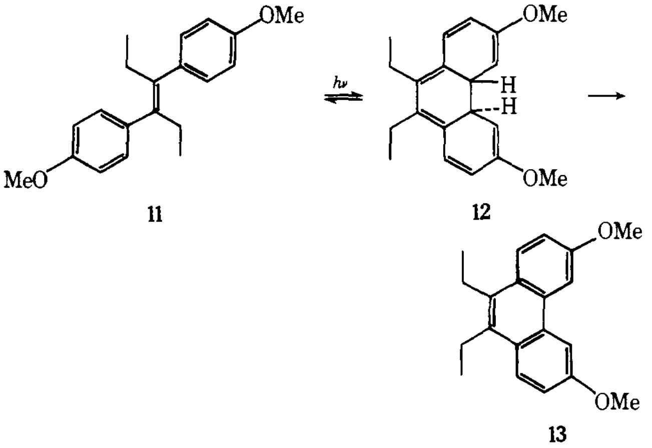
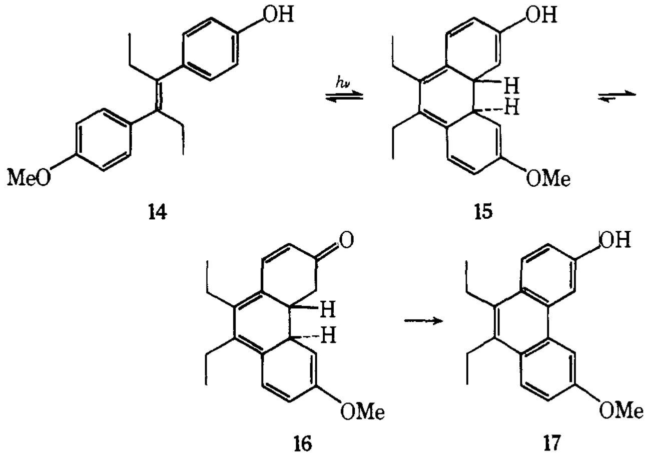


Figure 5. Sequential spectra from irradiation of 10^{-5} M solution of diethylstilbestrol in methanol-aqueous KH_2PO_4. Scans were at 2 min-intervals from 0 to 16 min.





quartz cuvettes, and irradiated at 254 nm, generation of orange species **16** (λ_{max} 458 nm) was observed. The DHP could not be isolated since it underwent smooth first-order decay in the dark to **14** (half-life of **16** was 18.2 min at 24 °C). Irradiation of **16** at 366 nm or exposure to sunlight also led to very rapid disappearance of the orange color. These results parallel the findings of Muszkat and Fischer[3] and of Ramey and Boekelheide[4] that DHP's in which just one inner hydrogen was replaced by methyl remained highly susceptible to both oxidation and reverse reaction. The ease of the thermal ring-opening reaction of **16** suggests that a nonconcerted process is involved in which the driving force is immediate aromatization of one ring of **16.** A concerted thermal ring opening is symmetry disallowed.

Conclusion

Photolysis of the stilbene derivative diethylstilbestrol (DES) led to the isolation of a dihydrophenanthrene (DHP) photoproduct. Since the ephemeral DHP is the key intermediate in the photooxidative cyclization of stilbenes, its isolation and characterization represents a unique opportunity to gain clear insight into the mechanism and stereochemistry of this general reaction.

The unusual stability of the DHP in the case of DES is due to a double keto-enol tautomerism to a tricyclic tetraenedione, which resists both the oxidative rearomatization to phenanthrene and the reverse ring-opening reaction. These two reactions were commonly responsible for the lack of success in numerous previous attempts to isolate DHP's.

Analysis of NMR data from the isolated DHP and from its tetradeuterated derivative confirmed the trans stereochemistry of the inner 4a,4b hydrogens and established a single, strainless conformation for the molecule. This trans configuration deemphasizes the likelihood of a hot ground state as being instrumental in the photocyclization reaction. The presence of nonbonding electrons in the carbonyl groups of the DHP is perhaps responsible for its resistance toward photochemical ring opening by converting the usual π,π^* lowest excited singlet in DHP's to an n,π^* state.

The overall mechanism is consistent with an initial reversible trans $\rightleftharpoons$ cis photoisomerization, with competitive photocyclization of the cis isomer to the DHP from a π,π^* excited singlet state, followed by a fast dark tautomerization of the DHP to an isolable dihydrophenanthrenedione.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 621, ultraviolet spectra on a Cary 15 or Cary 118, NMR spectra on a Varian A-60 or Perkin-Elmer R12B, and mass spectra on an Atlas CH-4 spectrometer. All chemicals were commerically available except for diethylstilbestrol monomethyl ether (**14**), which was prepared by a modification of the procedure reported by Rubin et al.,[8] mp (benzene-hexane) 114–115 °C.

3,4,4a,4b,5,6,-Hexahydro-3,6-dioxo-9,10-diethylphenanthrene (8). A solution of 0.517 g (1.93 mmol) of diethylstilbestrol in 140 ml of methanol and 0.1 M K_2HPO_4 was placed in a 250-ml graduate cylinder cut off at the 210-ml mark. A 6-in., 2.5-W low-pressure Hg lamp (Photochemical Products, San Gabriel, Calif.) was immersed in the solution, which was stirred magnetically and cooled by immersing the graduate cylinder in a water bath at 25 °C. The solution was irradiated for 6 h, during which time the solution changed from colorless to yellow to dark brown. Final bath temperature was about 35 °C. The electronic spectra of diluted aliquots indicated 62.5% conversion to **8.** The solution was stored in the refrigerator overnight and then filtered to separate a brown crystalline deposit which was dissolved in 50 ml of chloroform. The filtrate was extracted with three 50-ml portions of chloroform, and the four chloroform fractions were combined and washed with 100 ml of 0.1 M sodium hydroxide and then with two 50-ml portions of water. After evaporation of the chloroform in vacuo at 40 °C to about 10 ml, addition of 200 ml of isooctane resulted in immediate formation of a fluffy, yellow precipitate. The mixture was stored in the refrigerator overnight and then filtered by suction and air-dried to yield 0.203 g of golden-yellow solid (39% crude **8**). After accumulation of 0.83 g of crude **8**, recrystallization from toluene-heptane (50 and 30 ml) afforded 0.54 g (25%) of dense orange-yellow crystals: mp 200-207 °C dec; ν_{max} (KBr) 1651 cm^{-1} [(C=C)—C=O]; λ_{max} (MeOH) 406, 287, 221 nm (log ϵ 4.29, 4.36, 3.95); NMR τ ($CDCl_3$) 2.38 (2 H, d, J = 10.0 Hz, C*H*=CHCO), 3.86 (2 H, d, J = 10.0 Hz, CH=C*H*CO), 7.1 br and 7.7 br (4 H, m, CH_2CO), 7.38 (4 H, q, J = 7.5 Hz, CH_2CH_3), 7.73 (2 H, s, CH), and 8.84 (6 H, t, J = 7.5 Hz, CH_2CH_3); *m/e* 268 (M^+, 100%), 266 (1.3), 253 (4), 239 (53), 225 (6), 211 (90), 197 (11), 183 (49).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.50. Found: C, 80.72; H, 7.37.

4,4,5,5-Tetradeuterio-3,4,4a,4b,5,6,-hexahydro-3,6,-dioxo-9,10-diethylphenanthrene (8-*d*$_4$). A solution of 0.192 g (0.717 mmol) of **8** was dissolved with gentle warming in 145 ml of methanol-*d*. To this was added a solution of 0.212 g (9.26 mmol) of metallic sodium in 30 ml of methanol-*d*. The clear, orange-yellow solution was stirred at 35 °C for 3 h in the dark. The solution was then diluted with 150 ml of deuterium oxide and extracted with two 25-ml portions of deuteriochloroform. The chloroform was washed with two 50-ml portions of water and filtered; the filtrate was evaporated in vacuo at 40 °C to about 5 ml, and then the residue was diluted with 75 ml of heptane, resulting in precipitation of a fluffy, yellow solid. The mixture was chilled in an icebox, and the precipitate was collected by suction to afford 0.117 g (60% recovery) of yellow **8**-*d*$_4$. Spectra and other properties were identical with that of **8** except that the NMR showed loss of multiplets at τ 7.1 and 7.7, and the mass spectrum had *m/e* 272 (M^+, 100%), 268 (3), 257 (3), 229 (4), 215 (92), 199 (11), 187 (42).

Time-Lapse Spectrometry. Typically, starting materials were at or near a concentration of 3×10^{-5} M. Source of radiation was a Mineralight Model SL (254 nm) or Model LL (366 nm) 9-W handlamp. Solutions were placed in a 1-cm Teflon-stoppered quartz cuvette of 4-ml capacity, irradiated with the lamp flush against the cuvette for intervals timed with a stopwatch, and then scanned directly. When degassing was required, cuvettes were fitted with a graded seal incorporating a 10-ml Pyrex reservoir in which the solution was frozen in liquid nitrogen, evacuated to about 13 μ, and thawed; this freeze-pump-thaw cycle was repeated five or more times; the cuvette was then flame-sealed. Kinetics of the thermal decyclization of **16** was monitored after an initial prolonged irradiation of a degassed solution of **14**.

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Probing the Endo Cavity of Bicyclo[2.2.1]heptane Systems. NH Proton Exchange, Nitrogen Inversion, and Amine Quaternization of *exo*- and *endo*-2-Dimethylaminonorbornane

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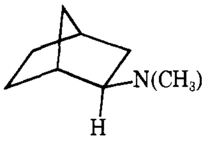
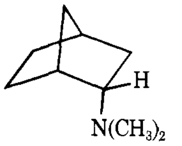
Abstract: We compare the rates of NH proton exchange, nitrogen inversion, and amine quaternization of *exo*- and *endo*-2-dimethylaminonorbornane. The exo and endo compounds do not display substantial differences as would be expected if the *endo*-dimethylamino group were subjected to unusual steric or solvation effects within the endo cavity.

Few observations have roused greater controversy among physical organic chemists than the rapid solvolysis of *exo*-2-norbornyl derivatives relative to their endo isomers. One school believes that the transition state for the exo compounds is *stabilized* by σ participation.[2] The other school maintains that the transition state for the endo derivatives is *destabilized* by steric hindrance to ionization.[3] Our entry into the debate begins here with the proposition that if departure of an endo leaving group is indeed inhibited by special steric or solvation effects, then other functionalities within the endo cavity should display modified behavior as well. In the following article the rates of NH-proton exchange, nitrogen inversion, and amine quaternization of *endo*-2-dimethylaminonorbornane are compared with the corresponding rates of the exo isomer.

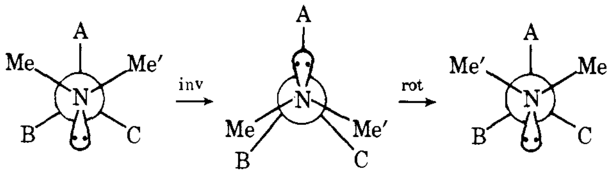


exo-I



endo-I

When *exo*-2-dimethylaminonorbornane (*exo*-I) is dissolved in an aqueous buffer of pH 2.70, the N-CH_3 groups of the protonated amine show a pair of doublets in the NMR (Figure 1A). The methyl groups (which are chemically shift nonequivalent because of the neighboring chiral center) have individual signals, both of which are split by the N proton. At pH 5.77, rapid exchange of the N proton with retention of configuration obliterates the spin-spin splitting, leaving a pair of singlets (Figure 1C). At pH values above 8.5 one observes only a sharp singlet (Figure 1G) because inversion of unprotonated amine destroys the diastereotopic nature of the N-CH_3 groups. As is evident from eq 1, inversion and rotation in either order (but not rotation alone) renders the N-CH_3 groups equivalent.



(1)

NH proton exchange of amines is *inhibited* by hydronium ion.[4] Clearly a *reverse* step in the exchange mechanism must be acid catalyzed (yielding an overall rate expression with H_3O^+ in the denominator). Such a mechanism, first formulated by Grunwald,[5] is given in eq 2; it describes all known proton-exchange reactions of ammonium salts. In ideal cases, each of the three component rate constants can be evaluated from observed rate constants and the pK_a of the amine. Since the rate constants in the mechanism, especially k_H, are sensi-

$$R_3N\mathit{H}^+\cdots OH_2 + H_2O \underset{k_{-a}}{\overset{k_a}{\rightleftarrows}} R_3N\cdots \mathit{H}OH + H_3O^+$$

$$R_3N\cdots \mathit{H}OH \xrightarrow{k_H} R_3N + \mathit{H}OH \qquad (2)$$

$$R_3N + H_3O^+ \xrightarrow{\text{fast}} R_3NH^+$$