(MeOH) 278 nm (ε 3760); NMR ($CDCl_3$) δ 0.92 (3 H, s, 18-CH_3), 0.93 (3 H, d, J = 7 Hz, 11-CH_3), 3.90 (3 H, s, -OCH_3), 6.42 (14, br s, 4-H), 7.95 (1 H, s, 1-H). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.95; H, 9.09; N, 4.51.

The mother liquors from the trituration above were chromatographed over silica gel using benzene–ethyl acetate solution as the eluent. Additional **28** was obtained, eluting with 2% ethyl acetate–benzene solution, and provided another 0.14 g after recrystallization from aqueous alcohol. Upon eluting with ethyl acetate (neat) 0.15 g of **29** was obtained. Recrystallization from ethyl acetate provided the pure compound: mp 181–185 °C; UV (MeOH) 275 nm (ε 3650); NMR ($CDCl_3$) δ 0.89 (3 H, s, 18-CH_3), 0.94 (3 H, d, J = 7 Hz, 11-CH_3), 3.90 (3 H, s, -OCH_3), 6.48 (1 H, br s, 4-H), 8.25 (1 H, br s, 1-H). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.75; H, 8.52; N, 4.39.

Acknowledgment. We acknowledge the assistance of Mr. R. Reuter of our development staff in the preparation of large quantities of the azatetralone and helpful discussions with Dr. R. B. Garland.

Registry No.—**1**, 30182-67-3; **2**, 5682-75-7; **3a**, 64761-52-0; **3b**, 64761-53-1; **3c**, 64761-55-3; **5** (X = CN), 56053-56-6; **6**, 56053-57-7; **7**, 65053-58-8; **9**, 56053-60-2; **10**, 56053-61-3; **11**, 64761-51-9; **12**, 56053-64-6; **13** (14α isomer), 64811-74-1; **13** (14β isomer), 64811-75-2; **14**, 64761-54-2; **15**, 64811-76-3; **18**, 58653-16-0; **19**, 58653-17-1; **20a**, 58653-18-2; **20b**, 64761-56-4; **21**, 58653-19-3; **23**, 58653-20-6; **24**, 64761-57-5; **25**, 64761-58-6; **26**, 64811-77-4; **27**, 64811-78-5; **28**, 64811-79-6; **29**, 64761-59-7; diethyl malonate, 105-53-3; methyl cyanoacetate, 105-34-0; cyanoacetimide, 107-91-5; dimethylformamide diethyl acetal, 1188-33-6; triethyl orthoformate, 122-51-0; methyl iodide, 74-88-4; benzyl chloride, 75-01-4; 2-methyl-cyclopenta-1,3-dione, 765-69-5; 2-bromo-3-dimethylamino-1-propene, 14326-14-8.

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(21) The chemical shift of the 11-methyl group of **26** was identical with that of its analogue in the carbocyclic series (cf. ref 17), where the stereochemistry had been unequivocally established.
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cis-4,4′-Stilbenediols. Synthesis from Dienestrol, Structure, and Photocyclization to Dihydrophenanthrenes

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Diels–Alder cycloaddition reactions between dienestrol or its diacetate and dienophiles maleic anhydride, 4-phenyl-1,2,4-triazoline-3,5-dione, dimethyl maleate, 1,4-naphthoquinone, and tetracyanoethylene yielded adducts representing 4,4′-stilbenediols with obligate cis configuration. These compounds are ideally suited for studying the photochemical conversion of stilbene-like molecules to dihydrophenanthrenes without intereference from the *trans*-stilbene isomers. The structures and stereochemistry of the Diels–Alder adducts were established by detailed interpretation of their NMR and mass spectra. UV irradiation of the synthesized *cis*-stilbenes caused photocyclization to the respective 4a,4b-dihydrophenanthrenes without interfering side reactions and with quantum yields in excess of 0.85.

The photooxidative ring closure of stilbenes to phenanthrenes proceeds through nonoxidized 4a,4b-dihydrophenanthrene (DHP) intermediates.[1] Most previous studies of the mechanism of the photocyclization step have been complicated by simultaneous cis–trans isomerization of starting stilbene, by rapid subsequent oxidation of DHP to phenanthrene, or by reverse ring opening of DHP to *cis*-stilbene. Naef and Fischer[2a] circumvented the cis–trans complication by use of precursor stilbenes[2b,c] constrained to cis conformation by their cyclic structures. These authors also eliminated subsequent oxidation to phenanthrenes by rigorous degassing or by substitution of methyl for hydrogen at the appropriate sites. However, thermal and photochemical ring opening of the DHP's remained a complication; the intermediates could not be isolated, but were observed only in situ in photoequilibrium with precursor stilbenes.

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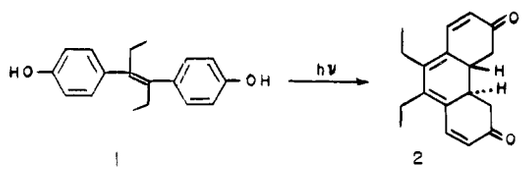
Scheme I



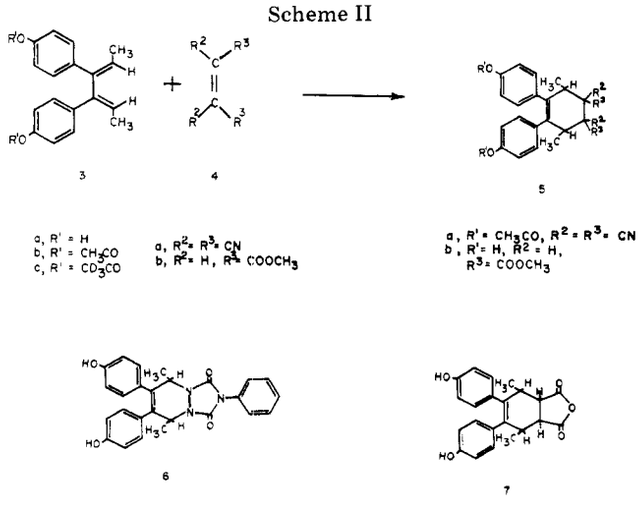
We have previously reported[3] that stilbenes with hydroxy substituents in the para positions of both aromatic rings, such as the estrogenic hormone diethylstilbestrol, undergo photocyclization to DHP's (Scheme I) that can isolated; these are stabilized by double enol–keto tautomerism, are generated quantitatively, are markedly resistant to oxidation, and are only minimally susceptible to ring opening. However, our previous studies of this class were complicated by cis–trans isomerization of the precursor stilbenes, a necessary reaction in the case of diethylstilbestrol.

We now report the synthesis of stilbene-like molecules by Diels–Alder reaction of the estrogenic hormone dienestrol with various dienophiles (Scheme II). The structural features of the resulting adducts are such that photolysis proceeds with complete sequestration of the *cis*-stilbene to DHP reaction, since not only are the adducts constrained to cis conformation, as in the work of Naef and Fischer,[2a] but also stability of the product DHP's is conferred by enol–keto tautomerism, as in our previous studies.[3] The detailed determinations of the structures of the adducts and their photolysis in alcoholic solution are described.

Results and Discussion

The Diels–Alder cycloaddition reactions with **3a** or **3b** readily yielded adducts **5–7**. Since the configuration of **3a** has been determined with accuracy,[4,5] its participation in (4 + 2) multicenter addition reactions is readily understood. The stereospecificity of the concerted Diels–Alder reaction requires that the two methyl groups of **3a** or **3b** be cis in all adducts. Although the phenyl rings in **3a** are twisted out-of-plane with respect to the olefinic bonds, the cis diene moiety is planar and retains the symmetry required for Diels–Alder reactions.[6] Whenever R^2 and R^3 of dienophile **4** are identical, only one adduct can be formed. Thus, single products **6** and **5a** were obtained from the addition of 4-phenyl-1,2,4-triazoline-3,5-dione to **3a** and that of tetracyanoethylene to dienestrol diacetate (**3b**), respectively. Adduct **6** exists in only one form due to inversion of the nitrogen. When substituents R^2 and R^3 are different, however, both endo and exo conformations are possible. Although the reaction of **3a** with maleic anhydride gave only one of the possible conformers, namely, the trans,trans adduct (**7**), the addition of dimethyl maleate yielded both stereoisomers (**5b**), one of which was isolated in a pure state by recrystallization and had a melting point 40 °C above that of the mixture. The reaction of **3a** with 1,4-naphthoquinone also yielded a mixture which, however, could not be resolved.

Scheme II



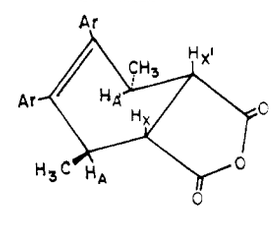
NMR Analysis. In general, the NMR spectra of the adducts followed first-order patterns and showed good agreement with the proposed structures. However, the methine protons in the adducts of **3a** with maleic anhydride, dimethyl maleate, and naphthoquinone and those of **3b** with tetracyanoethylene formed complex spin systems. Therefore, we examined the splitting pattern associated with the methine protons adjacent to the carbonyl groups in **7** as representative of the group.

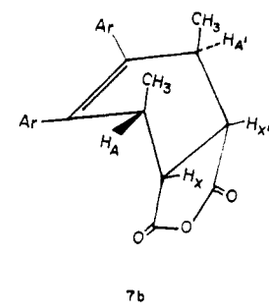
At 60 MHz, these protons generated an apparent quartet in the δ 2–4 spectral region. At 220 MHz, however, two additional weaker lines were observed, one on each side of the quartet. This complex multiplet was analyzed as the XX′ portion of an AA′XX′ system;[7] the other half of the four-spin complex consisted of the two adjacent methine protons which were part of **3a** before cycloaddition. The calculated values of the respective coupling constants were $^3J_{AA'} = 0$, $^3J_{AX} = 6$, $^3J_{AX'} = 0$, and $J_{XX'} = 9$ Hz. A simulated spectrum computed[8] with these values and chemical shifts of δ 2.29 and 3.68 for the A and X hydrogens, respectively, matched the experimentally recorded NMR spectrum.

There is little doubt that the cyclohexene ring of **7** formed in the Diels–Alder reaction is in a boat conformation. The alternate chair conformer has so much strain in the bicyclic moiety that we could not build the molecule with Dreiding molecular models. However, there are two possible boat configurations as the methyl groups can be either both axial (**7b**) or both equatorial (**7a**) (Scheme III). Furthermore, each of the two boat molecules may have the methine hydrogen atoms oriented cis,cis or trans,trans.

In view of the values of the coupling constants computed for the possible conformers, it is most likely that **7** exists in the trans,trans configuration and undergoes rapid ring inversion between the two boat conformers. In fact, a dynamic distribution with predominance of the conformer with axial methyl groups would generate an average $^3J_{AX}$ of 6 Hz, the value used to reproduce the experimental spectrum as described above.

Scheme III





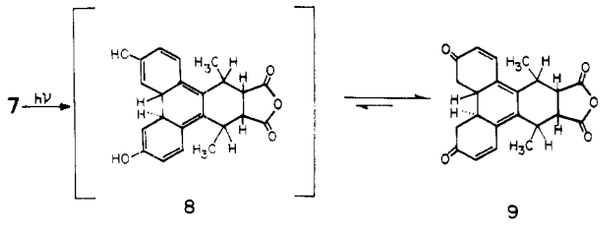
Mass Spectra. Adducts **5–7** showed molecular ions at the expected *m/e* values. With a few exceptions, the ions observed were readily attributable to the expected fragmentation. Three of them, *cis*-stilbenediols **5b, 6,** and **7,** displayed prominent peaks at *m/e* 107, 121, and 145, whereas diacetate **5a** did not. Conceivably, the three diols could undergo a retro-Diels–Alder reaction[9] to produce **3a,** which, in turn, may fragment to give ions at *m/e* 145 and 121. However, since **3a** itself gives an intense molecular ion peak at *m/e* 266 and since such a peak was observed only in the mass spectrum of **6,** the retro-Diels–Alder reaction does not appear to be a major fragmentation pathway in these adducts. Competing processes appear to be more important. High-resolution studies, undertaken to identify the ions, showed that the peak at *m/e* 145 had a composition of $C_{10}H_9O$ and the peaks at *m/e* 121 and 107 corresponded to C_8H_9O and C_7H_7O, respectively. In corresponding ions of **3c,** deuterium replaced a hydrogen. Metastable studies using the direct analyses of daughter ions (DADI) technique indicated that all these ions were formed from the base-peak fragments. Similarly, the ions at *m/e* 159 and 160 also arose from the base peaks of **3b** and **3c,** respectively. Metastable measurements of **5b** and **6** also showed that the ions at *m/e* 159, 145, 121, and 107 arose from the ion at *m/e* 266. Further work is in progress to determine the structures of these ions.

Photolysis. Dilute methanolic solutions of the synthesized *cis*-stilbenediols were irradiated with 254-nm light. The reactions were readily followed by monitoring the changes in the UV absorption spectra after short, consecutive exposures. The observed UV spectral changes demonstrated that the stilbenediol reactants underwent a clean and efficient photocyclization to diketo-DHP's. The reaction sequence is shown for the maleic anhydride adduct **7** in Scheme IV. Formation of DHP's was demonstrated by the appearance of highly characteristic absorbance maxima around 290 and 410 nm, which were virtually identical with maxima recorded for the isolated,[3] stable DHP **2.** The location of the peak at 410 nm agrees well with empirical calculations for the unusual tetraenedione system, but it is lower than that predicted for the transient hexadienediol tautomer **8** and lower also than those observed for various unstable DHP's.[1] A distinct isosbestic point at 253 nm is formed by the family of scans, thus demonstrating the absence of side reactions. By contrast, time-lapse spectrometry diagrams of stilbenes capable of cis–trans isomerization show an initial lack of isosbesticity during the period required to establish the cis–trans equilibrium.[3b] Furthermore, consecutive spectra show that oxidation to phenanthrene is essentially negligible in buffered neutral solutions, as evidenced by both the isosbestic point and the nonappearance of fine structure characteristic of polynuclear aromatic compounds. Phenanthrenes were produced, however, on irradiation of the adducts in acidic solutions. This behavior in acid is analogous[3b] to that of DHP **2.**

As shown in Scheme IV, the geometry of the inner 4a,4b hydrogens of DHP **9** is trans; this has previously been demonstrated[3b,d] and is a result of orbital symmetry requirements.

Solutions of the DHP's were stable indefinitely when stored in the dark. Neither phenanthrene formation nor ring opening to form the starting stilbenes was observed. This, together with the absence of cis–trans isomerization, makes these adducts ideal for study of the uncomplicated photocyclization of *cis*-stilbene to DHP. Preliminary quantum yield determinations for formation of DHP **9** from *cis*-stilbenediol **7** gave consistent values in excess of 0.85. The remarkable efficiency of this phototransformation is in accord with its observed generality and emphasizes its usefulness in both biochemical and chemical systems.

Scheme IV



Experimental Section

NMR spectra were obtained with a Varian Model A-60 spectrometer, using acetone-d_6 as the solvent and tetramethylsilane as the internal standard. A Varian HR-220 spectrometer was also used to obtain the NMR spectrum of **7** at 220 MHz. Mass spectra were obtained on a Varian MAT 311 instrument interfaced to a Varian MAT SS100MS data system. Some of the spectra were plotted by using a Varian Statos 21 electrostatic printer/plotter. The following conditions were used to obtain mass spectra: ionization energy, 70 eV; ionizing electron current, 300 μA; accelerating voltage, 3 kV; source temperature, 200 °C; and multiplier voltage, 2 kV. The samples were introduced by a direct insertion probe that was heated at a rate sufficient to provide usable spectra. The 10 most abundant ions are reported for each spectrum. The UV spectra were recorded on a Cary 15 spectrophotometer.

Dienestrol (3a). NMR δ 1.50 (d, $CHCH_3$, J = 6.5 Hz), 5.37 (q, $CHCH_3$, J = 6.5 Hz), 6.65–7.3 (m, aromatic protons), 8.45 (s, OH); mass spectrum, *m/e* (relative intensity) 266 (100), 251 (50), 237 (36), 121 (31), 145 (25), 267 (22), 107 (22), 210 (14), 236 (13), 252 (11), 173 (11).

Dienestrol Diacetate (3b). Mass spectrum, *m/e* (relative intensity) 266 (100), 308 (84), 350 (56), 251 (47), 237 (35), 267 (21), 249 (21), 265 (20), 121 (20), 351 (15), 145 (15), 43 (15).

Dienestrol Diacetate-d_6 (3c). Mass spectrum, *m/e* (relative intensity) 268 (100), 253 (96), 312 (94), 46 (93), 122 (55), 239 (42), 108 (37), 238 (36), 146 (34), 250 (30).

Dienestrol–Maleic Anhydride Adduct (7). A solution of 2 g of **3a** and 10 g of maleic anhydride in 150 mL of xylene was refluxed for 3 h and then cooled. Heptane was added, and the solution was refrigerated. Crystallization from $CHCl_3$–hexane and vacuum drying yielded 1.8 g of product (66%), mp 190–191 °C; NMR δ 1.12 (d, $CHCH_3$, J = 7 Hz), 2.70–3.20 (m, $CHCH_3$), 3.58–3.81 (m, O=CCH), 6.20–7.10 (m, aromatic), 8.20 (s, OH); mass spectrum, *m/e* (relative intensity) 364 (100), 277 (52), 121 (43), 365 (28), 292 (21), 107 (21), 251 (19), 278 (13), 237 (13), 131 (13).

Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.65; H, 5.46.

Dienestrol–4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (6). The dienophile was first synthesized following the procedure of Stickler and Pirkle[10] and used without actual isolation. A solution of 3 g of phenylurazole in 150 mL of CH_2Cl_2 and 30 g of Na_2SO_4 was stirred at 0 °C while N_2O_4 was introduced. The resulting red solution was concentrated in vacuo to approximately one-third of its original volume, the concentrate was added to a solution of 2.5 g of **3a** in 100 mL of benzene over a period of 45 min with stirring, and the solvent was removed in vacuo. Several crystallizations from MeOH gave 0.4 g of white crystals (10%), mp 253–254 °C; NMR δ 1.55 (d, $CHCH_3$, J = 7 Hz), 3.08 (s, OH), 4.66 (q, $CHCH_3$, J = 7 Hz), 6.55–7.22 (m, aromatic), 7.3–7.7 (m, *N*-phenyl); mass spectrum, *m/e* (relative intensity) 441 (100), 119 (97), 265 (85), 237 (77), 91 (69), 426 (68), 280 (57), 107 (56), 264 (48), 249 (47).

Anal. Calcd for $C_{26}H_{23}N_3O_4$: C, 70.73; H, 5.25; N, 9.52. Found: C, 70.90; H, 5.36; N, 9.26.

Dienestrol Diacetate–Tetracyanoethylene Adduct (5a). A solution of 0.67 g of **3b** and 0.3 g of tetracyanoethylene in 20 mL of benzene was held at room temperature for 12 h and then evaporated. The yield was 0.6 g of **5a** (60%), which was crystallized from MeOH and dried at 100 °C, mp 164–165 °C; NMR δ 1.51 (d, $CHCH_3$, J = 7 Hz), 2.16 (s, O_2CCH_3), 3.85 (brd q, $CHCH_3$, J = 7 Hz), 7.18 (m, aromatic); mass spectrum, *m/e* (relative intensity) 394 (100), 436 (30), 395 (27), 266 (12), 437 (10), 340 (9), 251 (9), 43 (9), 478 (8), 237 (6).

Anal. Calcd for $C_{28}H_{22}N_4O_4$: C, 70.28; H, 4.64; N, 11.71. Found: C, 70.29; H, 4.49; N, 11.42.

Dienestrol–Dimethyl Maleate Adduct (5b). A solution of 5 g of **3a** and 50 mL of dimethyl maleate was refluxed in 200 mL of xylene for 21 h. The solution was cooled and extracted with dilute NaOH. The extract was acidified with dilute H_2SO_4 and extracted with ethyl

ether. The ether extract was washed with water, dried, and evaporated to an oil. When 100 mL of benzene was added, the crystals that formed were collected and washed with 20 mL of benzene. These crystals, weighing 2.7 g (46%), mp 234–237 °C, after crystallization from C_6H_6–MeOH, gave the pure stereoisomer **5b**, mp 240–243 °C; NMR δ 0.98 (d, $CHCH_3$, J = 7 Hz), 2.67 (m, $CHCH_3$), 2.84 (m, O=CCH), 3.68 (two s, CO_2CH_3), 6.50–7.05 (m, aromatic), 7.92 (s, OH); mass spectrum, *m/e* (relative intensity) 291 (100), 350 (55), 410 (37), 107 (31), 292 (25), 59 (25), 121 (23), 145 (18), 351 (17), 290 (17).

Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39. Found: C, 70.06; H, 6.33.

The original benzene filtrate was evaporated, and crystallization of the residue from MeOH–H_2O gave 3.1 g of a mixture which, by both NMR and elemental analysis, appeared to be about 60% product, a mixture of two stereoisomers, and 40% unreacted **3a**. Most of the starting material was removed from the crude product by sublimation at 160 °C, and the residue was crystallized from MeOH–H_2O to give an isomeric mixture, mp 203–204 °C; NMR δ 1.16 (d, $CHCH_3$, J = 7 Hz), 3.00 (m, $CHCH_3$), 3.42 (m, O=CCH), 3.70 (s, CO_2CH_3), 6.50–7.00 (m, aromatic), 7.85 (s, OH); mass spectrum, *m/e* (relative intensity) 350 (100), 121 (49), 291 (41), 351 (39), 410 (32), 107 (23), 244 (17), 59 (16), 292 (10), 276 (10).

Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39. Found: C, 70.18; H, 6.41.

Dienestrol–1,4-Naphthoquinone Adduct. A solution of 3 g of **3a** and 3 g of naphthoquinone in 50 mL of xylene was heated at 150 °C for 4 h. The reaction mixture was cooled to give crystals of unreacted **3a**. The filtrate was diluted with hexane to yield a product which, after several crystallizations from dilute EtOH, gave a small amount of yellow crystals which melted with decomposition at 250 °C. No elemental analysis was obtained. The NMR spectrum indicated that the product was a mixture of two stereoisomers and that no residual **3a** was present. NMR δ 0.89 (d, $CHCH_3$, J = 7 Hz), 1.13 (d, $CHCH_3$, J = 7 Hz), 3.15 (s, OH), 3.30–3.58 (m, $CHCH_3$), 3.76–3.90 (m, $CHCH_3$), 6.44–7.05 (m, aromatic on phenolic rings), 7.90 (m, *o*-phenylene).

Photolysis of Adducts. Typically, starting materials were at or near a concentration of 3×10^{-5} M. A Mineralight Model SL (254 nm) 9-W hand lamp was used as the source of UV radiation. Solutions were placed in a 1-cm Teflon-stoppered quartz cuvette (4-mL capacity), irradiated with the lamp flush against the cuvette for intervals timed with a stopwatch, and then scanned directly in the spectrophotometer. No spectral changes were noted during storage in the dark in the absence of irradiation.

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Registry No.—**3a,** 13029-44-2; **3a**–naphthoquinone (isomer I), 64490-43-3; **3a**–naphthoquinone (isomer II), 64521-02-4; **3b,** 24705-62-2; **3c,** 64490-47-7; **5a,** 64490-48-8; **5b** (isomer I), 64490-49-9; **5b** (isomer II), 64550-40-9; **6,** 64490-50-2; **7,** 64490-51-3; **8,** 64490-52-4; **9,** 64490-53-5; maleic anhydride, 108-31-6; phenylurazole, 15988-11-1; dimethyl maleate, 624-48-6; naphthoquinone, 130-15-4; tetracyanoethylene, 670-54-2.

References and Notes

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Facile Synthesis of Hexahydroapoerysopine via Intramolecular Photoarylation of β-Enamino Ketones

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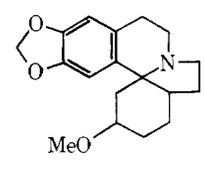
A novel synthesis of hexahydroapoerysopine dimethyl ether (**26**) has been achieved by using photochemical cyclization of β-enamino ketones as a key reaction. The reaction of 3,3a,4,5-tetrahydro-6-methoxy-2*H*-indole (**15**) with 3,4-dimethoxyphenethyl- (**9**) or 2-iodo-4,5-dimethoxyphenethyl iodide (**13**) afforded the corresponding *N*-phenethyl derivatives of 1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one, **17** and **18**, respectively; compound **17** was further brominated to give 7-bromo-1,2,3,3a,4,5-hexahydro-1-(3,4-dimethoxyphenethyl)-6*H*-indol-6-one (**22**). Upon irradiation, the halogenated β-enamino ketones **18** and **22** underwent intramolecular photoarylation and photoreduction, yielding 3,3a-dihydro-2*H*-apoerysopin-1-one dimethyl ether (**21**) and **17**, respectively. Reduction of **21** with $LiAlH_4$ gave the dimethyl ether derivatives of 3,3a,12b,12c-tetrahydro-2*H*-apoerysopin-1-one (**24**) and 2,3,3a,12c-tetrahydroapoerysopine (**25**); the latter was catalytically hydrogenated to 1,2,3,3a,12c,12b-hexahydroapoerysopine dimethyl ether (**26**).

Treatment of tetrahydroerythraline (**1**) under acidic conditions followed by methylation with diazomethane has been reported to yield an optically active base formulated as hexahydroapoerysopine dimethyl ether.[1,2] This reaction has been referred to as the "apo rearrangement".[3] Synthetic routes to such "apo derivatives" possessing the dearomatized ring D are very few in number.[4] We have now devised a new synthesis



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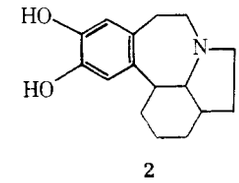

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