Stereospecific Acid-Catalyzed Rearrangements of 5,12-Dimethylpentacyclo[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]dodecane-6,11-diones with Their Strain Release to Bisnordiamantane and Diprotoadamantane Ring Systems

Ken-ichi Hirao,[1a] Mikio Taniguchi,[1a,d] Osamu Yonemitsu,*[1a] Judith L. Flippen,[1b] and Bernhard Witkop[1c]

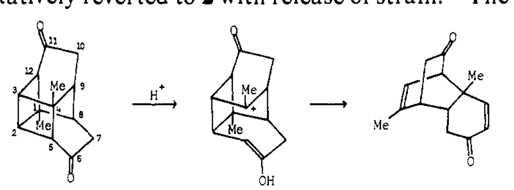
Contribution from the Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan, Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C. 20375, and Laboratory of Chemistry, NIAMDD, National Institutes of Health, Bethesda, Maryland 20014. *Received June 15, 1978*

Abstract: Treatment of 5,7,7,10,10,12-hexamethylpentacyclo[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]dodecane-6,11-dione (**3**) with trifluoroacetic or *p*-toluenesulfonic acid gave a bisnordiamantane (**4**) through two sets of stereospecific twofold Wagner–Meerwein rearrangements, with release of strain, in almost quantitative yield. When the same type of cage compound (**5**), with hydroxy groups instead of methyl groups in positions 7 and 10, was treated under similar conditions, its strain energy was released in a different way to give 10-acetyl-9-hydroxy-3,7,9-trimethyltricyclo[5.2.2.0^{2,6}]undec-10-ene-4,8-dione (**6**) in 70% yield through a series of reactions involving stereospecific Wagner–Meerwein rearrangement, Grob fragmentation, and retro-Michael cleavage. In the case of the third cage compound (**11**), in which two methyl groups at C-7 and C-10 were replaced by chloromethyl groups, half of the molecule of **11** isomerized to a protoadamantane (**14**) in 97% yield, because the electron-withdrawing chlorine changed the final step in the above series of reactions from retro-Michael cleavage to an aldol condensation. Further treatment of **14** with *p*-toluenesulfonic acid quantitatively gave a diprotoadamantane (**15**) through the same rearrangement involving the other half of the molecule. Finally the bisnor cage compound (**16**), lacking methyl groups at C-5 and C-12, on acid treatment gave several products with complete loss of the selectivity characteristic of the acid-catalyzed rearrangements.

When rigid cage systems undergo skeletal rearrangements and bond cleavages these reactions usually reflect steric forces inherent in the special three-dimensional geometry. In a highly strained cage compound release of strain energy triggers the first reaction which then may be followed by energetically favorable processes to give a stable end product. The reaction pathway, as a rule, depends on the nature of the ring system and its substituents, proper selection of which may result in regio- and stereospecific sequential one-step transformations leading to a new ring system inaccessible by conventional synthetic methods. We wish to report a remarkable example of alternative reaction pathways as a result of subtle changes of substituents in a pentacyclododecane system including a synthesis of bisnordiamantane and diprotoadamantane skeletons.

Results

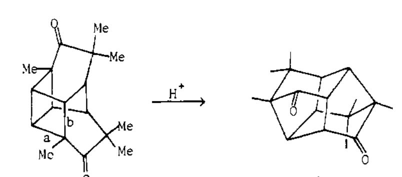
Pentacyclo[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]dodecane-6,11-diones synthesized photochemically via the Diels–Alder dimers (**2**) of cyclohexa-2,4-dienones in high yields[2] have a twofold axis of symmetry and a strained bicyclo[2.2.0]hexane. On treatment with trifluoroacetic acid at room temperature the cage compound **1**, having a methyl group at C-4, readily and almost quantitatively reverted to **2** with release of strain.[2e] The most



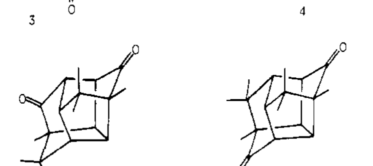
1 1a 2

important requirement for this acid-catalyzed reversion under release of ring strain has been assumed to be the stabilization of a carbocation at C-4 by a methyl group (**1a**).[2e,3] A cage compound having a methyl group at C-5, however, is expected to release most of the strain of its bicyclo[2.2.0]hexane system in a different way, viz., by stabilization of a carbocation at C-5 with a 1,2 shift of either bond a or bond b.

In the event, when 5,7,7,10,10,12-hexamethylpentacyclo[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]dodecane-6,11-dione (**3**)[2c,d,e] was heated in trifluoroacetic acid under reflux for 15 min, or in benzene with *p*-toluenesulfonic acid for 45 min, a different stereospecific rearrangement proceeded quite smoothly to give the isomeric product (**4**) almost quantitatively.[4] That **4** was isomeric with the starting material (**3**) was determined by mass spectrometry and elemental analysis. The carbonyl peak in the IR spectrum of **4** has shifted from 1695 cm^{-1} (six-membered ketone) to 1735 cm^{-1} (five-membered ketone). Both ^{1}H and ^{13}C NMR spectra indicate that **4** has a



3 4



4b 4a

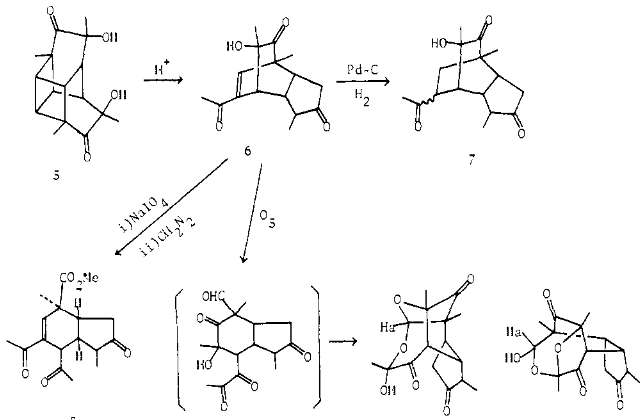
twofold axis of symmetry. Structures **4a** and **4b** are also possible candidates on the basis of mechanistic considerations (vide infra), but **4b** is excluded because of lack of symmetry. Although conventional spectral data fail to distinguish between **4** and **4a**, their dipole moments must differ; the estimated value for **4** is ca. 4.0 D, and for **4a** 0.0 D. The observed value, ca. 4.2 D, clearly proves the bisnordiamantane (**4**) to be the correct structure, a conclusion confirmed by X-ray analysis.[5]

Introduction of hydroxyls into C-7 and C-10 is expected to initiate and facilitate Grob fragmentation[6] with the formation of another ring system. Indeed, when **5**[2e] was heated in trifluoroacetic acid under reflux for 1 h, the isomeric product (**6**) was obtained in 70% yield. The structure of **6** was determined

0002-7863/79/1501-0408$01.00/0

by spectral data, chemical reactions, and finally by X-ray analysis.

The IR spectrum of **6** has three carbonyl groups, five-membered ketone (1730 cm^{-1}), six-membered ketone (1710 cm^{-1}), and enone (1660 cm^{-1}), and a hydroxyl group (3450 cm^{-1}), which must be tertiary because it is resistant both to Oppenauer and manganese dioxide oxidations. The ^{1}H NMR

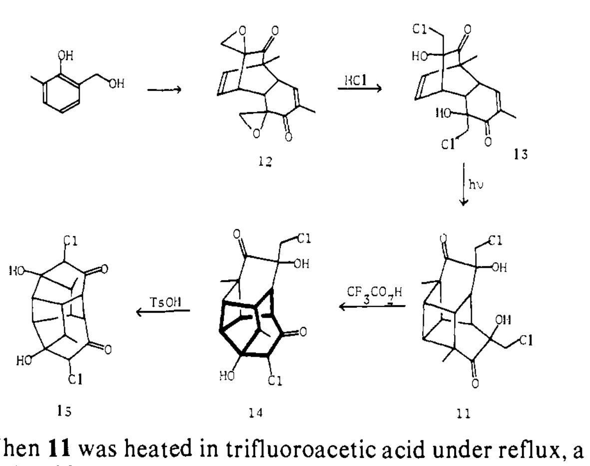


5 6 7 8 10 9 9a

spectrum shows that the four methyl groups of **6** belong to an acetyl, a secondary methyl, and two tertiary methyl groups; a vinyl proton appears as a doublet.

On catalytic reduction with Pd/C, **6** gave a dihydro compound **7**, lacking the vinyl proton in its NMR spectrum. Because **6** has an α-ketol group, it consumed 1 mol of sodium metaperiodate and changed to a keto acid, which was converted to its methyl ester (**8**). Ozonolysis of **6** in dichloromethane at -78 °C, after treatment with dimethyl sulfide, gave a recyclized product (**9**) arising from an initially formed keto aldehyde (**10**). Spectral data and mechanistic considerations support both structures **9** and **9a**. If **9a** were correct, acetylation of the hydroxyl group should shift the NMR signal Ha (δ 5.18) by at least 1 ppm in the downfield direction. The observed shift, however, is only 0.17 ppm, showing the correct structure to be **9**. These data, in conjunction with the ^{13}C NMR spectrum, prove the structure of **6**, which was finally confirmed by X-ray analysis.[5]

Our third substrate for the acid-catalyzed transformation of the pentacyclododecane system was compound **11**, which has electron-withdrawing chloromethyl groups at C-7 and C-10 instead of methyl groups. The Diels–Alder dimer (**12**), prepared from 3-methylsalicyl alcohol with aqueous sodium periodate,[7] was treated with hydrochloric acid to give **13**. On irradiation with a high-pressure mercury lamp with a Pyrex filter in the presence of cyclohexadiene, **13** was readily converted to **11**.



12 13 15 14 11

When **11** was heated in trifluoroacetic acid under reflux, a smooth acid-catalyzed rearrangement again took place to give

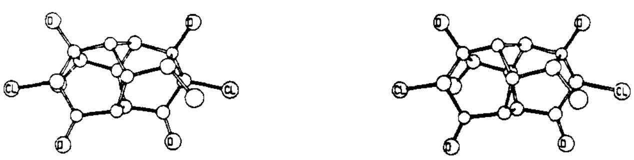


Figure 1. Stereodrawing of the structure of compound **15**.

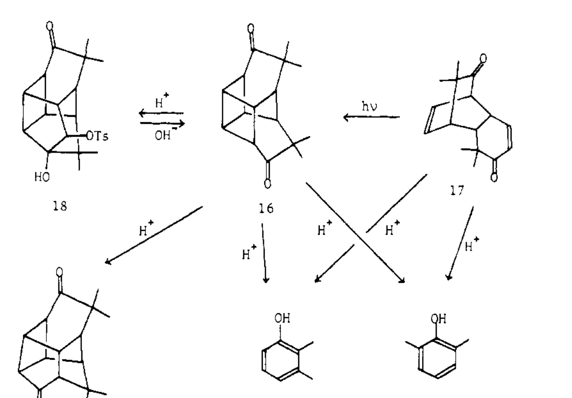
quantitatively the isomeric product (**14**). Treatment of **11** with p-toluenesulfonic acid in refluxing benzene for a short time also gave **14**. The spectral data of **14** are quite complex but indicative of the fact that half of the starting molecule (**11**) remains unchanged.

When the "semirearrangement" product **14** was further heated in benzene with excess p-toluenesulfonic acid for 5 h, the intact other half of the molecule rearranged quantitatively to give **15**, isomeric with **11** and **14**. The spectral data show **15** to be a symmetrical molecule. In the NMR spectrum, two methyl groups appear at the same position of δ 0.86 as a doublet, and two methine protons of α-chloro ketone groups at δ 5.25 as a singlet. Although the ^{13}C NMR spectrum and mechanistic considerations reveal the correct structure to be a diprotoadamantane (**15**) with a twofold axis of symmetry, an unequivocal proof was provided by X-ray analysis.

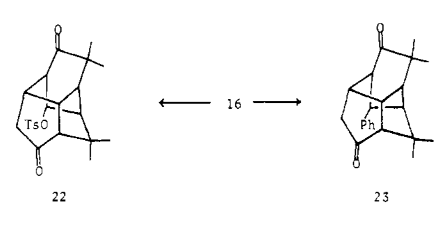
Compound **15** crystallizes in the orthorhombic space group *Pbac* with one molecule of water per asymmetric unit. Cell dimensions are a = 13.523 (9), b = 27.527 (4), and c = 8.594 (6) Å. There are eight molecules per unit cell corresponding to a calculated crystal density of 1.50 g/cm^3. The structure was solved by the symbolic addition procedure for centrosymmetric crystals[8] and the results with an R factor of 0.079 are displayed in Figure 1.

The molecule itself possesses noncrystallographic twofold symmetry. All bond lengths and angles lie within normal ranges. The crystal packing is influenced by the presence of hydrogen bonding which involves a water molecule as well as the adamantane molecule itself. The water participates in two hydrogen bonds as a donor and in a third as an acceptor. In addition there is an intermolecular hydroxyl to carbonyl hydrogen bond. Coordinates, thermal parameters, and tables of bond lengths and angles are described in the Experimental Section.

Finally, the bisnor compound **16** having no methyl groups for the stabilization of a carbocation at C-4 and C-5 was



18 16 17 19 20 21



22 16 23

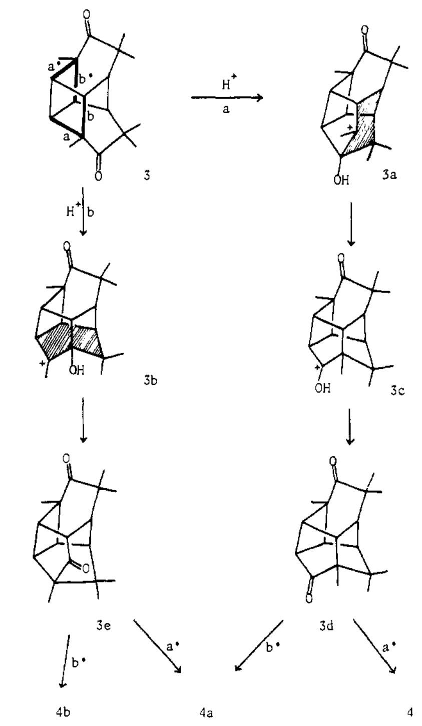
subjected to acid conditions. Compound **16** was synthesized photochemically in a high yield from the corresponding Diels–Alder dimer (**17**).[9] When **16** was heated in trifluoroacetic acid under reflux, it was completely recovered, but when **16** was heated with *p*-toluenesulfonic acid in refluxing benzene for a long time (38 h), the tosylate (**18**) accompanied by the isomeric product (**19**) and a small amount of a 4:1 mixture of 2,3-dimethylphenol (**20**) and 2,6-dimethylphenol (**21**) was isolated. The spectral data show **18** to be the tosylate formed by Wagner–Meerwein rearrangement of bond a in one moiety of **16**. On treatment with potassium hydroxide in aqueous ethanol, **18** readily reverted to **16** indicating the correct structure of **18**. Compound **19**, having the composition $C_{16}H_{20}O_2$ isomeric with that of the starting material, is the product of a twofold Wagner–Meerwein rearrangement, which was obtained in a high yield when **16** was heated with *p*-toluenesulfonic acid in a steel bomb.

Under more drastic conditions, viz., heating with excess *p*-toluenesulfonic acid in a bomb, unfortunately the other half of **16** did not rearrange to give a bisnordiamantane, but cleaved instead to yield a mixture of another tosylate (**22**) and the product (**23**) produced by nucleophilic attack of *p*-toluenesulfonic acid and benzene, respectively.

Discussion

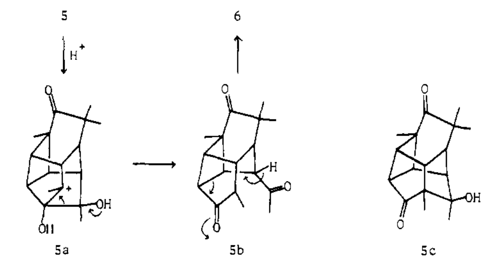
Because of the presence of a methyl group at C-5, protonation of one of the carbonyl groups in **3** leads to the formation of the methyl-stabilized carbocation at C-5 through a 1,2 shift of either bond a or bond b with release of strain in one of two four-membered rings. Since there is no clear difference with regard to geometrical requirements for the 1,2 shifts involving these two bonds on model inspection, the favored rearrangement of bond a must be expressed in terms of difference in stability between the rearranged cations **3a** and **3b**, both of which arise by conversion of the strained four-six-six-membered ring system to the more stable five-five-six system. The cationic six-membered ring in **3a** (shaded part) is present in a less strained normal chair conformation, whereas in **3b** the chair conformation is strongly distorted by a directly fused four-membered ring, destabilizing structure of **3b**.

On the basis of empirical force field calculations, Osawa recently reported that **3a** is the most stable among six possible



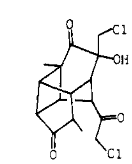
cationic species derived from the protonated starting material by one 1,2 shift and the energetic advantage of **3a** over **3b** was calculated to be ca. 15 kcal/mol.[10] The cation **3a** must readily isomerize to the OH-stabilized carbocation **3c**, which, though unfavorable with respect to stability of the ring skeleton itself, is easily deprotonated to the product of a twofold Wagner–Meerwein rearrangement **3d.**[11] There are some precedents of such rearrangements in simpler cases involving propellanones[12] and spiranones.[13] Another set of analogous twofold rearrangements involving bond a′ occurs in the other half of the molecule to give the bisnordiamantane (**4**). Again the rearrangement of bond a′ is more favorable by 11 kcal/mol than that of bond b′.[10]

Because the rearrangement of **3a** to **3c** is not necessarily a favorable process, the reaction process changes from rearrangement to Grob fragmentation when a hydroxyl group is present at C-7, e.g., **5** gives **5b** rather than **5c.** In this case, the



strain in the other half of the molecule is released in a different way via retro-Michael cleavage to give a completely different type of compound, **6**.

When **11** which has chloromethyl groups at C-7 and C-10 instead of methyl groups is treated with refluxing trifluoroacetic acid, half of the molecule of **11** isomerized to a protoadamantane (**14**), with partial release of strain of the bicyclo[2.2.0]hexane system. Again only bond a rearranges to form a carbocation at C-5, followed by Grob fragmentation. In this case, however, the electron-withdrawing substituent, chlorine, alters the final process of the acid-catalyzed rearrangement from retro-Michael cleavage (**5b** → **6**) to an aldol condensation (**5d** → **14**). Under more drastic conditions, the other half of

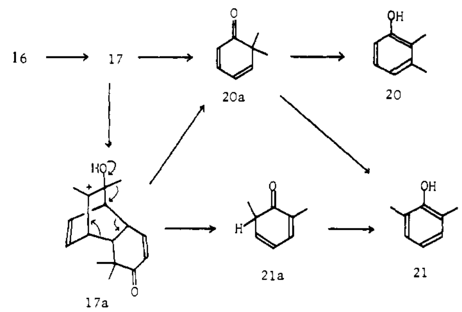


5d

the molecule undergoes the analogous rearrangement to give the diprotoadamantane (**15**).

Finally, **16** was chosen as a reference compound for these acid-catalyzed reactions initiated by the formation of methyl-stabilized carbocations. The absence of a methyl group at either C-4 or C-5 results in a decrease in both reactivity and selectivity, e.g., **16** is resistant to the action of trifluoroacetic acid, but on treatment with a stronger acid, anhydrous *p*-toluenesulfonic acid, both the acid-catalyzed cycloreversion with cleavage of bond b and the Wagner–Meerwein rearrangement of bond a take place simultaneously.

The formation of the two phenols (**20, 21**) can be explained as shown in the following scheme. The acid-catalyzed cycloreversion gives the Diels–Alder dimer (**17**), which must be the key intermediate en route to the phenols, because a mixture of the same ratio of phenols was obtained when **17** was heated under the same conditions. Compound **17** probably undergoes thermal retro-Diels–Alder reaction to give the monomeric cyclohexadienone (**20a**), which readily isomerizes to the two phenols.[14] Another pathway involving an acid-catalyzed twofold 1,2-methyl shift via **17a** may occur simultaneously to form **21**, because the sulfuric acid catalyzed isomerization of



20a was reported to give essentially pure 2,3-dimethylphenol (**20**) accompanied by less than 1% 2,6-dimethylphenol (**21**).[14]

Experimental Section

Acid-Catalyzed Reaction of 5,7,7,10,10,12-Hexamethylpentacyclo[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]dodecane-6,11-dione (3). 4,8,9,9,12,12-Hexamethylpentacyclo[6.3.0.1^{4,11}.0^{2,6}.0^{5,10}]dodecane-3,7-dione (4). A solution of **3** (272 mg, 1 mmol) and anhydrous TsOH (280 mg, 1.6 mmol) in benzene (50 mL) was heated under reflux for 45 min. The solution was washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and evaporated in vacuo to leave **4** (one spot on TLC) almost quantitatively. Recrystallization from hexane gave 238 mg (87.5%) of colorless prisms: mp 182–184 °C; IR (Nujol) 1735 cm^{-1}; MS *m/e* 272 (M^+), 257, 229, 149; ^{1}H NMR ($CDCl_3$) δ 0.84 (6 H, s), 0.96 (6 H, s), 1.03 (6 H, s), 2.38 (4 H, m), 2.48 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 11.6 (q), 20.6 (q), 26.8 (q), 48.4 (s), 52.2 (d), 53.8 (d), 57.2 (s), 57.5 (d), 211.7 (s). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.39; H, 8.87.

Dipole Moment of 4. Dielectric constants and densities of various concentrations of **4** in benzene were measured at 6.4, 23.0, and 38.0 °C. The dielectric constant measurements were conducted with a transformer bridge (TR-1B transformer bridge, Ando Electric Co. Ltd., Tokyo) in conjunction with a HP 4403A function generator (Yokogawa-Hewlett-Packard) and GC box (Ando Electric Co., type YS-1) operating at 3 kHz. The densities were measured in the usual pycnometers. The results are summarized in Table I. The dipole moment which was calculated by the method of Halverstadt and Kumler[15] was 4.2 D.

Acid-Catalyzed Reaction of 7,10-Dihydroxy-5,7,10,12-tetramethyl[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]dodecane-6,11-dione (5). 10-Acetyl-9-hydroxy-3,7,9-trimethyltricyclo[5.2.2.0^{2,6}]undec-10-ene-4,8-dione (6). A solution of **5** (276 mg, 1 mmol) in trifluoroacetic acid (TFA, 10 mL) was heated under reflux for 1 h and then concentrated. To a MeOH solution of the residue was added 10% Na_2CO_3, and the solution was stirred for 2 h at room temperature. After evaporation of the MeOH, the aqueous layer was extracted with $CHCl_3$. The extract was dried and evaporated to leave a pale orange solid, which was recrystallized from EtOAc to give 195 mg (70%) of **6**: mp 179–181 °C; IR (Nujol) 3450, 1730, 1710, 1660, 1610 cm^{-1}; UV (EtOH) 227 nm (ε 5000), 249 (3300), 314 (600); ^{1}H NMR ($CDCl_3$) δ 1.10 (3 H, d, J = 7 Hz), 1.33 (3 H, s), 1.40 (3 H, s), 1.5–2.8 (6 H, m), 2.34 (3 H, s), 3.72 (1 H, t, J = 2 Hz), 6.73 (1 H, d, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6 (q), 15.5 (q), 23.4 (q), 24.9 (q), 38.6 (d), 39.9 (t), 44.0 (d), 44.7 (d), 46.2 (d), 53.3 (s), 70.9 (s), 139.6 (d), 147.7 (s), 195.5 (s), 211.0 (s), 216.3 (s). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.42; H, 7.34.

10-Acetyl-9-bromoacetyl-3,7,9-trimethyltricyclo[5.2.2.0^{2,6}]undec-10-ene-4,8-dione (6′). To a benzene (10 mL) solution of **6** (60.7 mg, 0.22 mmol) was added pyridine (120 mg) and bromoacetyl bromide (93.4 mg, 0.46 mmol), and the solution was stirred at room temperature. After 2 days, the solution was diluted with benzene, washed with 5% HCl and saturated NaCl, dried over Na_2SO_4, and evaporated. The residue was recrystallized from EtOAc–hexane to give 34 mg (38%) of colorless prisms: mp 148–150 °C; IR (Nujol) 1730, 1670, 1620 cm^{-1}; MS *m/e* 398, 396 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.12 (3 H, d, J = 7 Hz), 1.42 (3 H, s), 1.66 (3 H, s), 2.34 (3 H, s), 1.1–2.6 (5 H, m), 3.62 (2 H, s), 4.36 (1 H, t, J = 2 Hz), 6.88 (1 H, d, J = 2 Hz). Anal. Calcd for $C_{18}H_{21}O_5Br$: C, 54.40; H, 5.30; Br, 20.15. Found: C, 54.50; H, 5.45; Br, 20.06.

10-Acetyl-9-hydroxy-3,7,9-trimethyltricyclo[5.2.2.0^{2,6}]undecane-4,8-dione (7). A MeOH (25 mL) solution of **6** (472 mg) was hydrogenated in the presence of 10% Pd/C (126 mg) at ordinary pressure for 1 h. After removal of the catalyst, the solvent was evaporated and the residue was dissolved in $CHCl_3$. A small amount of insoluble material was removed by filtration, the filtrate was concentrated, and the residue was recrystallized from EtOAc–hexane to give 215 mg of colorless prisms of **7**. The mother liquor was passed through a short column of silica gel to give 250 mg of colorless oil (one spot on TLC), which was recrystallized from EtOAc–hexane to give 60 mg of colorless prisms (total yield, 275 mg, 58%): mp 155–172 °C; IR (Nujol) 3400, 1740, 1715, 1680 cm^{-1}; MS *m/e* 278 (M^+); UV (EtOH) 214, 287 nm (ε 58). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.16; H, 7.98.

Table I. Dielectric Constants (ε) and Densities (*d*) of Various Molar Fractions of **4** in Benzene

molar fraction × 10^4	temp, °C	ε	*d*
5.12	6.4	2.256	0.8936
	23.0	2.233	0.8749
	38.0	2.211	0.8608
15.2	6.4	2.276	0.8947
	23.0	2.271	0.8772
	38.0	2.246	0.8615
31.5	6.4	2.335	0.8954
	23.0	2.324	0.8786
	38.0	2.302	0.8623
47.0	6.4	2.388	0.8963
	23.0	2.346	0.8793
	38.0	2.346	0.8635
64.1	6.4	2.462	0.8975
	23.0	2.430	0.8805
	38.0	2.389	0.8650

6,7-Diacetyl-1,4α-dimethyl-4β-methoxycarbonyl-3a,4,7,7a-tetrahydroindan-2-one (8). To an acetone (6 mL) solution of **6** (162 mg) was added $NaIO_4$ (1.5 g) in H_2O (10 mL), and the solution was stirred at 50 °C for 1.5 h. After evaporation of the acetone in vacuo, the residual aqueous layer was alkalified with 10% Na_2CO_3, extracted with $CHCl_3$ to remove **6**, acidified with HCl, and then extracted with EtOAc. The extract was dried and evaporated to leave 120 mg of crude acid: IR ($CHCl_3$) 3600–2300, 1730, 1700, 1665 cm^{-1}. The acid was dissolved in a small amount of MeOH and treated with excess CH_2N_2 in ether for 10 min. After evaporation of the solvent, the residue was purified by preparative silica gel TLC (EtOAc–hexane, 2:1) to give 74 mg (41.5%) of **8**. Recrystallization from EtOAc–hexane gave colorless prisms: mp 106–108 °C; IR (Nujol) 1735, 1725, 1710, 1670 cm^{-1}; MS *m/e* 306 (M^+); ^{1}H NMR (CCl_4) δ 1.14 (3 H, d, J = 7 Hz), 1.37 (3 H, s), 2.09 (3 H, s), 2.31 (3 H, s), 1.5–2.5 (3 H, m), 2.6–3.3 (3 H, m), 3.72 (3 H, s), 6.75 (1 H, s). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.36; H, 7.20.

Ozonolysis of 6. A dry ice–acetone cooling solution of **6** (300 mg) in CH_2Cl_2 (20 mL) was ozonized by bubbling O_3 through the solution for 1 h. The O_3 was replaced by N_2, and bubbling was continued for 30 min to remove excess O_3. After dimethyl sulfide (0.5 mL) was added, the solution was allowed to warm gradually to room temperature and then allowed to stand for 5 h. Evaporation of the solvent left an oil, which was chromatographed on a silica gel column and eluted with $CHCl_3$ to give 169 mg (50.5%) of fine, colorless prisms of **9**: mp 208 °C dec; IR (Nujol) 3230, 1730, 1710 cm^{-1}; MS *m/e* 308 (M^+); ^{1}H NMR ($CDCl_3$–CD_3OD) δ 1.18 (3 H, d, J = 7 Hz), 1.20 (3 H, s), 1.47 (6 H, s), 1.7–2.7 (6 H, m), 5.18 (1 H, s); ^{1}H NMR (Me_2SO-d_6) δ 1.04 (3 H, s), 1.04 (3 H, d, J = 7 Hz), 1.31 (6 H, s), 5.29 (1 H, s), 7.36 (1 H, s). Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.25; H, 6.51.

Acetate of 9. A pyridine (2 mL) solution of **9** (56 mg) and Ac_2O (254 mg) was allowed to stand at room temperature for 30 h. The reaction mixture was dissolved in EtOAc, washed with 10% Na_2CO_3, 1 N HCl, and saturated NaCl, dried (Na_2SO_4), and evaporated to leave an oil (one spot on TLC): ^{1}H NMR ($CDCl_3$) δ 1.15 (3 H, d, J = 7 Hz), 1.23 (3 H, s), 1.54 (6 H, s), 2.17 (3 H, s), 5.35 (1 H, s).

6,9-Bis(chloromethyl)-6,9-dihydroxy-1,4-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-3,11-diene-5,10-dione (13). To a stirred aqueous solution (1.5 L) of $NaIO_4$ (32.1 g, 0.15 mol) was added dropwise 3-methylsalicyl alcohol (17.88 g, 0.13 mol) at room temperature. After the stirring was continued for 2 h, the reaction mixture was cooled to

Table II. Fractional Coordinates for the Nonhydrogen Atoms of **15**[a]

atom	x	y	z
Cl	0.0880 (1)	−.0232 (0)	0.2333 (2)
O1	0.2895 (3)	0.0127 (1)	0.3071 (5)
O2	−.0495 (3)	0.0547 (1)	0.3616 (5)
C1	0.1183 (4)	0.0242 (2)	0.3708 (7)
C2	0.0507 (4)	0.0683 (2)	0.3549 (7)
C3	0.0715 (4)	0.1021 (2)	0.4981 (8)
C4	0.1729 (4)	0.0944 (2)	0.5723 (7)
C5	0.2488 (4)	0.0863 (2)	0.4421 (6)
C6	0.2257 (5)	0.0374 (2)	0.3638 (7)
C7	0.0728 (4)	0.1021 (2)	0.2109 (7)
C8	0.1115 (6)	0.0785 (2)	0.0618 (7)
ClA	0.3028 (1)	0.2507 (0)	0.5722 (2)
O1A	0.3860 (3)	0.1764 (1)	0.3685 (5)
O2A	0.0958 (3)	0.2161 (1)	0.6415 (4)
C1A	0.2316 (4)	0.2079 (2)	0.4617 (7)
C2A	0.1506 (4)	0.1813 (2)	0.5549 (7)
C3A	0.0852 (4)	0.1539 (2)	0.4339 (6)
C4A	0.1381 (4)	0.1428 (2)	0.2804 (7)
C5A	0.2438 (4)	0.1276 (2)	0.3139 (6)
C6A	0.2990 (5)	0.1712 (2)	0.3813 (7)
C7A	0.1877 (4)	0.1415 (2)	0.6683 (7)
C8A	0.2846 (6)	0.1461 (2)	0.7450 (8)
H_2O	0.0486 (3)	0.2898 (1)	0.4540 (5)

[a] The standard deviations, given in parentheses, are based solely on the least-squares results.

Table III. Thermal Parameters for the Nonhydrogen Atoms

atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	5.17	2.57	4.48	−0.81	−0.01	−0.66
O1	4.00	2.32	5.16	0.28	0.69	−0.70
O2	2.48	3.78	4.52	−0.53	0.43	0.37
C1	3.41	1.93	3.47	0.20	−0.10	−0.55
C2	2.41	2.83	2.83	−0.12	−0.18	0.39
C3	2.67	2.44	3.82	0.22	0.38	0.22
C4	3.53	1.91	3.05	0.51	−0.04	0.46
C5	2.61	2.28	2.78	0.11	0.35	0.19
C6	3.38	1.96	2.96	0.82	0.20	0.46
C7	3.75	2.34	3.46	0.15	−0.38	0.17
C8	6.82	3.70	2.57	−1.32	−0.19	0.56
ClA	4.61	2.47	4.26	−0.29	0.02	−1.18
O1A	2.73	3.40	6.03	0.00	0.52	−0.86
O2A	4.76	3.25	2.81	1.48	1.68	−0.58
C1A	3.51	2.34	3.19	−0.22	0.17	−0.56
C2A	3.87	2.66	2.85	0.45	0.92	−0.03
C3A	2.58	2.81	2.15	0.43	0.14	0.26
C4A	3.58	1.92	2.26	−0.09	−0.42	0.57
C5A	2.66	1.83	2.25	−0.19	0.55	−0.34
C6A	2.23	3.42	2.94	0.60	0.80	0.73
C7A	3.66	2.52	2.74	0.54	−0.03	0.40
C8A	6.27	2.94	4.03	0.96	−1.62	−0.27
H_2O	4.43	4.62	3.33	1.22	0.62	0.76

4 °C and allowed to stand for 2 h at the same temperature. The precipitated crystals were filtered and dried in a desiccator to give 11.2 g of the crude epoxide (**12**),[7] which was dissolved in dioxane (300 mL) and concentrated HCl (10 mL). The solution was stirred for 4 h at room temperature, and then concentrated in vacuo to leave a solid, which was recrystallized from EtOAc to give 9.8 g (69%) of fine prisms of **13**: mp 200–202 °C; IR (Nujol) 3475 (sh), 3425, 1710, 1682 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.27 (3 H, s), 1.78 (3 H, s), 3.49 (2 H, s), 2.9–3.5 (3 H, m), 3.56 (1 H, d, J = 10 Hz), 3.76 (1 H, d, J = 10 Hz), 5.38 (1 H, s), 5.58 (1 H, dd, J = 2, 9 Hz), 6.13 (1 H, s), 6.05–6.5 (2 H, m). Anal. Calcd for $C_{16}H_{18}O_4Cl_2$: C, 55.65; H, 5.22; Cl, 20.58. Found: C, 55.79; H, 5.29; Cl, 20.35.

7,10-Bis(chloromethyl)-7,10-dihydroxy-5,12-dimethylpentacyclo[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]dodecane-6,11-dione (11). A solution of **13** (3.0 g) in EtOAc (300 mL) containing cyclohexadiene (1 mL) was irradiated with a 100-W high-pressure mercury lamp (Pyrex filter) for 16 h. The reaction mixture was passed through a Celite mat, and the filtrate was concentrated to leave a solid, which was recrystallized from EtOAc to give 1.88 g (63%) of colorless prisms: mp 234 °C; IR (Nujol) 3260, 1718 cm^{-1}; MS m/e 346, 344 (M^+); ^1H NMR ($CDCl_3$–CD_3OD) δ 1.31 (6 H, s), 2.7–3.1 (6 H, m), 3.50 (4 H, s). Anal. Calcd for $C_{16}H_{18}O_4Cl_2$: C, 55.65; H, 5.22; Cl, 20.58. Found: C, 55.59; H, 5.27; Cl, 20.39.

Table IV. Fractional Coordinates for Hydrogen Atoms Located in Difference Maps[a]

atom	x	y	z
H-H_2O	−0.043	0.291	0.455
H-H_2O	0.055	0.293	0.351
H-1	0.099	0.004	0.481
H-3	0.003	0.098	0.578
H-4	0.172	0.063	0.662
H-5	0.329	0.082	0.479
H-7	−0.008	0.118	0.185
H-8	0.057	0.053	0.021
H-8	0.124	0.104	−0.004
H-8	0.185	0.064	0.078
H-1A	0.200	0.232	0.377
H-3A	0.004	0.169	0.422
H-4A	0.145	0.170	0.206
H-5A	0.289	0.114	0.207
H-7A	0.117	0.140	0.745
H-8A	0.298	0.116	0.813
H-8A	0.349	0.145	0.656
H-8A	0.287	0.168	0.803
H-O2	−0.072	0.044	0.253

[a] The hydrogen atom on the hydroxyl oxygen O2A was not found.

13-Chloro-5-chloromethyl-1,5-dihydroxy-2,7-dimethylpentacyclo[7.4.0.0^{3,8}.0^{4,11}.0^{7,10}]tridecane-6,12-dione (14). A solution of **11** (1.0 g) in TFA (15 mL) was heated under reflux for 10 h. After evaporation of the acid, the residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ and saturated NaCl, and dried (Na_2SO_4). Evaporation of the solvent left a solid, which was recrystallized from $CHCl_3$ to give 969 mg (97%) of colorless prisms: mp 216–218 °C; IR (Nujol) 3440, 1720, 1700 cm^{-1}; MS m/e 346, 344 (M^+), 328, 326, 308; ^1H NMR (Me_2SO-d_6) δ 0.96 (3 H, d, J = 7 Hz), 1.32 (3 H, s), 2.2–2.8 (6 H, m), 3.0–3.5 (3 H, m), 3.60 (1 H, d, J = 12 Hz), 3.95 (1 H, d, J = 12 Hz); 5.02 (1 H, s); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 10.9 (q), 15.8 (q), 42.2 (d), 42.2 (d), 44.8 (d), 46.0 (d), 46.4 (d), 47.6 (t), 47.6 (d), 52.5 (d), 53.0 (d), 70.1 (d), 74.9 (s), 78.3 (s), 204.7 (s), 212.3 (s). Anal. Calcd for $C_{16}H_{18}O_4Cl_2$: C, 55.65; H, 5.22; Cl, 20.58. Found: C, 55.41; H, 5.47; Cl, 20.50.

7,12-Dichloro-6,13-dihydroxy-5,14-dimethylpentacyclo[7.5.0.0^{2,6}.0^{3,13}.0^{4,10}]tetradecane-8,11-dione (15). A benzene (40 mL) solution of **11** (870 mg) and TsOH (3.7 g) was refluxed for 5 h. After evaporation of the solvent, the residue was triturated in 10% Na_2CO_3 to give a colorless precipitate, which was filtered, washed with H_2O, benzene, and a small amount of EtOAc, and dried on a desiccator to give 535 mg of **15**. The filtrate was extracted with EtOAc, and the extract was dried and evaporated to give 129 mg (total yield 664 mg, 76%). Recrystallization from MeOH gave colorless prisms: mp 290 °C dec; IR (Nujol) 3450, 3400, 1730 cm^{-1}; MS m/e 346, 344 (M^+); ^1H NMR (Me_2SO-d_6) δ 0.86 (6 H, d, J = 8 Hz), 2.1–2.5 (4 H, m), 2.7–2.9 (2 H, m), 3.4–4.2 (4 H, m), 5.25 (2 H, s); ^{13}C NMR (pyridine) δ 11.5 (q), 44.0 (d), 50.5 (d), 51.9 (d), 58.2 (d), 71.0 (d), 77.6 (s), 203.3 (s). Anal. Calcd for $C_{16}H_{18}O_4Cl_2$: C, 55.65; H, 5.22; Cl, 20.58. Found: C, 55.88; H, 5.23; Cl, 20.45.

X-ray Analysis of 15. On an automatic diffractometer 1288 independent reflections were collected, Cu Kα radiation, Ni filter, λ = 1.541 78 Å. The symbolic addition procedure for centrosymmetric crystals[8] was applied to solve the structure of **15** and the results are shown in Figure 1 and Tables II–VI. The numbering scheme (atoms in tables) is as follows.

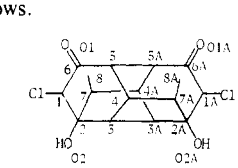


Table V. Bond Distances[a]

atom-atom		bond length, Å	atom-atom		bond length, Å
C1	C1	1.809	C5	C5A	1.583
C1	C2	1.527	C1A	C1A	1.795
C1	C6	1.503	C1A	C2A	1.545
C2	O2	1.411	C1A	C6A	1.528
C2	C3	1.569	C2A	O2A	1.422
C2	C7	1.578	C2A	C3A	1.562
C3	C4	1.531	C2A	C7A	1.551
C4	C5	1.537	C3A	C4A	1.533
C5	C6	1.539	C4A	C5A	1.522
C6	O1	1.204	C5A	C6A	1.530
C7	C8	1.530	C6A	O1A	1.195
C4	C7A	1.551	C7A	C8A	1.476
C3	C3A	1.539	C4A	C7	1.548

[a] Av C–H = 1.09 Å, av O–H = 1.05 Å. Average standard deviation for bonds not involving hydrogens is 0.009 Å.

Table VI. Bond Angles[a]

atom—atom—atom			<, deg	atom—atom—atom			<, deg
C1	C1	C2	112.3	C1A	C1A	C2A	114.8
C1	C1	C6	111.6	C1A	C1A	C6A	110.6
C2	C1	C6	112.8	C2A	C1A	C6A	110.3
O2	C2	C1	111.4	O2A	C2A	C1A	108.9
O2	C2	C3	107.3	O2A	C2A	C3A	112.2
O2	C2	C7	111.8	O2A	C2A	C7A	108.4
C1	C2	C3	107.1	C1A	C2A	C3A	106.8
C1	C2	C7	115.1	C1A	C2A	C7A	115.4
C3	C2	C7	103.4	C3A	C2A	C7A	105.2
C2	C3	C3A	106.9	C2A	C3A	C3	106.4
C2	C3	C4	113.4	C2A	C3A	C4A	113.8
C4	C3	C3A	99.8	C4A	C3A	C3	100.4
C3	C4	C5	108.6	C3A	C4A	C5A	109.4
C3	C4	C7A	102.8	C3A	C4A	C7	102.1
C5	C4	C7A	114.9	C5A	C4A	C7	114.3
C4	C5	C6	107.9	C4A	C5A	C6A	108.4
C4	C5	C5A	112.0	C4A	C5A	C5	111.7
C6	C5	C5A	108.3	C6A	C5A	C5	106.2
C1	C6	O1	125.6	C1A	C6A	O1A	123.6
C1	C6	C5	113.0	C1A	C6A	C5A	113.5
O1	C6	C5	121.7	O1A	C6A	C5A	122.9
C2	C7	C4A	103.4	C2A	C7A	C4	102.4
C2	C7	C8	118.2	C2A	C7A	C8A	120.6
C8	C7	C4A	115.8	C8A	C7A	C4A	115.2

[a] Average standard deviation is 0.5°.

7,7,10,10-Tetramethylpentacyclo[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]dodecane-6,11-dione (16). A. An EtOAc (300 mL) solution of 6,6-dimethylcyclohexadienone dimer (**17**, 1.2 g) was irradiated for 4 h as described above. After evaporation of the solvent, the residue was recrystallized from EtOAc–hexane to give 990 mg (82.5%) of colorless prisms: mp 136–138 °C; IR (Nujol) 1700 cm^{-1}; MS *m/e* 244 (M$^+$); ^{1}H NMR (CDCl$_3$) δ 0.97 (6 H, s), 1.12 (6 H, s), 2.05 (2 H, m), 3.05 (6 H, broad s); ^{13}C NMR (CDCl$_3$) δ 2.18 (q), 23.1 (q), 35.6 (d), 36.6 (d), 43.3 (d), 43.9 (s), 46.9 (d), 216.0 (s). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.58; H, 8.25.

B. A solution of **18** (30 mg) in EtOH (2 mL) and 10% KOH (1 mL) was heated at 50 °C for 2 h. After evaporation of the EtOH, the aqueous layer was extracted with benzene and the extract washed with H_2O, dried, and evaporated to leave **16**, which was recrystallized from EtOAc–hexane to give colorless prisms of **16**.

Acid-Catalyzed Reaction of 16. A. 9-Hydroxy-5,5,10,10-tetramethyl-8-tosyloxypentacyclo[7.3.0.0^{2,7}.0^{3,12}.0^{6,11}]dodecan-4-one (18). A benzene (10 mL) solution of **16** (200 mg) and TsOH (300 mg) was refluxed for 38 h. The solution was washed with saturated $NaHCO_3$ and saturated NaCl, dried, and evaporated to leave a solid, which was recrystallized from EtOAc–hexane to give 114 mg of **18**: mp 185–186.5 °C; IR (Nujol) 3500, 1700, 1600 cm^{-1}; MS *m/e* 416 (M$^+$), 261, 244, 145, 123; ^{1}H NMR (CDCl$_3$) δ 0.89 (3 H, s), 0.96 (3 H, s), 1.06 (3 H, s), 1.23 (3 H, s), 2.0–2.3 (3 H, broad s), 2.45 (3 H, s), 2.5–3.0 (5 H, m), 4.61 (1 H, d, J = 4 Hz), 7.33 (2 H, d, J = 8 Hz), 7.81 (2 H, d, J = 8 Hz). Anal. Calcd for $C_{23}H_{28}O_5S$: C, 66.35; H, 6.73; S, 7.71. Found: C, 66.10; H, 6.76; S, 7.45.

The mother liquor was evaporated and chromatographed on a silica gel column to give three fractions. The first fraction was 9 mg of a 4:1 mixture of 2,3-dimethylphenol (**20**) and 2,6-dimethylphenol (**21**). The second fraction was 90 mg of a 1:1 mixture of the starting material (**16**) and **19** (vide infra). The third fraction was an additional amount (11 mg) of **18** (total yield 125 mg, 37%).

B. **7,7,12,12-Tetramethylpentacyclo[6.4.0.0^{2,6}.0^{3,10}.0^{4,9}]dodecane-5,11-dione (19).** A benzene (25 mL) solution of **16** (200 mg) and TsOH (200 mg) was heated at 150 °C in a steel bomb for 24 h. The solution was washed with saturated $NaHCO_3$ and saturated NaCl and dried (Na_2SO_4). Evaporation of the solvent left 196 mg of an oil, which was chromatographed on a silica gel column to give two fractions. The first fraction was 10 mg of a mixture of 2,3-dimethylphenol (**20**) and 2,6-dimethylphenol (**21**). The second fraction was 154 mg (77%) of **19**, which was recrystallized from EtOAc–hexane: mp 107–109 °C; IR (Nujol) 1735, 1715 cm^{-1}; MS *m/e* 244 (M$^+$), 173, 159, 145, 131; ^{1}H NMR (CCl$_4$) δ 0.99 (3 H, s), 1.07 (3 H, s), 1.12 (3 H, s), 1.30 (3 H, s), 1.65–1.92 (3 H, m), 2.08 (1 H, d, J = 6 Hz), 2.60–3.10 (4 H, m); ^{13}C NMR (CDCl$_3$) δ 13.7 (q), 21.3 (q), 21.7 (q), 21.7 (q), 26.1 (d), 26.1 (d), 27.3 (d), 40.2 (d), 42.8 (d), 45.4 (d), 46.1 (s), 46.6 (s), 50.8 (d), 52.7 (d), 220.1 (s), 220.1 (s). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.79; H, 8.23.

C. **7,7,12,12-Tetramethyl-9-tosyloxytetracyclo[6.4.0.0^{2,6}.0^{3,10}]dodecane-5,11-dione (22) and 9-Phenyl-7,7,12,12-tetramethyltetracyclo[6.4.0.0^{2,6}.0^{3,10}]dodecane-5,11-dione (23).** A benzene (5 mL) solution of **16** (500 mg) and TsOH (1 g) was heated at 150 °C for 24 h as described above. Silica gel column chromatography gave three fractions. The first fraction was a mixture (58 mg, 12%) of **20** and **21**. The second fraction was 95 mg (14) of **23**. Recrystallization from EtOAc gave colorless needles: mp 228–230 °C; IR (Nujol) 1720, 1710, 1600, 1580 cm^{-1}; MS *m/e* 322 (M$^+$), 217, 142; ^{1}H NMR (CDCl$_3$) δ 1.10 (6 H, s), 1.18 (6 H, s), 1.62 (1 H, broad s), 2.0–3.5 (8 H, m), 6.9–7.4 (5 H, m); ^{13}C NMR (CDCl$_3$) δ 19.4 (q), 22.3 (q), 24.0 (q), 26.1 (t), 26.9 (q), 39.5 (d), 40.1 (d), 42.7 (d), 44.3 (s), 45.8 (d), 48.9 (s), 50.8 (d), 54.0 (d), 59.3 (d), 126.0 (d), 126.7 (d), 126.7 (d), 127.9 (d), 127.9 (d), 142.1 (s), 219.6 (s), 223.2 (s). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.15. Found: C, 82.02; H, 8.13.

The third fraction was 158 mg (21%) of **22**, which was recrystallized from EtOAc–hexane to give colorless prisms: mp 157–159 °C; IR (Nujol) 1735, 1710, 1600 cm^{-1}; MS *m/e* 416 (M$^+$), 352, 245, 244; ^{1}H NMR (CDCl$_3$) δ 1.01 (3 H, s), 1.05 (3 H, s), 1.08 (3 H, s), 1.15 (3 H, s), 2.44 (3 H, s), 1.5–5.1 (8 H, m), 4.65 (1 H, s), 7.35 (2 H, d, J = 8 Hz), 7.81 (2 H, d, J = 8 Hz); ^{13}C NMR (CDCl$_3$) δ 19.3 (q), 20.6 (t), 21.6 (q), 22.1 (q), 23.8 (q), 26.2 (q), 39.0 (d), 39.2 (d), 41.4 (d), 44.5 (s), 45.0 (d), 48.9 (s), 50.4 (d), 56.2 (d), 90.0 (d), 127.4 (d), 127.4 (d), 129.4 (d), 129.4 (d), 132.9 (s), 144.5 (s), 217.1 (s), 217.6 (s). Anal. Calcd for $C_{23}H_{28}O_5S$: C, 66.35; H, 6.73; S, 7.71. Found: C, 66.46; H, 6.65, S, 7.85.

Acid-Catalyzed Reaction of 17. A. A benzene (1 mL) solution of **17** (70 mg) and TsOH (70 mg) was heated at 150 °C for 4 h in a bomb. The solution was diluted with benzene, washed with saturated $NaHCO_3$ and saturated NaCl, dried, and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with benzene–hexane (2:1) gave 6 mg (8.6%) of **21** and 30 mg (43%) of **20**.

B. A benzene (6 mL) solution of **17** (80 mg) and TsOH (80 mg) was refluxed for 18 h. After evaporation of the solvent, the residue was chromatographed on a silica gel column to give 5 mg (6%) of **21** and 20 mg (25%) of **20**.

Acknowledgment. This research was supported in part by a grant from the Japan Society for the Promotion of Science (International Co-operative Research Project).

References and Notes

(1) (a) Hokkaido University; (b) Naval Research Laboratory; (c) National Institutes of Health; (d) Faculty of Pharmaceutical Sciences, Chiba University, Chiba 280, Japan.

(2) (a) T. Iwakuma, H. Nakai, O. Yonemitsu, D. S. Jones, I. L. Karle, and B. Witkop, *J. Am. Chem. Soc.*, **94**, 5136 (1972); (b) H. D. Becker and A. Konar, *Tetrahedron Lett.*, 5177 (1972); (c) H. D. Becker, *Justus Liebigs Ann. Chem.*, 1673 (1973); (d) T. Iwakuma, O. Yonemitsu, N. Kanamaru, K. Kimura, and B. Witkop, *Angew. Chem., Int. Ed. Engl.*, **12**, 72 (1973); (e) T. Iwakuma,

K. Hirao, and O. Yonemitsu, *J. Am. Chem. Soc.*, **96**, 2570 (1974); (f) H. D. Becker, B. Ruge, and T. Weslöf, *Tetrahedron Lett.*, 253 (1975).
(3) This reaction has also been interpreted in terms of the orbital interaction rule: S. Inagaki, H. Fujimoto, and K. Fukui, *J. Am. Chem. Soc.*, **98**, 4693 (1976).
(4) K. Hirao, M. Taniguchi, T. Iwakuma, O. Yonemitsu, J. L. Flippen, I. L. Karle, and B. Witkop, *J. Am. Chem. Soc.*, **97**, 3249 (1975).
(5) J. L. Flippen, *Acta Crystallogr., Sect. B*, **32**, 1269 (1976).
(6) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967).
(7) E. Adler and K. Holmberg, *Acta Chem. Scand., Ser. B*, **28**, 465 (1974).
(8) J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).
(9) K. Alder, F. H. Flock, and H. Lessenich, *Chem. Ber.*, **90**, 1709 (1957).
(10) E. Ōsawa, K. Aigami, and Y. Inamoto, *J. Chem. Soc., Perkin Trans. 2*, in press.
(11) Otherwise, the rearranged ketone **3d** may be formed directly from **3a** through a concerted 1,2 shift with deprotonation.
(12) For a review see R. L. Cargill, T. E. Jackson, N. P. Peet, and D. M. Pond, *Acc. Chem. Res.*, 7, 106 (1974).
(13) B. P. Mundy and R. D. Otzenberger, *J. Org. Chem.*, **38**, 2109 (1973).
(14) Cf. E. N. Marvell and E. Magoon, *J. Am. Chem. Soc.*, **77**, 2542 (1955); B. Miller, *ibid.*, **92**, 6252 (1970).
(15) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

Mechanistic Aspects of the Thermal Equilibration of Retinylidene Imines and Immonium Salts

Patrick C. Mowery* and Walther Stoeckenius

Contribution from the Cardiovascular Research Institute, University of California, San Francisco, California 94143. *Received July 6, 1978*

Abstract: The reactions of isomeric retinylidene *n*-butylimines and protonated imines in the dark were examined by proton nuclear magnetic resonance and ultraviolet absorption spectroscopy and by high-performance liquid chromatography. The immonium hydrochlorides were shown to decompose by a complex system of pathways. However, 13-*cis*-retinylidene-*n*-butylamine was shown to undergo thermodynamic equilibration with the trans isomer by general base catalysis, whereas the 9-cis isomer was thermodynamically stable. The specificity of the reaction for the 13-cis isomer suggests that it occurs via the 13-methylene enamine intermediate. Protonated retinylidene imines have been shown to be important as chromophores in the visual cycle and in a light-driven proton pump in certain halophilic bacteria. The mechanisms of action for these systems are briefly contrasted in the light of the result reported here.

Introduction

Retinal imines have long served an important role as models of the visual chromophore.[1] Interest in their study has been further augmented by the recent discovery of a light-driven proton pump in certain halophilic bacteria which catalyzes the photophosphorylation of ADP.[2] The pump has been isolated, and has been shown to consist of 25% lipid and 75% of a single protein called bacteriorhodopsin of molecular weight 25 000. Furthermore, its intense purple color is due to a retinyl moiety attached to an ϵ amino group of a lysine.[3] It exists in two forms: (1) the dark-adapted form, characterizable by a maximum visible spectral transition at 558 nm, which is believed to contain a 1:1 mixture of the chromophore as 13-*cis* and *all-trans*-ϵ-retinylidene-L-lysine;[4] and (2) a light-adapted state with a transition at 568 nm, in which it is believed to be essentially all trans.[4,5]

It is unclear whether a photolytic all-trans to 13-cis isomerization is important for a proton pumping,[6] although there is some evidence from chromophore extraction data that an intermediate exists with a 13-*cis*-retinyl chromophore.[7] If this is so, the 13-cis intermediate thermally reisomerizes to trans, since there must be a cyclic mechanism for the bacteriorhodopsin proton pump.[8]

The purpose of this paper is to demonstrate that at least one mechanism exists for the nonphotolytic rearrangement of the 13-cis imine to the all-trans form. The immonium hydrochloride, on the other hand, decomposes by several reaction pathways. Investigators are therefore cautioned to use care in the preparation and study of these compounds. Finally, the relevance of these findings to the visual cycle and to the bacteriorhodopsin system is briefly discussed.

Materials and Methods

Materials. *all-trans*-, 13-*cis*-, and 9-*cis*-retinal (Sigma) were checked for purity on a Waters ALC/GPC 204 liquid chromatograph outfitted with a dual-wavelength (254 and 365 nm) detector and a μ-Porasil column, as described by Pettei et al.[7] The eluent was 2% ether in hexane with a flow rate of 2.0 mL/min. Proton magnetic resonance spectra were taken on a Perkin-Elmer R12b spectrometer, outfitted with a temperature control, at 37 °C. Absorption spectra were recorded on a Cary 14 spectrometer. *N*-Butylamine (Mallinckrodt) was distilled prior to use and stored over molecular sieves. Retinals were used without purification for the NMR experiments, but were purified by high-performance liquid chromatography before studies involving electronic spectra were made.

Preparation of Imines. All operations were conducted in semidarkness at 0 °C. Retinal was allowed to react with a 0.05 molar excess of *n*-butylamine in anhydrous ether for 30 min. The solvent was removed on a rotary evaporator, and the excess amine was driven off by passing dry nitrogen over the residue for 30 min. The protonated imine was prepared by washing the residue with ether saturated with anhydrous hydrogen chloride and removing the solvent on the rotary evaporator. Excess acid was further removed by a nitrogen purge. Samples were dissolved in chloroform or (for NMR experiments) chloroform-*d* containing 1% tetramethylsilane.

Results

NMR Studies. Our interest in this study originated when we encountered difficulties in obtaining ^{13}C NMR spectra of 13-*cis*-retinylidene-*n*-butylamine, owing to its conversion to the trans isomer at ambient temperatures. We were able to conveniently follow the isomerization by ^1H NMR (Figure 1), and noted that the half-life was roughly 1 h. In a separate experiment, we followed the decay of the 13-cis imine at 37 °C by LC, using 2% ether in hexane as the eluent, and found a decay in the 13-cis isomer from 85 to 45% in 80 min for a 0.1 M solution.

In NMR experiments, the immonium hydrochloride was

0002-7863/79/1501-0414$01.00/0