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Optical Resolution Studies of Cyclophosphamide

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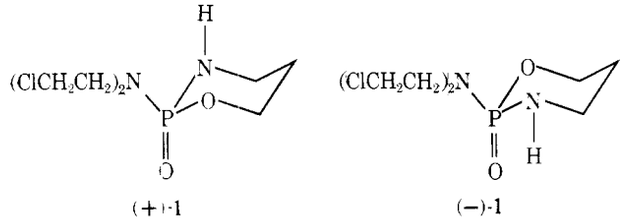
Cyclophosphamide (1) has been resolved by fluoride displacement (with c-$C_6H_{11}NH_3F$) of the optically active α-NpPhMeSi group of each chirality from the endocyclic nitrogen of the cyclophosphamide moiety in α-NpPhMeSi-c-$(NCH_2CH_2CH_2OP(O))N(CH_2CH_2Cl)_2$ ((−)-*S*(P)-*R*(Si)-**4**) and (+)-*R*(P)-*S*(Si)-**4**. The latter enantiomers were separated in high purity from their diastereomers ((+)-*R*(P)-*R*(Si)-**5** and (−)-*S*(P)-*S*(Si)-**5**, respectively) by recrystallization. The enantiomeric **5** derivatives could not be purified of **4** by a variety of techniques. Each diastereomeric mixture of **4** and **5** was synthesized by allowing the lithium salt of **1** (formed from **1** and *n*-BuLi) to react with (−)- and (+)-α-NpPhMeSiCl at low temperature. A simple method for the synthesis of anhydrous crystalline (±)-**1** is also described. The separation of the enantiomeric NH protons of anhydrous (±)-**1** in benzene-d_6 observed in the presence of the chiral shift reagent EuOpt offers a convenient method for estimating the optical purity of the enantiomers.

Introduction

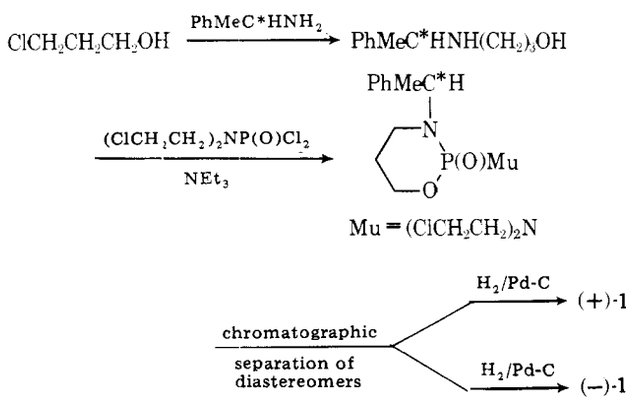
Racemic cyclophosphamide hydrate (Cytoxan, 2-[bis(2-chloroethyl)amino]-2-oxo-1,3,2-oxazaphosphorinane, (±)-**1**) is very effective in the clinical control of a variety of cancers.[1] After our efforts to resolve (±)-**1** were underway, Stec and



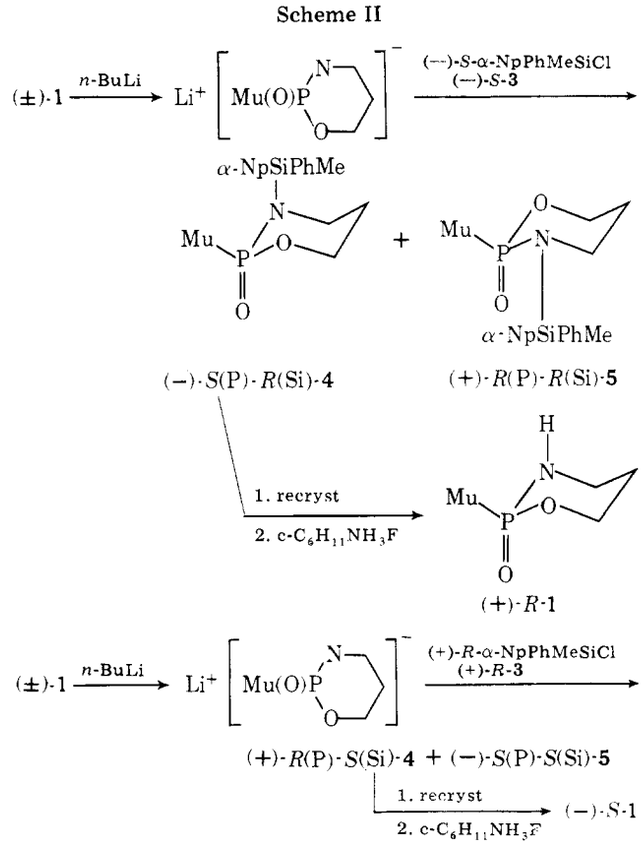
co-workers[2] published their approach to this problem which is outlined in Scheme I. In collaboration with Cox et al.[3] they showed that (−)-**1** is more efficacious against PC6 mouse tumors and the latter group demonstrated that (+)-**1** is preferentially metabolized in human patients.[3] Recently, the absolute configuration of (+)-**1** was shown to be *R* from the anomalous dispersion of x rays from the chlorine and phosphorus atoms.[4]

In view of the possibility that metabolic selectivity for a particular enantiomer may depend on the biological system under consideration, we decided to pursue the path outlined in Scheme II, since it would be of valuable aid in our current

Scheme I



Scheme II



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efforts to resolve two clinically used derivatives of cyclophosphamide, namely, isophosphamide and trophosphamide.

Experimental Section

(−)-(*S*)-2-[Bis(2-chloroethylamino)]-2-oxo-3(*R*)-α-naphthylphenylmethylsilyl-1,3,2-oxazaphosphorinane (−)-*S*(P)-*R*(Si)-4. (−)-(*S*)-α-Naphthylphenylmethylsilyl chloride [(−)-*S*-3] was prepared from (+)-(*R*)-α-naphthylmethylphenylsilane [(+)-*R*-2] ($[\alpha]^{25}_D$ +32.4°; *c* 2.51 in cyclohexane; optical purity is 95.4% based on $[\alpha]^{25}_D$ +33.7°; *c* 4.00 in cyclohexane) as previously described.[5] To a stirred solution of racemic cyclophosphamide, (±)-1 (5.259 g, 20.14 mmol), in 30 mL of freshly dried ($LiAlH_4$) and distilled THF was added via syringe 10 mL of a 2 M *n*-hexane solution of *n*-butyllithium at −78 °C under a nitrogen atmosphere. After stirring for 10 min, a solution of (−)-*S*-3 (5.430 g, 19.20 mmol) in 10 mL of dry ether was quickly syringed into the solution. Following continued stirring at −78 °C for 1 h, the solvent was removed under vacuum.

The tarry residue was chromatographed with chloroform on 80 g of silica gel (Baker, 60–200 mesh) to afford 9.541 g (97.9% yield) of a 1:1 mixture of (−)-*S*(P)-*R*(Si)-4 and (+)-*R*(P)-*R*(Si)-5 as a colorless paste which foamed on vacuum drying ($[\alpha]^{25}_D$ −4.1°; *c* 92.4 CH_2Cl_2). The ^1H NMR spectrum in $CDCl_3$ revealed the presence of the diastereomeric CH_3 protons [δ 1.06 (s, 1.5 H) and 1.09 (s, 1.5 H)]. Other assigned proton resonances are δ 1.55–1.90 (m, 2 H, CCH_2C), 3.04–3.65 (m, 10 H, $ClCH_2CH_2$, endocyclic CH_2N), 4.00–4.56 (m, 2 H, CH_2O), 7.20–8.08 (m, 11.5 H, C_6H_5, $C_{10}H_7$ of (−)-*S*(P)-*R*(Si)-4 and C_6H_5, six protons of $C_{10}H_7$ of (+)-*R*(P)-*R*(Si)-5), and 8.39–8.50 (m, 0.5 H, one proton of $C_{10}H_7$ of (+)-*R*(P)-*R*(Si)-5, see Discussion). The ^{31}P chemical shifts of the diastereomers appeared at ($CDCl_3$) 11.7 and 11.3 ppm downfield of 85% H_3PO_4.

After recrystallizing three times from benzene–*n*-pentane (ca. 1:1) at 5 °C, further recrystallization gave no further increase in rotation of solutions of the colorless needles of (−)-*S*(P)-*R*(Si)-4 ($[\alpha]^{25}_D$ −21.8°; *c* 1.53, CH_2Cl_2; mp 132.5–133.5 °C) which were obtained in 21% yield based on half the quantity of **2**: ^1H NMR ($CDCl_3$) δ 1.05 (s, 3 H, CH_3), 1.60–1.84 (m, 2 H, CCH_2C), 3.10–3.65 (m, 10 H, $ClCH_2CH_2$, endocyclic CH_2N), 4.10–4.50 (m, 2 H, CH_2O), 7.20–8.08 (m, 12 H, C_6H_5, $C_{10}H_7$). The ^{31}P chemical shift ($CDCl_3$) appeared at 11.8 ppm downfield of 85% H_3PO_4 and the P=O stretching frequency (KBr) at 1240 cm^{-1}. The mass spectrum (70 eV, 140 °C) revealed the parent ion at *m/e* 506.11138 (calcd 506.11131) and a base peak at *m/e* 267 corresponding to α-NpPhSiCl$^+$.

Because of its poor recrystallizing properties, diastereomer (+)-*R*(P)*R*(Si)-5 could not be isolated in an optically pure state (see Discussion).

An effort was made to synthesize the above diastereomers by the reaction of (±)-1 with (−)-*S*-3 in the presence of Et_3N. Into a solution of **1** (3.338 g, 12.78 mmol) and Et_3N (1.80 mL, 12.9 mmol) in dry ether (50 mL) was added dropwise a solution of (−)-3 (3.612 g, 12.77 mmol) in ether (30 mL) while stirring and cooling at 0 °C. After addition, the reaction mixture was allowed to stir at room temperature for 2 days and then cooled to −78 °C. The precipitate was collected and from it crude racemic 5 was obtained nearly quantitatively by extraction with THF and evaporation of the solvent. Recrystallization from MeOH gave crystals of (±)-5 as plates [mp 145.0–146.0 °C (dec)] in 56.6% based on half the quantity of (−)-*S*(3). Its ^1H NMR spectrum in $CDCl_3$ showed δ 1.08 (s, 3 H, CH_3), 1.72 (m, 2 H, CCH_2C), 3.05–3.70 (m, 10 H, $ClCH_2CH_2$, $PNCH_2$), 4.00–4.55 (m, 2 H, PCH_2O), 7.35–7.94 (m, 5 H, C_6H_5; 6 H of $C_{10}H_7$), 8.35–8.50 (m, 1 H of $C_{10}H_7$). The high-resolution mass spectrum (70 eV, >200 °C) showed a parent *m/e* at 506.10992 (calcd for $C_{24}H_{29}Cl_2N_2O_2SiP$, 506.11131) and a base peak at *m/e* 267 corresponding to α-NpPhSiCl$^+$ ion. The IR spectrum (KBr) revealed ν_{PO} at 1250 cm^{-1}.

The filtrate of the reaction mixture was chromatographed on silica gel (50 g) with chloroform to afford 1.800 g of crude (±)-4 in 55.6% yield as a colorless oil. The oil was recrystallized from benzene–hexane (1:1) to give 1.087 g (34.2% yield) of (±)-4 as needles [mp 124.5–126.5 °C (dec)]. The ^1H NMR spectrum in $CDCl_3$ was identical to that of the separated enantiomers of 4 as was the position of the ν_{PO} frequency in the IR spectrum (KBr). The high-resolution mass spectrum (70 eV, 140 °C) showed a parent *m/e* peak at 506.10942 (calcd for $C_{24}H_{29}Cl_2N_2O_2SiP$: 506.11131) with a base peak at *m/e* 267. The relative heights of several peaks in the spectrum varied from (±)-4 to (±)-5 [e.g., (±)-4 429 < 491, whereas for (±)-5 491 < 429].

(+)-(*R*)-Cyclophosphamide, (+)-*R*-1. A solution of (−)-*S*(P)-*R*(Si)-4 (0.865 g, 1.71 mmol) and cyclohexylammonium fluoride (0.276 g, 2.36 mmol) in 20 mL of CH_2Cl_2 was stirred at room temperature. By monitoring the reaction with TLC (ether eluant) it was shown that (−)-*S*(P)-*R*(Si)-4 (R_f 0.6) was no longer detectable after about 2 h. The solvent was then evaporated from the reaction mixture to give a semisolid to which was added about 15 mL of benzene. The benzene filtrate was then chromatographed on 30 g of silica gel using a 195:5 chloroform–methanol mixture to give 0.390 g of (+)-*R*-1 as a colorless oil (87.6% yield; $[\alpha]^{25}_D$ +2.1°; *c* 3.89 MeOH). Recrystallizing once from ether afforded optically pure product as prisms (0.311 g; 69.9% yield; mp 64.5–65.6 °C; $[\alpha]^{25}_D$ +2.3°; *c* 3.03 MeOH; ^{31}P NMR ($CDCl_3$) δ 12.5, (C_6D_6) δ 11.7; R_f 0.3 5% MeOH in $CHCl_3$) which compared well with the literature data[2] (mp 65–66 °C; $[\alpha]^{25}_D$ +2.3°; *c* 12.2 MeOH; ^{31}P NMR (MeOH–H_2O) δ 13.7).

An attempt was made to reduce the Si–N bond of (−)-*S*(P)-*R*(Si)-4 by adding a benzene solution of this compound (0.585 g, 1.15 mmol in 20 mL of solvent) to an ether solution of $LiAlH_4$ (0.089 g, 9.4 mequiv in 10 mL of solvent) at room temperature. Distillation of the ether was followed by refluxing the reaction mixture at 90 °C overnight. Excess $LiAlH_4$ was decomposed with acetone and treated with crushed ice and 1 mL of concentrated HCl. Extraction with ether followed by drying the extract with Na_2SO_4, filtration, and evaporation of the solvent under vacuum gave a tarry residue which was chromatographed on silica gel with benzene. (+)-α-NpPhMeSiH was obtained in 13% yield and 82% optical purity ($[\alpha]^{25}_D$ +28°; *c* 0.36 c-C_6H_{12}). Subsequent elution gave (−)-α-NpPhMeSiOH in 31% yield and 17% optical purity ($[\alpha]^{25}_D$ −3.4°; *c* 0.88 c-C_6H_{12}). No evidence for 1 could be observed.

(+)-*R*(P)-*S*(Si)-4. This compound was prepared analogously to (−)-*S*(P)-*R*(Si)-4 using (−)-(*S*)-α-naphthylphenylmethylsilane ($[\alpha]^{25}_D$ −32.5°; *c* 4.04 cyclohexane; optical purity 96.5%; mp 61.5–62.5 °C). The product was recrystallized three times from ca. 1:1 benzene–pentane at 5 °C in 21.4% yield ($[\alpha]^{25}_D$ +21.8°; *c* 1.41 CH_2Cl_2; mp 133.0–134 °C dec) and its ^1H NMR spectrum was identical with that of (−)-*S*(P)-*R*(Si)-4.

(−)-(*S*)-Cyclophosphamide, (−)-*S*-1. The same reaction which produced (+)-*R*-1 was used to produce (−)-*S*-1 from (+)-*R*(P)-*S*(Si)-4. The product was recrystallized once from ether in 65.8% yield and its properties ($[\alpha]^{25}_D$ −2.3°; *c* 3.17 MeOH; mp 64.5–65.5 °C) compared well with those found by Stec and co-workers.[2]

(−)-(*S*)-cyclophosphamide in lower optical purity was obtained from a sample of (+)-*R*(P)-*R*(Si)-5 which was crude because of our failure to effect its purification (see Discussion). The 0.635-g sample ($[\alpha]^{25}_D$ +9.2°; *c* 6.35 CH_2Cl_2) consisted of (+)-*R*(P)-*R*(Si)-5, (−)-*S*(P)-*R*(Si)-4, and α-NpPhMeSiOH (apparently from partial hydrolysis experienced in workup) in ca. 11:4:1 ratio as determined by ^1H NMR spectroscopy. Its reaction with c-$C_6H_{11}NH_3F$ under the conditions described above afforded (−)-*S*-1 in about 80% yield with an optical purity of 65% ($[\alpha]^{25}_D$ −1.5°; *c* 2.64 MeOH). The optical purity was verified to within 5% by the relative integrations of the somewhat broadened NH proton NMR singlets [(+)-1, δ 5.10, 1 H; (−)-1, δ 4.88, 5.7 H] observed in a C_6D_6 solution made up of 0.238 g of the product, 0.0592 g of EuOpt (13.8:1 mol ratio) in 0.7 mL of solvent.

Racemic cyclophosphamide, (±)-1. A solution of bis(2-chloroethyl)aminophosphoric dichloride (73.5 g, 28.4 mmol) in THF (150 mL) and a solution of 3-aminopropanol (21.3 g, 28.4 mmol) and triethylamine (79.0 mL, 56.8 mmol) in THF (150 mL) was added dropwise simultaneously into 300 mL of stirred dry THF over a period of 3 h at 0 °C and then the reaction mixture was stirred overnight at room temperature. Triethylammonium hydrochloride was filtered off and the filtrate evaporated under vacuum. The residue was chromatographed on silica gel (100 g) with chloroform–methanol (195:5) to give a colorless oil which was dried over P_4O_{10} under vacuum. The dried material was recrystallized from dry ether at −78 °C to afford 55.2 g (74% yield) of anhydrous (±)-1 as prisms (mp 51.5–52.5 °C) which remained crystalline on storing under vacuum. A mass spectrum (70 eV) revealed the parent ion at *m/e* 261.6 (lit.[2] 260; calcd 261.1). Selected IR assignments are ν_{NH} (KBr) 3280, 3220 (sh), $\nu_{P=O}$ 1214 cm^{-1}, ν_{NH} (CCl_4 solution) 3380, 3200, $\nu_{P=O}$ 1235 cm^{-1}. The 100-MHz NMR spectrum exhibited the following features in $CDCl_3$: δ 1.84 (m, 2 H, $^3J_{HH}$ = 5.0 Hz, $CH_2CH_2CH_2$), 3.00–3.74 (m, 11 H, $ClCH_2CH_2$, $PNCH_2$, NH) and 4.04–4.60 (m, 2 H, $POCH_2$); and in C_6D_6: δ 1.25 (m, 2 H, $^3J_{HH}$ = 5.0 Hz, $CH_2CH_2CH_2$), 2.45–3.00 (m, 2 H, $PNHCH_2$), 3.00–3.50 (m, 8 H, $ClCH_2CH_2$), 3.50–4.20 (m, 2 H, $POCH_2$), and 4.55 (s, 1 H, NH). On adding tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) in a molar ratio of (±)-1:EuOPt of 26:1 in benzene, the signal for the NH protons separated completely (δ 4.55 and 4.75). By comparing, the remaining signals separated only slightly except for the $CH_2CH_2CH_2$ proton multiplet for which no separation could be observed.

Hydrated (±)-1 can be dried over P_4O_{10} at room temperature to afford material suitable for optical resolution by the route described

here. Azeotropic distillation of the water with CH_2Cl_2 was not very satisfactory inasmuch as the last traces of CH_2Cl_2, which appeared to be difficult to remove, reacted with the *n*-butyllithium.

Discussion

Since fluoride cleavage of the Si–N bond in (−)-*S*(P)-*R*(Si)-**4** (Scheme II) is not expected to affect the phosphorus chiral center, (−)-*S*(P)-*R*(Si)-**4** must have the *S* configuration at phosphorus in order to produce (+)-*R*-**1**. That this compound has the *R* configuration at silicon is strongly indicated by the well-documented observation that α-NpPhMeSiCl undergoes inversion upon nucleophilic attack by pyrrole or its lithium salt and upon $LiAlH_4$ reduction.[6] Thus, (−)-*S*- or (+)-*R*-α-NpPhMeSiCl is expected to invert upon reaction with the nitrogen of the lithium salt of (±)-**1**, leading to the two pairs of diastereomers **4** and **5** shown in Scheme II. In the foregoing argument it is assumed that silylation of the anion of **1** occurs only on the ring nitrogen.[7] Although the ratio of fluoride to **4** in this reaction was originally 2:1, repetition with a 1:1 ratio produced very similar results. While the formation of α-NpPhMeSiF in the last step is expected to be stereospecific, this product was found to have racemized during chromatographic workup of the reaction mixture.

One of the aromatic protons in the enantiomers of **5** appears at rather low field in the $CDCl_3$ ^1H NMR spectrum (m, δ 8.39–8.50) in contrast to the absence of this multiplet in the spectrum of the enantiomers of **4**. It is conceivable that the conformation of the α-NpPhMeSi group in **5** is such that the proton at the C-8 position of the naphthyl substituent is experiencing deshielding from the periphery of the phenyl group, whereas such a conformation is not favored in diastereomeric **4**. Further evidence for the sensitivity of this proton to diamagnetic anisotropy effects is the movement of this resonance to lower field in C_6D_6. The diastereomers have slightly different ^{31}P chemical shifts (**4**, δ 11.8; **5**, δ 11.3). The conformation shown in Scheme II for the cyclophosphamide ring of **4**, **5**, and **1** is not unreasonable in view of the structural results obtained from x-ray diffraction studies of cyclophosphamide,[8] isophosphamide,[9] trophosphamide,[10ab] and several ring-substituted derivatives[10b] which exhibit an equatorial mustard group in the solid state. It should be noted, however, that stereoelectronic influences are capable of inverting this conformation in the solid state, since 4-hydroperoxyisophosphamide possesses an axial $ClCH_2CH_2NH$ group. Moreover, an equilibrium between both conformers in systems of this type is undoubtedly present in solution.[11,12]

According to the assignments deduced from the ^1H NMR spectra of anhydrous (±)-**1**, the NH proton which is apparently masked by the $ClCH_2CH_2$ and $PNCH_2$ protons in $CDCl_3$ is shifted downfield by C_6D_6 into a window in the spectrum at about 4.5 ppm. Addition of the EuOpt shift reagent to such a benzene solution causes one of the enantiomeric NH proton resonances to move downfield by ca. 0.2 ppm. This observation permits estimation of the optical purity of the resolved enantiomers of **1** and allows the assignment of the downfield NH resonance to (+)-*R*-**1** and the upfield one to (−)-*S*-**1**. The enhanced separation of the NH proton resonance in (±)-**1** in the presence of a lanthanide shift reagent is reasonable in view of its singlet nature and its close proximity to the complexing site which from the available evidence in similar systems appears to be the phosphoryl oxygen.[11] Recently, Zon et al.[13] showed that the separation of the α- and β-CH_2 proton NMR resonances of the mustard moiety of (±)-**1** in the presence of the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) can also be used to determine the enantiomeric homogeneity of **1**. The heptafluoropropyl derivative of this shift reagent used in the present work offers the advantage that the ratio of **1** to reagent is considerably less (26:1) than with the trifluoromethyl derivative (1:1[13]). The ^{31}P chemical shifts in $CDCl_3$ of hydrated (±)-**1** (12.3 ppm) and anhydrous (±)-**1** (12.5 ppm) appear in the normal range, although they lie slightly to higher fields than the shift for **1** in a water–methanol solution.[2]

It was found that the lithiation of racemic cyclophosphamide must be carried out at low temperature to prevent its decomposition (possibly by intra or intermolecular nucleophilic attack of the anionic nitrogen on a CH_2Cl carbon[14]) prior to reaction with the enantiomers of **3**. In spite of the fact that THF is sufficiently basic to racemize optically active **3** slowly whereas Et_2O apparently is not, the former solvent was employed for the metallation reaction (using Et_2O to dissolve **3** for addition to metallated (±)-**1**). This was done because of the lower solubility of (±)-**1** and reduced product yields obtained when Et_2O alone was used. The use of Et_3N to facilitate the reaction of (±)-**1** with the enantiomers of **3** produced completely racemized **4** and **5** owing to more rapid racemization of optically active **3** in the presence of base. Substantially similar results were obtained with 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU).

All attempts to separate diastereomeric **4** and **5** by TLC, column chromatography (alumina and silica gel), and high-pressure liquid chromatography have so far failed. This result seems somewhat puzzling in view of the relative ease with which Stec and co-workers were able to separate the diastereomers in Scheme I by column chromatography.[2] Fortunately (−)-*S*(P)-*R*(Si)-**4** and (+)-*R*(P)-*S*(Si)-**4** are less soluble in benzene–pentane and form much more well-developed crystals than their diastereomers [(+)-*R*(P)-*R*(Si)-**5** and (−)-*S*(P)-*S*(Si)-**5**, respectively], and a separation of **4** could be accomplished in each case. Further recrystallizations aimed at purifying **5** were unsuccessful in eliminating diastereomeric **4** as a contaminant.

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Registry No.—(±)-**1**, 60007-95-6; (+)-*R*-**1**, 60030-72-0; (−)-*S*-**1**, 60007-96-7; (+)-*R*-**2**, 1025-08-7; (−)-*S*-**2**, 1025-09-8; (−)-*S*-**3**, 960-82-7; (+)-*R*-**3**, 13132-42-8; (±)-**4**, 64840-26-2; (−)-*S*(P)-*R*(Si)-**4**, 64870-01-5; (+)-*R*(P)-*S*(Si)-**4**, 64870-02-6; (±)-**5**, 64840-27-3; (−)-*S*(P)-*S*(Si)-**5**, 64911-63-3; (+)-*R*(P)-*R*(Si)-**5**, 64870-03-7; (−)-α-NpPhMeSiOH, 1028-62-2; bis(2-chloroethyl)aminophosphoric dichloride, 127-88-8.

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Photochemical Conversion of Methoxy-Substituted 6/6-Fused Cross-Conjugated Cyclohexadienones into Isomeric Tricyclodecenones[1]

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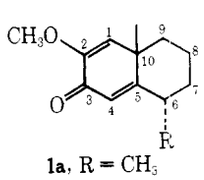
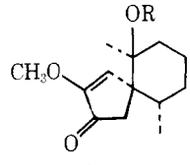
2-Methoxy 6/6-fused cross-conjugated cyclohexadienones of type **1** were irradiated in anhydrous dioxane. In addition to the expected lumiproducts, novel isomeric tricyclodecenone derivatives of type **5** were obtained as primary photoproducts. Phenolic compounds tentatively assigned structures of type **6** were also produced as primary photoproducts. The structure of the *p*-iodobenzoate **14**, a heavy-atom derivative of the tricyclodecenone **5b**, was established by x-ray crystallography. Possible modes of formation of enones of type **5** are discussed.

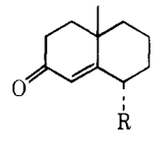
Recently, we reported the synthesis of the 2-methoxy 6/6-fused cross-conjugated cyclohexadienone **1a** and investigated its photochemical behavior on irradiation in protic solvents such as glacial and aqueous acetic aicd.[2] The expected spiro acetoxy- and spiro hydroxyenones **2a** and **2b**, respectively, were obtained and shown to be useful intermediates for the total synthesis of (±)-α-vetispirene.[2] We have now carried out irradiations of **1a** and the related normethyldienone **1b** in the aprotic solvent dioxane and wish to report these results.



1a, R = CH_3
b, R = H

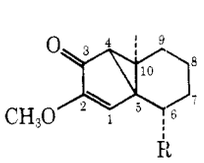


2a, R = Ac
b, R = H

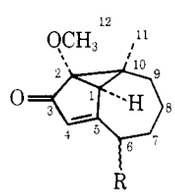


3a, R = CH_3
b, R = H

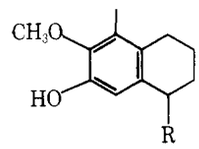
Dienone **1b** was prepared from the octalone **3b** by a route similar to that employed for the synthesis of **1a** from the corresponding octalone **3a**.[2] Dilute solutions (ca. 0.5%) of **1a** or **1b** in anhydrous dioxane were irradiated for 6.0 h at room temperature with a 7-W Hanau NK-20 low-pressure mercury lamp. Analysis of the photolysis mixtures by gas–liquid chromatography (GLC) using an internal standard showed that two tricyclic enones and a phenol were produced in ca. 25, 15, and 15% yields each from each of the dienones. In each case ca. 15% of the starting dienone remained at the end of the irradiation period. On the basis of the evidence presented below, the major enones were assigned the normal lumiproduct structures **4**, while the minor enones were assigned the tricyclic structures **5**. The phenolic products have been tentatively assigned structures **6**.



4a, R = CH_3
b, R = H



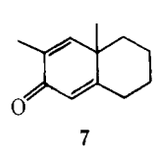
5a, R = CH_3
b, R = H



6a, R = CH_3
b, R = H

The phenolic products appeared to be primary photoproducts based on experiments in which a mixture of the isolated enones **4b** and **5b** were irradiated under similar conditions to the dienones **1**. In neither case were detectable amounts of the phenol **6b** formed. Enone **5b** was essentially unchanged under the irradiation conditions, whereas **4b** was almost completely destroyed, being largely converted into nonvolatile material. In one run the course of the photolysis of dienone **1b** was monitered carefully by GLC analysis. This revealed that after a short irradiation period, before **4b** was further rearranged, the kinetic ratio of primary photoproducts **4b** and **5b** was 4.4:1.

The tentative assignments of the structures of the phenols **6** were by analogy to the work of Kropp,[3] in which the 2-methyldienone **7** was shown to yield the phenol **8** as a primary photoproduct on irradiation in methanol or acetic acid. Phenol **8** was produced by a photochemically induced 1,2-methyl shift. This was a novel rearrangement pathway since cross-conjugated cyclohexadienones do not generally yield phenols as primary photoproducts. Phenolic products are often observed in dienone photolysis, but they normally arise by secondary processes in which initially formed lumiproducts are further rearranged.[4] Since phenols are formed as primary products from the irradiation of the 2-methoxydienones, it seems likely that they are also derived from a simple 1,2-methyl shift.



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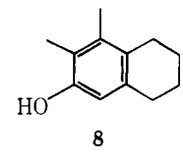

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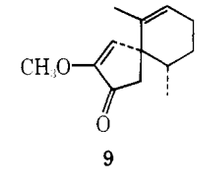

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The spectral properties of the lumiproducts **4a** and **4b** were consistent with the assigned structures (see the Experimental Section). In addition, compound **4a** was converted into the known spiro dienone **9**[2] by cleavage of the external bond of the cyclopropane ring with sulfuric acid in acetic anhydride under the conditions described by Marshall and Johnson[5] for the conversion of the related normethoxy lumiproduct into the corresponding spiro dienone. This information seemed to provide excellent evidence for the structural assignments.

The spectral properties of the enones **5a** and **5b** as well as

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