Stereoselectivity of Proton Loss for "E1-Like" 1,3-Eliminations in Tertiary, Benzylic Systems

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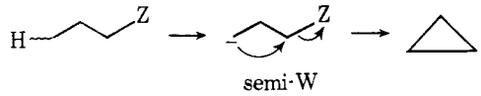
Our objective was to learn whether γ-proton loss from a carbocation to form a cyclopropane ring prefers the semi-W or semi-U pathway. We examined two rigid, tricyclic systems in which the intermediate carbocation in the overall 1,3-elimination is tertiary and carries a *p*-anisyl group. One substrate, 2-chloro-2-*p*-anisylnoradamantane, was synthesized from 2-noradamantanone by action of *p*-anisyllithium, to give the tertiary alcohol, followed by treatment with dry HCl in pentane. The other substrate, 2-chloro-2-*p*-anisylbrendane, was obtained by a similar sequence from 2-brendanone. When heated in hexane, these tertiary chlorides underwent net 1,3-elimination to produce their respective cyclopropyl products, 2-*p*-anisyltriaxane and 2-*p*-anisyldeltacyclane. To elucidate stereochemistry of the proton loss, we synthesized the corresponding 4-axial-*d*- and 4-equatorial-*d* analogues in the noradamantyl series and the corresponding 9-exo-*d* analogues in the brendyl series. The deuterium losses in the 1,3-eliminations were determined mass spectrally. After correction for an isotope effect (k_H/k_D) of 2.04 in the noradamantyl series, the stereoselectivity for γ-proton loss was 7.4/1 in favor of equatorial over axial (i.e., semi-W over semi-U). In the brendyl skeleton loss of the exo proton (i.e., semi-W) was favored over loss of the endo proton (i.e., semi-U) by a factor of ca. 27/1. Our findings with these two tertiary skeletons are contrasted with those reported for secondary norbornyl systems.

Stereochemistry of cyclopropane ring formation via 1,3-elimination has been explored in several cyclic and open-chain systems; and recent publications summarize developments in the field.[2] Such eliminations involve configurational changes at two centers, and most of the common reactions fall into three broad categories, according to whether one or both centers become stereorandomized before closure of the ring.

In the first category the initial geometry at *both* centers is maintained until the ring bond is formed. This category would include all concerted 1,3-eliminations, as well as stepwise processes via ions or radicals that preserve stereochemical integrity; and there are four distinct geometric arrangements for the ring-forming transition state. These have been termed W, U, exo-Sickle, and endo-Sickle,[4] and examples of the first three types in this category have been described.[2,5,6]

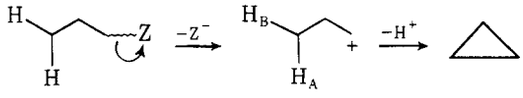
The second category comprises stepwise 1,3-eliminations via a carbanion that destroys configuration at the *electrofugal* center prior to the ring-forming event. (An analogous pathway in 1,2-elimination is often termed ElcB.)[3] Almost invariably in these cases the cyclopropyl bond forms by inversion at the nucleofugal center, and so a semi-W transition state is highly favored in this category[7] (eq 1).



(1)

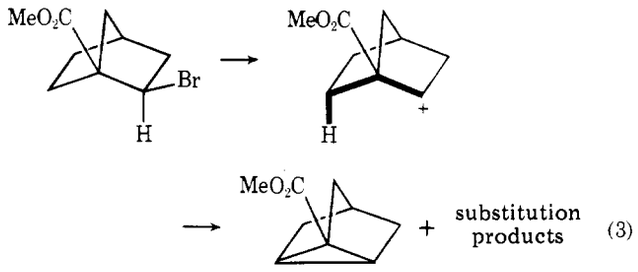
semi-W

The third category is made up of stepwise 1,3-eliminations involving an initial carbocation that destroys configuration at the *nucleofugal* center before ring closure. A typical situation in 1,3-elimination of HZ would be ionization to a configurationless cation followed by loss of a γ proton (eq 2).[8] In



(2)

brief stereochemical notation loss of H_A would be termed semi-U and loss of H_B is named semi-W.[4] This third category has received very little attention stereochemically.[9] A pertinent study is that by Werstiuk, who solvolyzed a deuterated analogue of 1-carbomethoxy-2-*exo*-norbornyl bromide at 112 °C in 20% H_2O–EtOH with NaOAc buffer (eq 3).[10] In the cyclopropyl product he found a preference of at least 15:1 for loss of the 6-endo proton (i.e., semi-U path) after adjustment for an isotope effect k_H/k_D of 1.6. Whether the $COOCH_3$ unit or

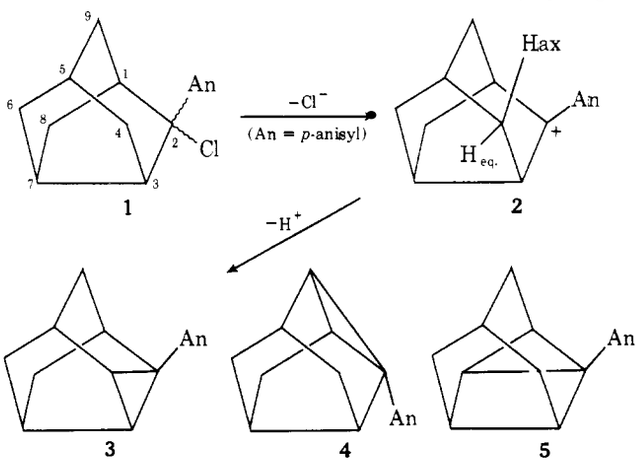


(3)

the peculiarities of norbornyl cations in any way influence this stereoselectivity is not known, although Lenoir reported that a CO_2CH_3 at C-1 does slow the solvolysis rate of *exo*-norbornyl bromide by a factor of ca. 1.6×10^4.[11]

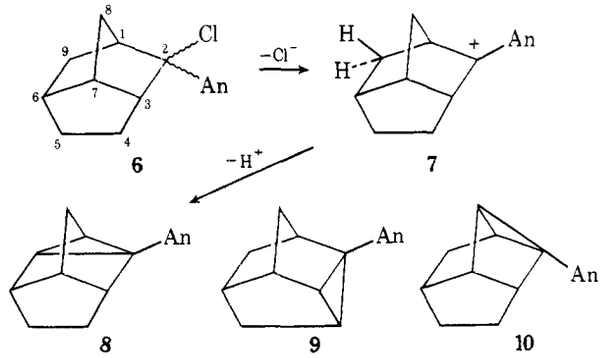
We present here a stereochemical study of HCl loss in a 1,3-elimination that belongs to category three (eq 2). To ensure formation of a carbocation intermediate we examined chlorides that are tertiary and that also contain a *p*-anisyl group, to provide exceptionally powerful driving forces for an "E1-like" process.[12] Noradamantane and brendane were selected as template skeletons for our study. These rigid tricyclic systems possess appropriately oriented C–H bonds that are γ to the nucleofugal center. In each skeleton the stabilized carbocation (see **2** and **7**) is flanked by bridgehead carbons, and so competitive 1,2-eliminations to produce olefins are precluded.

In a tertiary, noradamantyl chloride functionalized at C-2 (**1**, An = *p*-anisyl) the derived cation **2** can lose a γ hydrogen



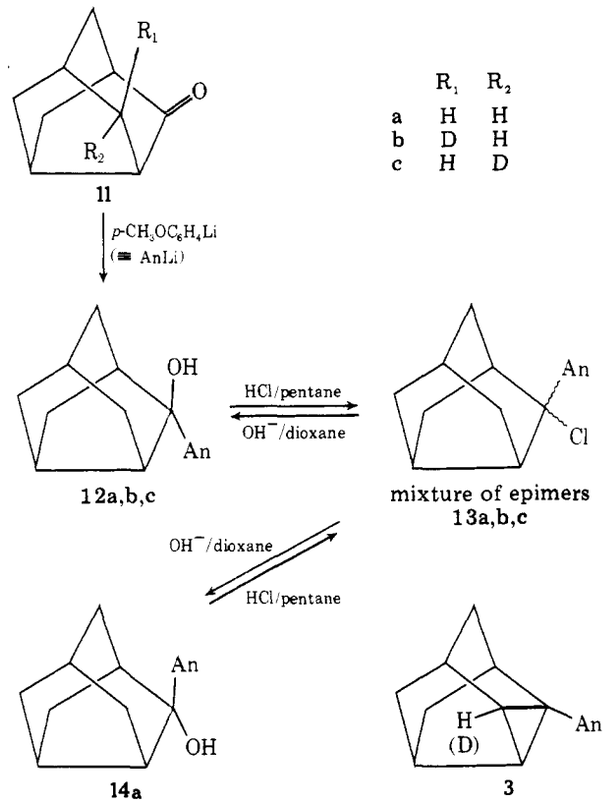
from C-4, C-9, or C-8, to produce respectively the three cyclopropyl products, **3**, **4**, and **5**. The parent skeletons in **3**[13] and **4**[14] are readily accessible tetracyclic systems, and molecular models suggest that **3** should be the least strained of the three hydrocarbons. [Our present study with C-4 deuterium labeled substrates establishes that the major 1,3-elimination product is, in fact, 2-*p*-anisyltriaxane (**3**).] A principal objective was to synthesize tertiary chloride **1** suitably monodeuterated at C-4 and to learn whether there is any preference for loss of the axial (i.e., semi-U) or equatorial (semi-W) hydrogen in the formation of **3**.

In the brendane system the cation **7** derived from the tertiary chloride **6** can, in principle, lead to three cyclopropyl



products, **8**, **9**, and **10**, corresponding to removal of a γ proton from C-9, C-4, and C-8, respectively. Our present work with deuterium labeling shows that the least strained product **8** (2-*p*-anisyldeltacyclane[14,15]) is formed predominantly. We undertook to synthesize tertiary chloride **6** and, with a deuterated analogue, to determine exo–endo selectivity in loss of a C-9 hydrogen.

Syntheses of Noradamantyl Substrates. Treatment of noradamantan-2-one[15] (**11a**) with *p*-anisyllithium followed



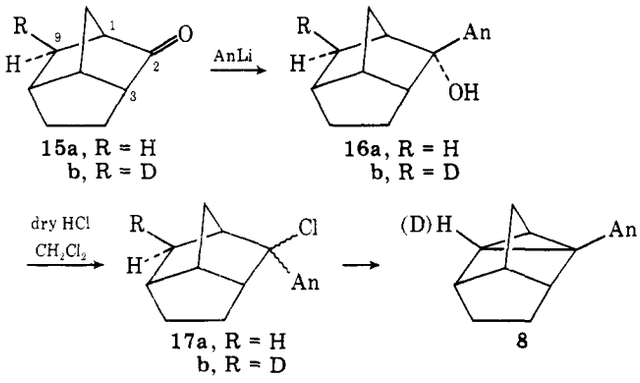
by nonacidic workup affords as principal product the corresponding tertiary alcohol **12a** (mp 69.5–70 °C). The axial configuration for the OH group is not certain but is expected if we presume approach of the aryllithium from the more accessible equatorial face of the carbonyl group. (This view is supported by the known reduction of the same ketone with lithium aluminum hydride, which produces axial alcohol almost exclusively.[15]) The analytical and spectral data and the chemical transformations of **12a** are compatible with its expected structure. For example, ^{1}H NMR shows no low-field carbinyl hydrogen characteristic of secondary alcohols, and treatment with Brown's reagent ($Na_2Cr_2O_7$, H_2SO_4, H_2O) does not oxidize the alcohol but, because of the acidity, only isomerizes it partially to the epimer **14a** (mp 77–78 °C), which we isolated by preparative TLC and characterized analytically and spectrally. Mixtures of the two epimers are readily assayed by gas chromatography.

The alcohol **12a** was converted to the solid tertiary chloride **13a** ($C_{16}H_{19}OCl$) by mild treatment with dry HCl in pentane at 0 °C according to conditions developed by Brown and Rei[16] for tertiary alcohols. In accord with its tertiary structure, the ^{1}H NMR spectrum of chloride **13a** showed no low-field proton typical of secondary halides and gave an instantaneous precipitate with alcoholic silver nitrate. This chloride seems to be a mixture of epimers, but because of the lability of the halogen we were unable to confirm this positively. For example, the chloride melted over a 2–5 °C range, and samples from different runs had melting points that fell between 72 and 87 °C. In the ^{1}H NMR, the CH_3O appeared as two singlets, too closely spaced to be integrated separately for intensity. The chloride decomposed on attempted gas chromatography to give 2-*p*-anisyltriaxane together with an unidentified product. The lability of the chlorine in **13a** was also evident on attempted thin layer chromatography, because substantial hydrolysis to alcohols occurred on the TLC plates. With KOH in dioxane chloride **13a** was converted completely to an 85:15 mixture of alcohols **12a** and **14a**. When this alcohol mixture was treated with HCl in pentane, it reverted to chloride **13a**. The hydrolysis of **13a** is surely of S_N1 type and, interestingly, the capture of OH is not highly stereoselective. This behavior of tertiary, benzylic carbocations contrasts with that of secondary 2-noradamantyl cations, which capture nucleophiles virtually exclusively from the equatorial (i.e., exo) direction.[17]

Chloride **13a** underwent elimination of HCl when heated neat at 205 °C and produced largely 2-*p*-anisyltriaxane (**3**). This hydrocarbon (mp 97–98 °C) was chromatographically separated from minor by-products and showed a cyclopropyl C–H stretch vibration at 3045 cm^{-1}. Its ^{1}H NMR spectrum exhibited the expected aromatic and OCH_3 peaks, and no olefinic C–H. That this cyclopropyl product has structure **3** rather than one of the other two possibilities (**4** or **5**) is supported most directly by results with deuterated precursors to be described.

Our synthesis of labeled chlorides **13b** and **13c** began with the authentic epimeric 4-*d*-noradamantan-2-ones, which were prepared by stereoselective homoketonization routes recently developed.[18] 4-(a)-*d*-Noradamantan-2-one (**11b**), with the label >98% configurationally axial, was converted to the corresponding tertiary alcohol **12b** and then to chloride mixture **13b** by the same procedures that were used for the nonlabeled analogues. The 4-equatorial-*d* ketone **11c** was similarly converted to the corresponding tertiary alcohol **12c** and tertiary chloride **13c**.[19] The deuterium in **11c** is only 85% configurationally equatorial[18] and, accordingly, our 1,3-elimination results had to be corrected for the presence of 15% axial-*d*. This correction turns out to be virtually nonconsequential (see later).

Synthesis of Brendyl Substrates. Addition of *p*-anisyllithium to brendan-2-one (**15a**)[14] produced the corresponding tertiary alcohol **16a** (mp 55.5–57 °C), whose ^{1}H NMR showed no carbinyl proton characteristic of a secondary alcohol. The



OH configuration is provisionally thought to be endo based on the known preference of lithium aluminum hydride to reduce brendan-2-one almost exclusively to *endo*-brendan-2-ol.[20] Treatment with dry HCl in methylene chloride at room temperature converted **16a** to the tertiary chloride **17a** (mp 93–95 °C), which gave an instantaneous positive silver nitrate test and whose ^{1}H NMR showed no low-field absorption typical of secondary halides. Even though this chloride appeared homogeneous, its ^{1}H NMR shows the CH_3O as two extremely closely spaced singlets, so we suspect an epimer mixture. When chloride **17a** was heated neat at 205 °C, the major product was 2-*p*-anisyldeltacyclane (**8**, mp 58.5–59.5 °C) whose IR showed cyclopropyl C–H stretch at 3055 cm^{-1}. Its ^{1}H NMR indicated no olefinic protons and had the expected aromatic and OCH_3 absorptions. That this 1,3-elimination product is 8 and not either of the other possible cyclopropyl structures (**9** or **10**) becomes evident later from our deuterium studies.

The only *d*-labeled precursor synthetically accessible in the brendane series was 9-*exo*-*d*-brendan-2-one (**15b**) containing 4% d_0, 82% d_1, and 14% d_2, which we prepared as reported.[18] The deuterium at C-9 is virtually entirely exo (>95%), and the d_2 species are known to have the second deuterium at C-3.[18,21] This second deuterium presents no complication since it is not involved in the 1,3-elimination of **17b** → **8**. In fact it provides an additional way to compute, mass spectrally, the *d* loss in the elimination. The labeled ketone **15b** was converted to the tertiary alcohol **16b** and to the tertiary chloride **17b** (5% d_0, 83% d_1, 12% d_2) by the procedures developed for the natural abundance material.

1,3-Elimination Results. Because of the extreme ease of ionization of the C–Cl bond in our tertiary substrates, we had hoped to effect stepwise 1,3-dehydrochlorination in several neutral and alkaline solvents. Unfortunately, however, substitution products predominated overwhelmingly in various media and were not accompanied by significant quantities of cyclopropyl product. However, we found that 1,3-elimination occurred in diluted hexane at ca. 225 °C (sealed tube), and so our stereochemical study was necessarily restricted to this single solvent. The ease with which our chlorides were prepared from the alcohols with dry HCl in pentane showed that even in nonpolar media these highly stabilized carbocations are readily formed. As a further check that our halides would ionize in hexane, we heated a dilute solution of chloride **13a** in hexane containing a small amount (ca. 2.5%) of acetic acid. From the resulting mixture of acetates and starting chlorides, we were able to separate **12a acetate,** which had the expected spectral properties and whose structure was confirmed by saponification to authentic **12a.** The epimeric acetate (i.e., **14a acetate**) was also formed, but we were unable to separate it in pure form from the mixture. Similar replacement of chlorine by OAc occurred when we heated chloride **13a** in hexane containing suspended tetrabutylammonium acetate.

In the noradamantyl series, chloride **13a** at 225 °C in hexane gave 2-*p*-anisyltriaxane **3** (ca. 70%) plus two minor by-products (12 and 18%) which were not identified. Hydrocarbon **3** was separated and purified chromatographically, and controls were run to show that none of the cyclopropyl product was produced during chromatography. Identical treatment of deuterated analogues **13b** and **13c** gave labeled 2-*p*-anisyltriaxane, whose mass spectrum revealed the deuterium content and hence the stereoselectivity in the proton loss. At this temperature the release of HCl (and DCl) is evidently irreversible because no dideuterated cyclopropyl species were observed from our monolabeled noradamantyl chlorides. [Reversibility would produce some dideuterated species because 2-*p*-anisyltriaxane (**3**) has a symmetry plane, and a ring bond that is reopened by DCl need not be the one that already carries a labeled carbon.] In the brendyl series similar dehydrochlorination of 2-*p*-anisylbrendyl chloride (**17a** and labeled analogue **17b**) gave almost exclusively (97%) 2-*p*-anisyldeltacyclane (**8**), which was purified chromatographically and, for the labeled case, analyzed for deuterium.

Table I. Mass Spectral Deuterium Assay of 2-*p*-Anisyltriaxane from Dehydrochlorination of 4-*d*-2-Chloro-2-*p*-anisylnoradamantane at 225 °C in Hexane[a]

Run	Substrate[b]	Cyclopropyl product 3 % d_0	Cyclopropyl product 3 % d_1	% D lost	Fractional % D lost
1	Axial-*d* (**13b**)[c]	17	83	6	6.7
2	Axial-*d* (**13b**)[c]	16	84	5	5.6
3	Equat-*d* (**13c**)[d]	70	30	61	77.8[e]
4	Equat-*d* (**13c**)[d]	71	29	62	79.1[e]

[a] All mass spectral numbers are estimated to be ±1–2%. [b] Concentration ca. 2.5×10^{-2} M. [c] The axial-*d* chloride had 11% d_0, 89% d_1. [d] The equatorial-*d* chloride had 9% d_0, 91% d_1. [e] Corrected for 15% configurational inhomogeneity (see footnote 22).

Table I summarizes the mass spectral results for 2-*p*-anisyltriaxane obtained from duplicate runs on each labeled chloride **13b** and **13c.** The axial-*d* substrate **13b** lost 6.2 fractional % of its deuterium (average of runs 1 and 2) in the 1,3-elimination, and the equatorial-*d* substrate **13c** lost 78.5% (average of runs 3 and 4). This last value is corrected for the 15% configurational inhomogeneity in **13c.**[22] From these data the computed isotope effect (k_H/k_D) is 2.04 if we assume, reasonably, that k_H/k_D is the same for cleavage of an axial or an equatorial C–H bond.[23] This value may be compared with one reported earlier (k_H/k_D = 2.1) for 1,3-proton abstraction in acetolysis of *exo*-norbornyl brosylate to form nortricyclane[5a] and with Werstiuk's value of 1.6 in the 1-carbomethoxynorbornyl systems described above.[10] When the isotope effect of 2.04 in our present study is taken into account, the inherent preference for equatorial-H loss over axial-H loss (i.e., semi-W vs. semi-U) is 7.4/1 in this *p*-anisylnoradamantyl system. How much (if any) of this preference for semi-W is attributable to steric as opposed to stereoelectronic factors cannot presently be assessed; but note that the equatorial and axial hydrogens at C-4 in cation **2** have rather similar steric environments.

Table II summarizes relevant data for duplicate dehydrochlorinations on deuterated tertiary brendyl chloride **17b.** The presence of 12% d_2 species in the substrate is immaterial because the second deuterium is at C-3[18] where it plays no relevant role in the 1,3-elimination. However, it does permit the *d* loss to be calculated from the $d_1 \rightarrow d_0$ change as well as from the $d_2 \rightarrow d_1$ change. The d_1–d_0 mass spectral measurements are probably the more accurate because larger numbers are involved; nevertheless, both methods agreed well, cf. average values of 93.5 vs. 92 (Table II and footnotes *b* and *c*) for fractional % D lost. Clearly, this exo-*d* substrate loses most of its

Table II. Mass Spectral Deuterium Assay of 2-*p*-Anisyldeltacyclane from Dehydrochlorination of *9-exo-d*-2-Chloro-2-*p*-anisylbrendane[a] at 225 °C in Hexane

Run	Cyclopropyl product % d_0	% d_1	% d_2	% D lost[b]	Fractional % D lost[b,c]
1	81	18	1	76	92
2	84	15	1	79	95

[a] The substrate had 5% d_0, 83% d_1, 12% d_2. The deuterium at C-9 is virtually entirely exo (>95%).[18] [b] Computed from the amount of d_1 species that became d_0. [c] When computed from the change $d_2 \rightarrow d_1$, the % D lost is 11 (run 1) and 11 (run 2). The corresponding fractional % D lost are 92 and 92.

deuterium. Because only one *d* epimer was available for study, an isotope effect cannot be calculated. However, if we adopt the same value for k_H/k_D (2.04) found with the noradamantyl substrates, we compute the inherent preference for loss of exo H (i.e., semi-W) over endo H (semi-U) to be 27/1. Thus the inclination for semi-W is even higher in the brendyl skeleton than it was in the noradamantyl system (cf. 7.4/1). Steric accessibility of the exo H may be of added importance in the brendyl case because the endo H has extra hindrance due to the ethano bridge.

The preference for semi-W in our two substrates contrasts with the bias for semi-U observed by Werstiuk for secondary halides in the norbornyl series.[10] Because his solvent was aqueous ethanol whereas ours was hexane (where ion pairing should be more pronounced), the different stereoselectivities may be dictated by the media. However, if solvent alone is not responsible for the differences, and if the three skeletons examined to date are representative, it appears that stereochemistry of γ-hydrogen loss from a carbocation may not be subject to overriding stereoelectronic control.

Experimental Section

General. Except where noted otherwise the following information applies. Melting points were taken in open capillary tubes in a Thomas-Hoover apparatus. They are corrected and are rounded to the nearest 0.5 °C. Infrared spectra were recorded in carbon tetrachloride solution on a Perkin-Elmer Model 337 or 457 grating infrared spectrophotometer. A Perkin-Elmer Model 900 analytical gas chromatograph with a hydrogen flame ionization detector was used. Nuclear magnetic resonance spectra were run on a Varian Associates HA-100 or A-60 instrument with tetramethylsilane as the internal reference. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6 single-focusing instrument. Spectra used in the identification of new compounds were run at 70 eV; spectra of deuterated samples were recorded at 15 eV. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., and Galbraith Laboratories, Inc. Anhydrous sodium sulfate or magnesium sulfate was the drying agent unless specified.

We purified technical grade pentane (Eastman) by stirring it over concentrated sulfuric acid, washing with 10% aqueous sodium bicarbonate, drying, filtering, and distilling. A mixture of hexanes was dried by distillation from sodium; the dried solvent was stored over 4A molecular sieves. The term "hexane" refers to this dried and distilled mixture. Ten percent silver nitrate/silica gel for column chromatography was prepared by addition of a solution of silver nitrate (4.99 g) in 7 ml of water to 50.13 g of silica gel.

Analytical and preparative (20 × 20) thin layer chromatography (TLC) was performed on silica gel plates. Silica gel with 2% silver nitrate was made from 1.5 g of silver nitrate in 170 ml of water and 75 g of silica gel. High-pressure liquid chromatography (HPLC) was done on a Perkin-Elmer Model 1220 with a UV detector (254 nm) and a Xil-X-1 column, 2.6 × 50 mm; mobile phase 20% chloroform/80% hexane; flow rate 1 ml/min; ambient temperature. These solvents were previously distilled and degassed.

2-(a)(?)-Hydroxy-2-*p*-anisylnoradamantane. Noradamantan-2-one[15] (0.50 g, 3.68 mmol) in 10 ml of ether was added dropwise to *p*-anisyllithium[24] (prepared from 36.8 mmol of *p*-bromoanisole and 36.8 mmol of *n*-butyllithium) at 0 °C in 5 min. The mixture was stirred at room temperature for 1 h and poured onto ice. Workup of the ether layer left a yellow oil, which was chromatographed on silica gel with pentane and ether to give 2-*p*-anisylnoradamantan-2-ol (needles from ligroin, mp 69.5–70 °C, 86% yield, >97% pure by GLC): IR 3595 (O–H stretch), 2920, 2835 (methoxyl C–H), 1615, 1505, 1300, 1250, 1185, 1040 cm^{-1}; δ ($CDCl_3$) 7.38–6.76 (m, 4 H, aromatic), 3.72 (s, 3 H, CH_3O), 2.76–1.11 (complex multiplets, 12 H), 1.68 (sharp singlet projecting out of multiplets, 1 H, OH). Prominent mass spectral peaks are at *m/e* 244, 226, 185, 163, 150, 135 (base), 121, 77, and 55.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.87; H, 8.41.

In other runs with 1.2 equiv each of *n*-butyllithium and *p*-bromoanisole and 1.0 equiv of ketone, we obtained lower yields (e.g., 70%), but the alcohol was pure after one recrystallization from pentane *without* any column chromatography. It showed only one peak on two different GLC columns (t_R 10 min on 1.5% SE-30, 9 ft × 0.125 in., 230 °C; t_R 8 min on 5% XE-60, 2% Carbowax 20M on Chromosorb W, 4 ft × 0.125 in., 190 °C) and only one spot on analytical TLC (30% ethyl acetate in hexane).

2-(e)(?)-Hydroxy-2-*p*-anisylnoradamantane. The tertiary alcohol **12a** (470 mg) in ether (25 ml) was stirred with Brown's reagent[25] (1.5 ml) for 15 min. The crude product after workup was chromatographed on preparative TLC plates (30% ethyl acetate in hexane) and gave two major components. The faster moving one (R_f 0.5) was identified by IR and NMR as the starting alcohol (166 mg, mp 68–69 °C). The slower (R_f 0.4) component had mp 71.5–73 °C (88 mg) after one recrystallization from pentane, and showed one peak on GLC (t_R 6 min on 5% XE-60 2% Carbowax 20M on Chromosorb W, 4 ft × 0.125 in., 190 °C): IR 3600, 2935, 2875, 2835, 1610, 1510, 1465, 1330, 1250, 1180, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 7.28–6.65 (m, 4 H, aromatic), 3.74 (s, 3 H, methoxyl CH), 2.7–1.1 (complex multiplets, 13 H with the OH singlet evident at 1.48; in $CDCl_3$ this OH shifted to 2.14 and was a sharp singlet). The analytical sample had mp 77–78 °C (from pentane).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.54; H, 8.40.

Generation of Anhydrous Hydrogen Chloride. The Brown chlorination apparatus[16] was modified to preclude a pressure-controlled reaction. An ordinary glass buret filled with concentrated hydrochloric acid was inserted through a rubber stopper at the top of a suction flask containing well-stirred concentrated sulfuric acid. The flask was connected by Tygon tubing and a vacuum adapter to the reaction vessel, which was equipped with a stirrer, a rubber septum for introduction of the sample by syringe, and a vacuum adapter leading to an aqueous sodium hydroxide trap. This apparatus permitted manual control of the generation of anhydrous hydrogen chloride.

2-Chloro-2-*p*-anisylnoradamantane. The modified chlorination set-up was assembled and purged with dry hydrogen chloride. 2-(a)-Hydroxy-2-*p*-anisylnoradamantane (**12a**, 0.274 g) in 18 ml of pentane was chlorinated at 0 °C for 70 min (6.0 ml of concentrated hydrochloric acid used). The reaction mixture was aspirated gently and then vacuum was applied at 0 °C for 2 h. 2-Chloro-2-*p*-anisylnoradamantane (0.274 g, 93% yield) solidified and was recrystallized from ligroin to flat, rectangular plates, mp 73–75 °C. The chloride gave an immediate positive test with alcoholic silver nitrate solution: ν 2945, 2870, 2840 (methoxyl C–H), 1615, 1520, 1470, 1320, 1260, 1185, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.44–6.78 (m, 4 H, aromatic), 3.82 (s, with a sharp spike on the high field side, 3 H, CH_3O), 2.93–1.32 (complex multiplets, 12 H). Prominent mass spectral peaks are at *m/e* 262, 227, 226, 186, 185 (base), 172, 170, 153, 121, 115, and 77.

Anal. Calcd for $C_{16}H_{19}OCl$: C, 73.13; H, 7.29. Found: C, 73.29; H, 7.11.

In other runs the IR of various chloride mixtures were quite similar, with differences only in relative band intensities. A run conducted for 20 min gave 84% of chloride, mp 79–82 °C after one recrystallization from pentane. GLC (on 5% XE-60 2% Carbowax 20M on Chromosorb W, 4 ft × 0.125 in., 190 °C) decomposed the chloride to give two overlapping peaks with t_R 5 and 7 min, respectively. In attempts to isolate the two decomposition products, we combined several batches of chloride **13a** for preparative GLC at 190 °C and 30 psi on a column 6 ft × 0.25 in. made from 5% XE-60, 2% Carbowax 20M on ABS 80/100. The major component (t_R 12 min) was collected (98% pure) and identified as 2-*p*-anisyltriaxane by comparison of ^1H NMR and IR spectra with those of authentic material. The other product (t_R 16 min) could not be obtained pure and remains unidentified.

Hydrolysis of Chloride Mixture. The chloride (mp 79–82 °C from above, 130 mg) and sodium hydroxide (40 mg) in dioxane (10 ml) and water (10 ml) was heated overnight at 80 °C. The solvent was removed in vacuo, water (10 ml) was added, and the mixture was extracted with pentane (3 × 30 ml), washed with brine (100 ml), and dried. Solvent

removal left 110 mg of crude product, mp 67–69 °C after one recrystallization from pentane, 90 mg (75%). A $AgNO_3$ test was negative, and TLC showed two components with R_f values corresponding to those of alcohols **12a** and **14a**. GLC showed appropriate t_R of 6 and 8 min and a ratio of 85:15, which was confirmed by two ^1H NMR (CCl_4) singlets at δ 3.70 and 3.72 (CH_3O) in the same ratio.

Conversion of Alcohol Mixture to Chloride Mixture. Treatment of the 85:15 mixture of **12a** and **14a** (50 mg) with dry HCl (generated from 1.0 ml of concentrated hydrochloric acid) for 10 min gave a chloride mixture, mp 81–83 °C (32 mg, 60%). The IR was very similar to that of the chloride **13a** obtained from alcohol **12a**.

2-*p*-Anisyltriaxane. 2-Chloro-2-*p*-anisylnoradamantane (65 mg) was heated neat at 205 ± 5 °C for 45 min and vacuum distilled. Analytical GLC of the crude product (44 mg, mp 65–77 °C) showed two peaks (96 and 4%). Column chromatography of the mixture on 10% silver nitrate/silica gel with pentane gave pure 2-*p*-anisyltriaxane (mp 97–98 °C, one peak on GLC): IR 3045 (cyclopropyl C–H), 2945, 2855, 2840 (methoxyl C–H), 1620, 1515, 1470, 1295, 1240, 1175, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 6.99–6.58 (doublet of doublets, 4 H, aromatic), 3.68 (s, 3 H, CH_3O), 2.68 (broad doublet, 3 H, bridgeheads), 2.33 (broad singlet, 2 H, cyclopropyl), 2.03–1.54 (complex multiplet, 3 H, equatorial methylene), 1.34 (d, 3 H, axial methylene).[13] Principal mass spectral peaks are at *m/e* 226, 186, 185 (base), 172, 170, 153, 141, 128, 115, and 77.

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.76; H, 7.96.

2-*p*-Anisylbrendan-2-ol. Brendan-2-one[14,15] (2.6 g, 19 mmol) in 40 ml of ether was added slowly to *p*-anisyllithium[24] (from 144 mmol of *p*-bromoanisole) at 0 °C. The mixture was stirred at room temperature for 90 min, poured onto ice, and worked up to leave a yellow oil. Column chromatography on silica gel with pentane and ether gave >99% pure (by GLC) 2-*p*-anisylbrendan-2-ol (needles from ligroin, mp 55.5–57 °C, 75% yield): IR 3595 (O–H stretch), 2945, 2835 (methoxyl C–H), 1610, 1505, 1470, 1255, 1180, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–6.77 (m, 4 H, aromatic), 3.72 (s, 3 H, CH_3O), 2.54–1.25 (complex multiplets, 12 H), 1.46 (sharp singlet superimposed on multiplets, 1 H, OH).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.91; H, 8.48.

2-Chloro-2-*p*-anisylbrendane. The modified chlorination setup was flushed with dry hydrogen chloride, and 2-*p*-anisylbrendan-2-ol (0.050 g) in 5 ml of methylene chloride was injected. The alcohol was treated at room temperature with anhydrous hydrogen chloride, generated for 1.5 h from 7.0 ml of concentrated hydrochloric acid. The solution was dried, filtered, and evaporated to an oil, which instantaneously gave a positive test with alcoholic silver nitrate solution. The 2-chloro-2-*p*-anisylbrendane was recrystallized from ligroin to flat plates: mp 93–95 °C; IR 2945, 2870, 2840 (methoxyl C–H), 1620, 1515, 1470, 1320, 1255, 1180, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.35–6.66 (m, 4 H, aromatic), 3.71 (two very closely spaced singlets, 3 H, CH_3O), 3.08–0.84 (complex multiplets, 12 H). Prominent mass spectral peaks are at *m/e* 262, 227, 226 (base), 211, 198, 197, 186, 185, 159, 153, 141, 128, 121, 117, 115, 91, and 77.

Anal. Calcd for $C_{16}H_{19}OCl$: C, 73.13; H, 7.29. Found: C, 72.94; H, 7.10.

2-*p*-Anisyldeltacyclane. 2-Chloro-2-*p*-anisylbrendane was heated neat at 205 ± 5 °C for 1 h and vacuum distilled. Column chromatography of the crude product (ca. 25% yield) on 10% silver nitrate/silica gel with pentane eluted an oil (99% pure by GLC), which solidified when scratched (mp 58.5–59.5 °C): IR 3055 (cyclopropyl C–H), 2945, 2870, 2840 (methoxyl C–H), 1620, 1515, 1475, 1295, 1180, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 6.92–6.58 (doublet of doublets, 4 H, aromatic), 3.67 (s, 3 H, CH_3O), 2.21 (s, 1 H, bridgehead), 2.08 (s, 1 H, bridgehead), 1.82 (s, 1 H, bridgehead), 1.76–1.47 (complex multiplet, 6 H, methylene), 1.20 (s, 2 H, cyclopropyl). Principal mass peaks appeared at *m/e* 226 (base), 211, 198, 197, 185, 159, 153, 141, 121, 115, 91, and 77.

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.83; H, 7.83.

Dehydrochlorination of 2-Chloro-2-*p*-anisylnoradamantane in Hexane. 2-Chloro-2-*p*-anisylnoradamantane (26 mg) and 4 ml of dry hexane in a sealed tube were heated at 225 ± 5 °C for 4 h. Analysis of the contents by GLC (at 150 °C, 50 psi on 5% SE-30 on silanized 60/80 Chromosorb W) indicated three peaks in the ratio of 12, 70, and 18%. Column chromatography of the mixture on 10% silver nitrate/silica gel gave 2-*p*-anisyltriaxane (the major component of the crude mixture) in 99% purity. An infrared spectrum was identical with that of authentic 2-*p*-anisyltriaxane described earlier.

Dehydrochlorination of 2-Chloro-2-*p*-anisylbrendane in Hexane. 2-Chloro-2-*p*-anisylbrendane (30 mg) and 4 ml of dry hexane in a sealed tube were heated at 225 ± 5 °C for 4 h. GLC analysis (as immediately above) showed 97% 2-*p*-anisyldeltacyclane and a 3% impurity. The crude product was chromatographed on 10% silver nitrate/silica gel to provide a solid (99% pure by GLC) whose GLC retention time and infrared spectrum were identical with those of authentic 2-*p*-anisyldeltacyclane.

Controls in Chromatographic Workup. Column chromatography of 2-chloro-2-*p*-anisylnoradamantane on 2% silver nitrate/silica gel with pentane eluted no chlorides or 2-*p*-anisyltriaxane in the pentane fractions. Alcohols produced by hydrolysis on the column were eluted only in the ether fractions. Thus, after dehydrochlorination experiments any residual starting chlorides are trapped on the column as alcohols in our isolation procedure and do not undergo 1,3-elimination on the column.

Ionization of 2-Chloro-2-*p*-anisylnoradamantane in Hexane. Method I. A solution of the chloride **13a** (100 mg) in hexane (20 ml) containing glacial acetic acid (0.5 ml with 1% acetic anhydride) was refluxed for 2 days. The cooled solution was washed consecutively with 10% $NaHCO_3$ (50 ml), water (50 ml), and brine (50 ml), dried and evaporated to leave a liquid (87 mg). Analytical high-pressure liquid chromatography showed two peaks corresponding to alcohols **12a** and **14a**, followed by a broad, unsymmetrical peak. (Separately we showed that HPLC of the original chloride gives two peaks whose retention times are identical with those shown by authentic alcohols **12a** and **14a**.) For separation the total crude product from this experiment was chromatographed on preparative TLC plates (20 × 20 cm, 1.5 mm, silica gel with 2% silver nitrate) with 30% ethyl acetate in hexane. Three bands were obtained.

The fastest band (R_f 0.75) gave 40 mg of liquid acetate, which showed only one spot on analytical TLC: ^1H NMR (CCl_4) δ 7.32–6.65 (m, 4 H, aromatic), 3.75 (s, 3 H, OCH_3), 3.55–3.25 (broad triplet, 1 H), 1.90 (s, $COCH_3$), 2.6–1.0 (m, 14 H); IR 2910, 1740, 1610, 1370, 1240, 1180, 1140 cm^{-1}. Saponification of this acetate (30 mg) in refluxing methanolic KOH under nitrogen for 4 h gave, on conventional workup with ether, 25 mg, mp 69–70 °C (after one recrystallization from pentane). This alcohol showed only one spot on TLC (silica gel, 20% ethyl acetate in benzene), and the IR was identical with that of authentic 2-(a)(?)-hydroxy-2-*p*-anisylnoradamantane (**12a**).

The second TLC band was very close to the first and gave 20 mg of product whose IR, etc., suggested that it was a mixture of the alcohol **12a** and the acetate of **14a**.

The third TLC band gave 20 mg of crude alcohol whose IR was virtually identical with that of the alcohol **14a**.

Method II. 2-Chloro-2-*p*-anisylnoradamantane (**13a**, 130 mg) in hexane (40 ml, previously distilled from molecular sieve 4A) containing suspended tetrabutylammonium acetate (900 mg, dried in vacuo overnight at 78 °C) was heated at reflux overnight. Undissolved salt was separated and the solution was evaporated in vacuo. Preparative TLC (silica gel, 20% ethyl acetate in hexane) gave two principal bands and some minor ones. The fastest band (R_f 0.7) gave 7 mg of liquid whose IR was virtually identical with that of **12a acetate** obtained by method I. The slower band (R_f 0.4) gave 110 mg shown to be a 14:86 mixture on GLC. After recrystallization from pentane the product had mp 71–73 °C and its IR closely resembled that of authentic epimeric alcohol **14a**.

Deuterated Ketones.[18] Homoketonization of 2-acetoxytriaxane in sodium methoxide–methanol-*O*-d_1 as reported provided 4-*d*-noradamantan-2-one (9% d_0, 91% d_1), with the deuterium 85 relative percent equatorial and 15 relative percent axial. Homoketonization in methanol-*O*-d_1 containing sulfuric acid-d_2 gave the deuterated ketone (9% d_0, 91% d_1) with the deuterium >98% axial.

Alkaline homoketonization of 2-acetoxydeltacyclane as reported gave exclusively deuterated brendan-2-one (4% d_0, 82% d_1, 14% d_2) with one deuterium at the 9-exo position (no detectable endo epimer); and the 14% d_2 species has the second deuterium at the C-3 bridgehead.[18,21] Acid homoketonization is known to give a mixture of brexan-2-one and brendan-2-one; the C-9 deuterium in the latter ketone is also entirely exo.[18]

Deuterated Substrates. Deuterium-labeled alcohols were prepared from the corresponding deuterated ketones exactly as we described for the unlabeled ketones. Also, the deuterated chlorides were prepared from the deuterated alcohols by the same procedures used in the analogous natural abundance compounds. The 1,3-eliminations were conducted as before and the mass spectral results are in Tables I and II in the text. Spectral data on the deuterium labeled compounds are summarized below.

4-(e)-*d*-2-(a)-Hydroxy-2-*p*-anisylnoradamantane (12c): mp 71.5–72 °C; ν 3593 (O–H stretch), 2940, 2860, 2835 (methoxyl C–H), 2180 (C–D stretch), 1615, 1515, 1475, 1305, 1250, 1180, 1070, 1040, 1020 cm^{-1}; ^1H NMR (CCl_4) δ 7.36–6.67 (doublet of doublets, 4 H, aromatic), 3.72 (s, 3 H, CH_3O), 2.72–1.05 (complex multiplets, 12 H,

with a sharp singlet at 1.33 (OH) standing out).

4-(a)-*d*-2-(a)-Hydroxy-2-*p*-anisylnoradamantane (12b): mp 70–71.5 °C; ν 3595 (O–H stretch), 2940, 2880, 2840, (methoxyl C–H), 2225 (C–D stretch), 1620, 1515, 1475, 1310, 1250, 1180, 1070, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 7.82–6.64 (doublet of doublets, 4 H, aromatic), 3.70 (s, 3 H, CH_3O), 2.68–1.05 (complex multiplets, 12 H).

4-(e)-*d*-2-Chloro-2-*p*-anisylnoradamantane (13c, 9% d_0, 91% d_1): mp 68–70 °C; ν 2940, 2870, 2835 (methoxyl C–H), 2175 (C–D stretch), 1615, 1510, 1310, 1255, 1180, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.31–6.65 (complex multiplet, 4 H, aromatic), 3.74 (s with spike, 3 H, CH_3O), 3.20–1.26 (complex multiplets, 11 H).

4-(a)-*d*-2-Chloro-2-*p*-anisylnoradamantane (13b, 11% d_0, 89% d_1): mp 81–83.5 °C; ν 2940, 2870, 2835 (methoxyl C–H), 2225 (C–D stretch), 1620, 1515, 1470, 1320, 1255, 1180, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.35–6.67 (complex multiplet, 4 H, aromatic), 3.75 (s with spike, 3 H, CH_3O), 3.19–1.31 (complex multiplets, 11 H).

9-*exo*-*d*-2-*p*-Anisylbrendan-2-ol: mp 55–55.5 °C; ν 3595 (O–H stretch), 2950, 2865, 2835 (methoxyl C–H), 2185 (C–D stretch), 1615, 1510, 1470, 1355, 1300, 1250, 1185, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.34–6.65 (doublet of doublets, 4 H, aromatic), 3.71 (s, 3 H, CH_3O), 2.54–1.18 (complex multiplets, 11 H), 1.13 (s, 1 H, OH).

9-*exo*-*d*-2-Chloro-2-*p*-anisylbrendane (5% d_0, 83% d_1, 12% d_2): ν 2950, 2870, 2835 (methoxyl C–H), 2175 (C–D stretch), 1615, 1510, 1470, 1300, 1255, 1185, 1045 cm^{-1}; ^1H NMR (CCl_4) δ 7.38–6.65 (complex multiplet, 4 H, aromatic), 3.74 (two very closely spaced singlets, 3 H, CH_3O), 3.10–0.90 (complex multiplets, 11 H).

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Registry No.—**3,** 61062-27-9; **8,** 61062-28-0; **11a,** 17931-67-8; **11b,** 61062-31-5; **11c,** 61116-69-6; **12a,** 61062-29-1; **12a** acetate, 61062-32-6; **12b,** 61062-30-4; **12c,** 61116-70-9; **13a** isomer 1, 61062-33-7; **13a** isomer 2, 61116-71-0; **13b** isomer 1, 61062-34-8; **13b** isomer 2, 61116-72-1; **13c** isomer 1, 61116-73-2; **13c** isomer 2, 61116-74-3; **14a,** 61116-75-4; **15a,** 1521-92-2; **15b,** 61092-31-7; **16a,** 61062-35-9; **16b,** 61062-36-0; **17a** isomer 1, 61062-37-1; **17a** isomer 2, 61116-76-5; **17b** isomer 1, 61062-38-2; **17b** isomer 2, 61116-77-6; *p*-anisyllithium, 14774-77-7; *p*-bromoanisole, 104-92-7.

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(22) Illustrative calculation (run 3). Of the total % *d* loss (61%), the amount that came from the 15% axial-*d* component is 0.8% (i.e., 6.2 × 15 × 91). Therefore the amount lost from the equatorial-*d* component is 60.2% (i.e., 61 − 0.8). The corrected fractional % *d* loss is 60.2/85 × 91 = 77.8. For run 4 this corrected value comes to 79.1.

(23) Let P = inherent preference for loss of equatorial H vs. axial H; let Y = isotope effect (k_H/k_D) for cleavage of C–H (equatorial or axial). For the axial-*d* substrate:

$$\frac{\text{fractional \% equat H lost}}{\text{fractional \% axial D lost}} = P \times Y$$

For the equatorial-*d* substrate:

$$\frac{\text{fractional \% equat D lost}}{\text{fractional \% axial D lost}} = \frac{P}{Y}$$

Substitution of the appropriate average percentages from Table I and solving the two equations simultaneously gives $Y = 2.04$ and $P = 7.4$.

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