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Stereochemistry of Deuteron Attack on the 3α,5α-Cycloandrost-6-ene System[1]

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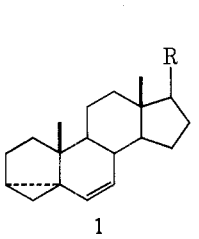
Acid-catalyzed hydration of the 3α,5α-cycloandrost-6-ene system gives the 3β-hydroxyandrost-5-ene system in high yield. In the presence of D_2O, irreversible deuteron attack at the 7 position occurs equally from the α and β faces of the steroid. Elimination of methanol from 7β-deuterio-6β-methoxy-3α,5α-cycloandrostan-17β-ol occurs by pyrolysis with 70% loss of the 7β-deuterium (cis elimination), by alumina catalysis with 48% loss of the 7β-deuterium, and by electron impact in the mass spectrometer with no loss of the 7β-deuterium.

Although it had been observed in 1946[2] that acid-catalyzed hydration of 3α,5α-cyclocholest-6-ene (**1**, R = C_8H_{17}) gives rise to cholesterol, no further study of this reaction had been reported. Acid-catalyzed rearrangements of related vinyl cyclopropanes have, however, been examined in considerable depth.[3,4] Since this hydration appeared to offer a useful method for the introduction of deuterium at the 7 position of the biologically important 3β-hydroxy-Δ^5-steroids, we have determined the direction of addition of the proton (deuteron) to the 3α,5α-cyclo-Δ^6 system.



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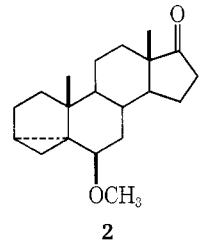

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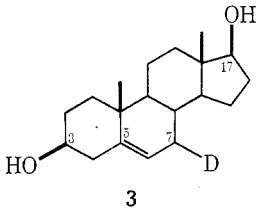

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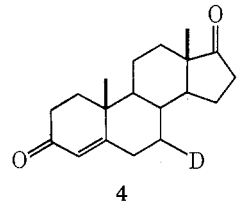

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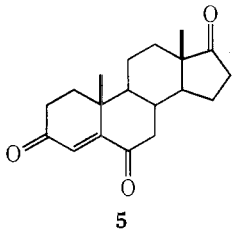

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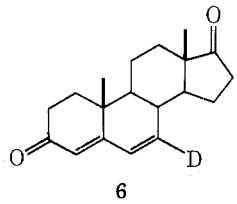

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3α,5α-Cycloandrost-6-en-17-one[5] (**1**, R = O) was prepared by the standard procedure of converting 3β-hydroxyandrost-5-en-17-one *p*-toluenesulfonate to 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**), which on treatment with alumina in refluxing xylene gave **1**, R = O, in 14% yield. Attempts to convert the 3-*p*-toluenesulfonate directly to the 3α,5α-cycloandrost-6-ene system with potassium *tert*-butoxide in *tert*-butyl alcohol, or treatment with alumina or barium oxide in refluxing xylene, led instead to the formation of the 3,5-diene.

Hydration of 3α,5α-cycloandrost-6-en-17-one (**1**, R = O) with D_2SO_4 and D_2O in dimethyl sulfoxide at 90°, followed by acid-catalyzed exchange of the 16-deuterium, gave 3β-hydroxyandrost-5-en-17-one with incorporation of 94% of one nonexchangeable deuterium atom per molecule.

With bis(2-methoxyethyl) ether (diglyme) which had been distilled from a mixture with D_2O, 3α,5α-cycloandrost-6-en-17β-ol (**1**, R = OH) was converted by D_2SO_4–D_2O to androst-5-ene-3β,17β-diol (**3**, 87% d_1, 13% d_2), which crystallized on cooling the sealed tube. Chromium trioxide oxidation[6] and isomerization with dilute hydrochloric acid gave androst-4-ene-3,17-dione (**4**, 100% d_1, 0% d_2). Unlabeled androst-5-ene-3β,17β-diol was recovered essentially unlabeled after treatment with D_2SO_4–D_2O–diglyme under the conditions of the hydration reaction, and in experiments in which 3α,5α-cycloandrost-6-en-17β-ol was recovered, it too was unlabeled. The additional 13% of deuterium is therefore incorporated at positions 2, 3, 4, or 6 during the ring-opening hydration reactions.

That the deuteron attack on the vinyl cyclopropane (**1**, R = OH) had occurred at the 7 position was established since no loss of label occurred from the derived androst-4-ene-3,17-dione (100% d_1) under conditions (D_2SO_4–D_2O–diglyme) which caused incorporation of five deuterium atoms into testosterone at carbons 2, 2, 4, 6, and 6. A by-product in the chromium trioxide oxidation of deuterated androst-5-ene-3β,17β-diol (**3**) is androst-4-ene-3,6,17-trione (**5**).

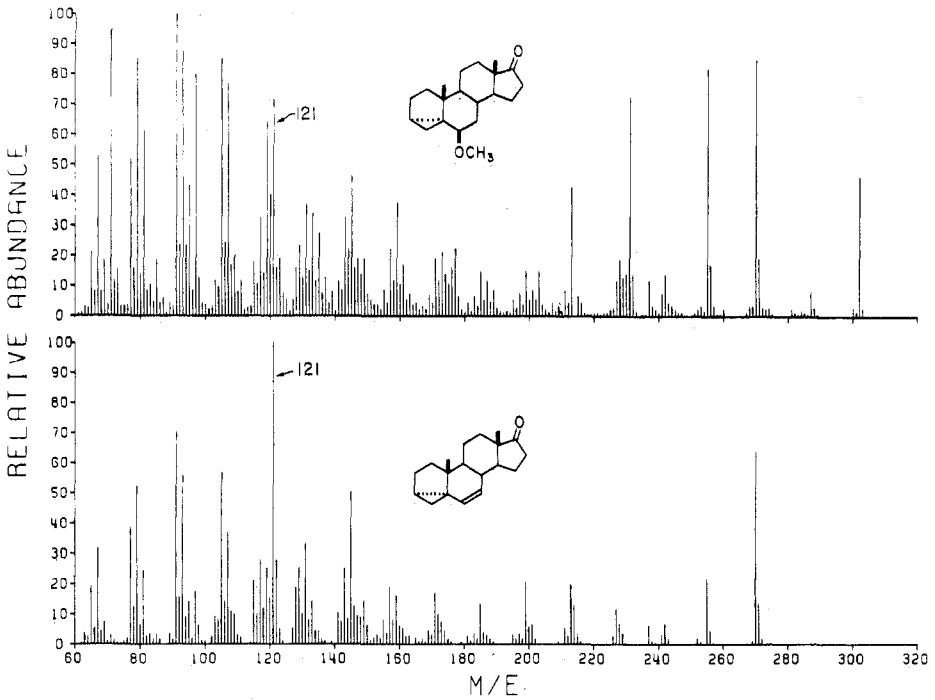

Figure 1. Mass spectra of 6β-methoxy-3α,5α-cycloandrostan-17-one and 3α,5α-cycloandrost-6-en-17-one.

This enetrione contained no excess deuterium; the presence of the 6-ketone had allowed exchange of hydrogen at the 7 position presumably during the acid treatment. The mass spectrum of the deuterated androst-4-ene-3,17-dione (**4**) showed an abundant peak at *m/e* 124 characteristic of steroid-4-en-3-ones.[7] This peak would have been at *m/e* 125, had the introduced label been attached to a ring A or positions 6 or 8. In the 3α,5α-cyclo-Δ^6 system, the geometry of the rings is such that the trigonal C-6 is very close to the bisected conformation found most favorable[8] for overlap of a 6-carbonium with the cyclopropane ring, and indeed the protonation giving a tetrahedral C-7 causes C-6 to move from this optimal orientation. This cyclopropyl carbonium ion is clearly preferred to the less stable[9] allyl carbonium ion which would be formed by attack of the proton (deuteron) on the cyclopropane ring. Conjugated vinyl cyclopropanes[3,4] are thus an exception to the rule[10] that cyclopropanes are more reactive toward the addition of acid than are olefins.

The stereochemistry of deuterium substitution at the 7 position was not immediately clear. The ir spectrum of 7-deuterio-3β-hydroxyandrost-5-en-17-one showed the presence of bands indicative of both axial α (2102, 2132 cm^{-1}) and equatorial β (2143 cm^{-1}) deuterium.[11] The NMR spectrum of a vinyl 6 proton coupled only to 7α-H (7β-D) is known to be a sharp singlet, while vinyl 6-H coupled to 7β-H (7α-βr) gives a sharp doublet, J = 5 Hz.[12] The 7-deuterio-3β-hydroxyandrost-5-en-17-one and 7-deuterioandrost-5-en-3β,17β-diol diacetate derived from the ring opening–hydration reactions had 6-H as a broad singlet or indistinct doublet of half-band width 8 Hz indicating that the products were mixtures of 7α- and 7β-D.

The orientation of the deuterium at the 7 position was established by chloranil dehydrogenation, which has been shown to remove the 7α hydrogen atom in the conversion of steroid Δ^4-3-ketones to the 4,6-dien-3-ones.[12] Androst-4-ene-3,17-dione-7ξ-*d* (**4**, 100% d_1), prepared as described, gave on chloranil dehydrogenation androsta-4,6-diene-3,17-dione (**6**, 46% ± 2% d_1) under conditions where dehydrogenation had progressed to the extent of 70%, and 49 ± 2% when the reaction was 87% complete. Further reaction caused appreciable formation of the 1,4,6-trien-3-one. The unreacted androst-4-ene-3,17-dione had lost no deuterium. The ring-opening hydration reaction therefore occurs with hydrogen attack on the 7 position equally from the α and β directions. Since no more than one deuterium atom is incorporated at the 7 position during the hydration, and since this step is not stereospecific, the addition of the deuteron at the 7 position is not reversible under these reaction conditions.

The hydration reaction was also carried out on 3α,5α-cyclocholest-6-ene (**1**, R = C_8H_{17}) and gave 7-deuteriocholesterol (90% d_1). With 3α,5α-cyclopregn-6-en-20-one (**1**, R = $COCH_3$),[5] the 7-deuteriopregnenolone formed was contaminated with the 17 epimer and contained four additional deuterium atoms due to the exchange at the 17 and 21 positions; on treatment with acid, only the 7 deuterium (84% d_1) remained; the mixture of the 17 epimers was separated by column chromatography to give pregnenolone-7-*d*.

3α,5α-Cycloandrost-6-en-17-one (**1**, R = O) and its precursor, 3α,5α-cyclo-6β-methoxyandrostan-17-one (**2**), were examined by combined GLC–mass spectrometry using the stainless steel gauze, solid injection technique.[12,13] During GLC of the 6β-methoxy compound (**2**) partial pyrolytic decomposition occurred in the flash heater (245°) to give a GLC peak well separated from that of the methyl ether. The retention time and mass spectrum of this product (M^+ 270) are identical with those of 3α,5α-cycloandrost-6-en-17-one (**1**, R = O), and different from those of androsta-3,5-dien-17-one, though the 3,5-dien-17-one itself differs only slightly, but significantly, in mass spectrum from 3α,5α-cycloandrost-6-en-17-one. In addition, the mass spectrum of 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**) (Figure 1) shows a strong *m/e* 270 corresponding to loss of the elements of methanol; the fragmentation pattern below *m/e* 270 is not that of 3α,5α-cycloandrost-6-en-17-one.

Since 7β-deuterio-3β-hydroxyandrost-5-en-17-one[12] was available, it was possible to determine if cis elimination occurred with loss of the 7β-hydrogen during loss of methanol from 6β-methoxy-3α,5α-cycloandrostan-17-one by (a) pyrolysis, (b) electron impact, and (c) alumina catalysis. 7β-Deuterio-3β-hydroxyandrost-5-en-17-one (99% d_1) was

converted to the 3-*p*-toluenesulfonate and thence to 7β-deuterio-6β-methoxy-3α,5α-cycloandrostan-17-one (99% d_1).

(a) The ions at *m/e* 271 (M − CH_4O), and 256 (M − CH_4O-CH_3) showed complete retention of the deuterium; loss of methanol on electron impact involves no loss of 7β-hydrogen, and hence no 1,2-cis elimination.

(b) The product M^+ 270, formed by pyrolytic loss of methanol from the methyl ether in the flash heater, contained only 31% d_1 indicating approximately 70% cis elimination of deuteriomethanol.

(c) On refluxing with xylene and alumina as before, the 7β-deuterio-6β-methyl ether was converted to 3α,5α-cycloandrost-6-en-17-one containing 52% d_1. Although cis elimination is important in both cases, neither pyrolysis nor alumina-catalyzed removal of methanol appears to be stereospecific. It is not known if there is an isotope effect operating in these processes.

The stereochemistry of alumina-catalyzed elimination of methanol in solution has not been studied previously; the dehydration of 1-decalols on passage of the vapor over alumina at 280–400° has been rationalized[14] in terms of a predominantly trans mechanism.

The mass spectra of 3α,5α-cyclosteroids with a 6 double bond or 6β-hydroxy or 6β-methoxy substituents (Figure 1) all show *m/e* 121 as a prominent ion. Since the weight of this fragment does not depend upon the nature of the 17 substituent, it probably corresponds to ring A and part of ring B with cleavage of C-7/8 and C-9/10. The presence of deuterium at C-7 causes this ion of 3α,5α-cycloandrost-6-en-17-one (**1**, R = O) and of 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**) to become *m/e* 122. The relative abundance of *m/e* 121 and 122 indicates 90% retention of deuterium in the ion from **1**, R = O, and 60% from **2**.

Experimental Section

Combined gas–liquid chromatography–mass spectrometry was carried out on an LKB 9000 instrument with helium carrier gas, and OV-1 on Gas-Chrom Q (Applied Science Laboratories, State College, Pa.) as the stationary phase. Samples in the solid state, adsorbed on stainless steel gauze,[13] were injected into the flash heater at 230°, and the chromatographic column was kept at 200° except where otherwise noted. The molecular separator was maintained at 250°, and the ion source at 270°. Melting points were determined on a Kofler block. NMR spectra were measured on a Varian A-60 spectrometer in deuteriochloroform solution. Chemical shifts are reported in parts per million downfield from tetramethylsilane.

3β-Hydroxyandrost-5-en-17-one-*7,16,16-d*$_3$. A solution of 3α,5α-cycloandrost-6-en-17-one (**1**, R = O, 300 mg, 1.11 mmol) in dimethyl sulfoxide (25 ml) with 4 *N* D_2SO_4 in D_2O (5 ml) in a sealed tube was kept at 90° for 24 hr. On cooling, crystals formed in the tube. The solution was diluted with water, when further crystallization occurred. The product was filtered off and washed with water, giving 298 mg (1.03 mmol, 93% yield). Thin layer chromatography and GLC–MS showed the product to be greater than 95% 3β-hydroxyandrost-5-en-17-one (76% d_3, 24% d_2). The NMR spectrum differed from that of authentic nondeuterated material only in the broad singlet at 5.40 ppm (C-6 H); in the nondeuterated steroid this is an ill-defined doublet. Recrystallization from methanol raised the melting point from 131–138° to 147–150°, undepressed on mixing with an authentic sample of 3β-hydroxyandrost-5-en-17-one of mp 149–151°.

3β-Hydroxyandrost-5-en-17-one-*7-d*$_1$. 3β-Hydroxyandrost-5-en-17-one-*7(αβ),16,16-d*$_3$ (240 mg, 0.83 mmol) in methanol (15 ml), water (1.3 ml), and KOH (270 mg) was left at room temperature under N_2 for 5 hr. Extraction (EtOAc), washing (H_2O), and crystallization from methanol gave 3β-hydroxyandrost-5-en-17-one-*7-d*$_1$ (215 mg, 90% yield), mp 149–151°. GLC–MS and TLC showed the product to be homogeneous and to contain 94% d_1 and 6% d_0 species. The ir spectrum (CCl_4) showed bands at 2102, 2132 (axial C–D), and 2143 cm^{-1} (equatorial C–D).

Androst-5-ene-3β,17β-diol-*7-d*$_1$ (3). Diglyme was left over a molecular sieve (Linde 4A) for 1 week. Of this, 150 ml and D_2O (15 ml) were mixed and distilled and the fraction boiling at 161–163° was collected and stored in sealed ampoules. 3α,5α-Cycloandrost-6-en-17β-ol (**1**, R = β-OH, 350 mg, 1.30 mmol) in the diglyme (5 ml) and 4 *N* D_2SO_4 in D_2O (5 ml) in a sealed tube was heated to 75°. The crystals of steroid changed rapidly to an oil, but on leaving for 18 hr at 75°, crystals had again appeared. On cooling, the contents of the tube became a crystalline mass. Two recrystallizations of the solid from methanol gave the diol (**3**) (330 mg, 88% yield), mp 175°, undepressed on mixing with authentic material of mp 176–177°. TLC and GLC–MS showed the diol to be >98% pure and to consist of 87 ± 3% d_1 and 13% d_2 species. In a similar run in which some starting material was recovered after 3 hr of reaction, deuterium had been incorporated in the diol, **3**, but not in the recovered starting material.

Chromium trioxide oxidation[6] and conjugation of the diol with 4 *N* hydrochloric acid–acetone (1:5) gave androst-4-ene-3,17-dione (100 ± 3% d_1), together with a minor product, androst-4-ene-3,6,17-trione (0% d_1). The two products were readily separable by GLC and identified by retention time and mass spectrum.

Treatment of androst-5-ene-3β,17β-diol with D_2SO_4–diglyme at 90° for 68 hr, followed by dilution with a large excess of water, and filtration gave crystals of the starting material containing, in two separate runs, 0 and 4% of one excess deuterium atom per molecule.

Chloranil dehydrogenation of the deuterated androst-4-ene-3,17-dione (**4**) was performed as described previously[12] under benzene reflux for 24 hr. The product by GLC–MS showed approximately 87% conversion to the 4,6-dien-3-one (**6**), and contained 49 ± 2% d_1. It was later found convenient to perform the dehydrogenation with 1 mg or less of enone in a sealed tube, and to apply a portion of the reaction solution directly to the stainless steel gauze for injection into the GLC–MS instrument.

6β-Methoxy-3α,5α-cycloandrostan-17-one-*7β-d*$_1$ (2). 3β-Hydroxyandrost-5-en-17-one-7α-$d_{0.04}$-7β-$d_{0.95}$ (100 mg), obtained via reduction of the 7α-bromide-17-ketal with lithium aluminum deuteride,[12] was converted to the 3-*p*-toluenesulfonate, and thence to 6β-methoxy-3α,5α-cycloandrostan-17-one-7β-d_1 (**2**). Chromatography on alumina allowed removal of a minor contaminant of the same molecular weight (M^+ 303), presumably 3β-methoxyandrost-5-en-17-one. Although **2** has not yet been obtained crystalline in this laboratory even after careful chromatography, TLC and NMR evidence indicated that it is homogeneous. GLC–MS (flash heater, 254°) showed peaks for both 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**), retention time 10.8 min, and 3α,5α-cycloandrost-6-en-17-one (**1**, R = O), retention time 8.2 min. The retention times and mass spectra were consistent with the assigned structures on comparison with unlabeled standards. On reducing the GLC flash-heater temperature to 170°, the proportion of 3α,5α-cycloandrost-6-en-17-one decreased. The mass spectrum of the 6β-methoxy-3α,5α-cycloandrostan-17-one (**2**) had M^+ 303, 96% d_1; and prominent fragment peaks at *m/e* 271 (M − 32, M − CH_4O) and 256 (M − 32 − 15, M − CH_4O − CH_3), both of which also correspond to the retention of 96% d_1. The GLC peak corresponding to 3α,5α-cycloandrost-6-en-17-one had molecular ions at *m/e* 270 and 271, 31% d_1.

3α,5α-Cycloandrost-6-en-17-one-*7-d*. 6β-Methoxy-3α,5α-cycloandrostan-17-one-7β-$d_{0.96}$ (5 mg) in xylene (10 ml) with alumina (Brinkmann, activity I, 500 mg) was refluxed for 1 hr. GLC–MS showed 3α,5α-cycloandrost-6-en-17-one to be the major product, but with some remaining starting material (M^+ 303). Chromatography on alumina (1.5 g, activity I) and elution with carbon tetrachloride gave 3α,5α-cycloandrost-6-en-17-one-*7-d*, homogeneous on TLC, mp 124–132°, undepressed on mixing with authentic unlabeled steroid of mp 133–139°. GLC–MS gave a single peak corresponding in retention time and MS to the authentic material; four mass spectral scans were taken approximately evenly spaced over the peak; the ratios of M^+ 270 to 271 showed the presence of successively 59, 54, 51, and 46% d_1 in excess of natural abundance, evidence of isotope separation of GLC; the average of all four, or of the central two scans, gives 52% d_1. In a repeat of the above sequence there was obtained 3α,5α-cycloandrost-6-en-17-one containing 51% d_1.

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trometer was purchased through a special grant from the American Cancer Society (Massachusetts Division).

Registry No.—1 (R = O), 1224-07-03; 1 (R = OH), 55058-89-4; **2**, 55102-65-3; α isomer **3**, 55102-66-4; β isomer **3**, 55058-90-7; 3β-hydroxyandrost-5-en-17-one-7α,16,16-d_3, 55058-91-8; 3β-hydroxyandrost-5-en-17-one-7β,16,16-d_3, 55102-67-5; 3β-hydroxyandrost-5-en-17-one-7α-d_1, 55058-92-9; 3β-hydroxyandrost-5-en-17-one-7β-d_1, 55102-68-6; 3α,5α-cycloandrost-6-en-17-one-7-d, 55058-93-0.

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(1) This is publication No. 1484 of the Cancer Commission of Harvard University. This work was presented in part: Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1968, No. ORGN 55.

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Interpretation of the Pseudocontact Model for Nuclear Magnetic Shift Reagents. VI. Determination of the Stereoisomeric Relationships of Four Structurally Isomeric Methylbicyclooctenols[1]

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Assignment of stereochemistry to the four isomeric 5-hydroxy-6-methylbicyclo[2.2.2]oct-2-enes was accomplished by both qualitative and quantitative analyses of lanthanide induced shift (LIS) NMR data. The chemical relationships between these isomers and their epimeric precursors, *endo*- and *exo*-6-methylbicyclo[2.2.2]-oct-2-ene-5-ones, allowed assignment of stereochemical features to these as well. Since some LIS indices could not be assigned accurately, a computer program was designed to use indices of low precision. The combination of auto-assignment (signal assignment by computer) and the ordinary LIS computation distinguished the four isomers by the R-factor ratio test. Statistical analysis shows that the distinction is at the 98% or greater confidence level.

The utility of lanthanide shift reagents for clarification of complex nuclear magnetic resonance spectra (LIS–NMR) and the consequent simplification of structural assignments is well established.[4] Quantitative treatment of the lanthanide-induced chemical shift has led to important decisions about the validity of the pseudocontact model,[5] structure verification,[6] and the statistical basis for the evaluations of the agreement factor.[7] Many examples of the properly judicious application of qualitative techniques for structural resolutions also have appeared.[8] We wish to document a technique of serial addition using europium(III) tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) [Eu(fod)$_3$] which makes possible a convincing qualitative assignment of stereochemistry to four isomeric methylbicyclooctenols. The same data then are treated quantitatively in a useful extension of the R-factor method to confirm the stereochemical assignments. The good agreement between the two methods contributes to the literature of corroboration which must be constructed before the R-factor method can be trusted in cases where qualitative approaches fail.

Results

The isomeric ketones *endo*- and *exo*-6-methylbicyclo[2.2.2]oct-2-en-5-one (**1N** and **1X**) and the four isomeric 6-methylbicyclo[2.2.2]oct-2-en-5-ols *endo*-CH$_3$, *endo*-OH (**2Nn**); *endo*-CH$_3$, *exo*-OH (**2Nx**); *exo*-CH$_3$, *exo*-OH (**2Xx**); and *exo*-CH$_3$, *endo*-OH (**2Xn**) were required to identify the thermolysis products in other studies.[10] Scheme I outlines the synthetic procedures used to prepare the required compounds. Prompt work-up of the product of step 1 afforded one of the epimeric ketones (later shown to be **1N**) in pure form. Delayed work-up, or subsequent treatment of **1N** by base, afforded a 65:35 mixture of **1N** and **1X**. Although analytical gas–liquid chromatography (GLC) was adequate to analyze the ketone mixture, all attempts at preparative separation failed.

Reduction of **1N** and the **1N–1X** mixture provided the four isomeric alcohols as shown. These were separated readily and purified by preparative GLC into alcohols a (mp 30–31°), b (mp 67–68°), c (mp 43–44°), and d (mp 82–84°). Jones oxidation of alcohol d, after identification as **2Xn**, afforded ketone **1X** nearly free of epimer **1N**, and proved the only feasible route to this material.

The usual spectroscopic techniques served to confirm the gross structures of compounds **1** and **2** as shown, but except for observation of intramolecular H bonding in alcohols a and d (identifying them[11] as the **2Xn, 2Nn** pair) and notation of the common methyl relationships (**1N**, a + b; **1X**, c + d), definitive stereochemical assignments were not possible. The NMR spectra of alcohols a–d then were run in $CDCl_3$ with both tetramethylsilane (Me_4Si) and $CHCl_3$ internal standards. Each sample was serially treated with successive additions of Eu(fod)$_3$ such that (1) each sample had ca. twice as much Eu(fod)$_3$ as the preceding one, and (2) the final mole ratio of alcohol:Eu(fod)$_3$ was ca. 4:1 (see Experimental Section). NMR spectra were recorded after