The Crystal and Molecular Structure of Cholestan-4-one-3-spiro(2,5-oxathiolane)

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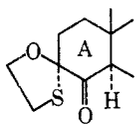
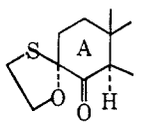
The crystal and molecular structure of cholestan-4-one-3-spiro(2,5-oxathiolane) has been determined by single-crystal X-ray diffraction techniques. The space group is $P2_1$ with two molecules in the unit cell of dimensions $a = 16.636 \pm 0.003$, $b = 6.563 \pm 0.001$, $c = 12.982 \pm 0.003$ Å, $\beta = 102.59 \pm 0.01°$ (at $20 \pm 2°$). The final R factor for 3076 independent reflections is 0.062. The steroid molecule has normal geometry, but the A ring and the oxathiolane ring are both distorted owing to a dipole interaction between the oxygen atoms associated with these two rings. The oxathiolane ring has an envelope configuration, in which significant differences were observed for the lengths of the two C–S and the two C–O bonds.

Reaction of 4-hydroxy-cholest-4-en-3-one with 2-mercaptoethanol yields four isomeric hemithioketals, among which may be isolated[2a] two whose A-ring configurations are I and II. By a combination of optical



I



II

rotatory dispersion, circular dichroism, and spectroscopic measurements, the stereochemistry at C-3 for I and II could be derived[2] with a fair degree of certainty. Anomalies were observed, however, in the carbonyl Cotton effect and in the carbonyl stretching frequency in the infrared (ir) spectra, suggesting distortions in the A rings. If present, these distortions could invalidate the conclusions drawn from the various physical and chemical measurements. Since very little information is in the literature about the effects of α-alkoxy groups on C=O stretching frequencies in cyclic systems, or about thioalkyl group effects, the positive identification of the stereochemistry of C-3 is of some importance.

Experimental Section

The crystals used in this investigation were supplied by C. H. Robinson of Johns Hopkins University. The unit cell dimensions[3] were found to be $a = 16.636 \pm 0.003$, $b = 6.563 \pm 0.001$, $c = 12.982 \pm 0.003$ Å, $\beta = 102.59 \pm 0.01°$ (at $20 \pm 2°$) for the monoclinic space group $P2_1$. The density calculated for two molecules of $C_{29}H_{48}O_2S$ per unit cell is 1.106 compared with a density of 1.117 g cm^{-3} obtained by flotation of a crystal in an aqueous solution of potassium iodide. The single crystal melting point is 145°.

Diffraction intensities were measured for 3076 independent spectra with 2θ less than 148°, by the stationary crystal-stationary counter method[4] using Cu Kα radiation monochromatized by balanced nickel and cobalt filters and by electronic pulse height discrimination. The shape anisotropy of the crystal was determined to be 4%, and, with $\mu R = 0.02$, no absorption corrections were deemed necessary.

The sulfur atom was located on the Harker section of the Patterson synthesis, and this atom was used to solve the structure by the routine application of the heavy atom method.[5]

The positional parameters of all atoms were refined by least squares, using a block diagonal approximation to the least-squares normal equations. Initially, isotropic thermal parameters were used for the atoms, and these were replaced by anisotropic parameters as refinement progressed. When the R factor had been reduced to 0.092, a three-dimensional Fourier difference synthesis was computed and the forty-eight hydrogen atoms in the molecule were located. After a further three cycles of least-squares refinement, keeping the isotropic thermal parameters of the hydrogen atoms fixed at 4.0 Å,^{2} the refinement was terminated with an R factor of 0.062.

Description and Discussion of the Structure

The positional parameters, corrected for the rigid body motions of the molecule,[6] are given in Table I.[7] These parameters have standard deviations which are equivalent to approximately 0.003 and 0.04 Å for nonhydrogen and hydrogen atoms, respectively. Interatomic distances and angles are summarized in Figure 1. The standard deviations are in the ranges 0.004–0.008 Å for distances between carbon, oxygen, and sulfur atoms, 0.04–0.06 Å for distances between hydrogen and other atoms, and are approximately 0.3, 1, and 4° for bond angles of the types C–C–C, C–C–H, and H–C–H, respectively.

Bond distances at the ring junctions in the steroid nucleus (C-5–C-10, C-8–C-9, C-13–C-14) are noticeably longer than expected for sp^3–sp^3 bonds, while the other bonds in the B and C rings (steroid nomenclature) have normal lengths. The D-ring bonds are also longer than normal sp^3–sp^3 bonds, but similar lengthening of these bonds is commonly observed in steroid D rings. It is interesting to note that the observed configuration of the D ring agrees, in spite of the strain expected to be introduced owing to the fusion of the C and D rings, remarkably well with that calculated by Hendrickson[8] for a minimum energy configuration of a free cyclopentane ring (see Figure 2).

The positions of the atoms in the side chain are influenced by varying degrees of nonrigid body vibrations, particularly for atoms C-24 and C-27, and it will be noticed that the bond distances to these atoms are shorter than expected. In both cases, corrections for

(1) The Medical Foundations of Buffalo, Buffalo, N. Y. 14203

(2) (a) C. H. Robinson and L. Milewich, Abstracts, the 153rd National Meeting of American Chemical Society, Miami Beach, Fla., April 1967, No. O, 196. (b) C. H. Robinson, L. Milewich, G. Snatzke, W. Klyne, and S. R. Wallis, *J. Chem. Soc.*, in press.

(3) All X-ray measurements were carried out on a General Electric single-crystal orienter.

(4) T. C. Furnas, "Single Crystal Orienter Manual," General Electric Co., Milwaukee, Wis., 1957.

(5) See, for example, H. Lipson and W. Cochran, "The Determination of Crystal Structures, the Crystalline State," Vol. III, Bell, London, 1953.

(6) V. Schomaker and K. N. Trueblood, *Acta Cryst.*, **B24**, 63 (1968).

(7) Material supplementary to this article (a copy of the refined positional and thermal parameters of the nonhydrogen atoms, before correction for thermal motion, and a listing of the comparison between the observed and calculated structure amplitudes) has been deposited as Document number 10,011 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington, D. C. 20540. A copy may be secured by citing the Document number and by remitting $1.25 for photoprints, or $1.25 for 35-mm microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

(8) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961).

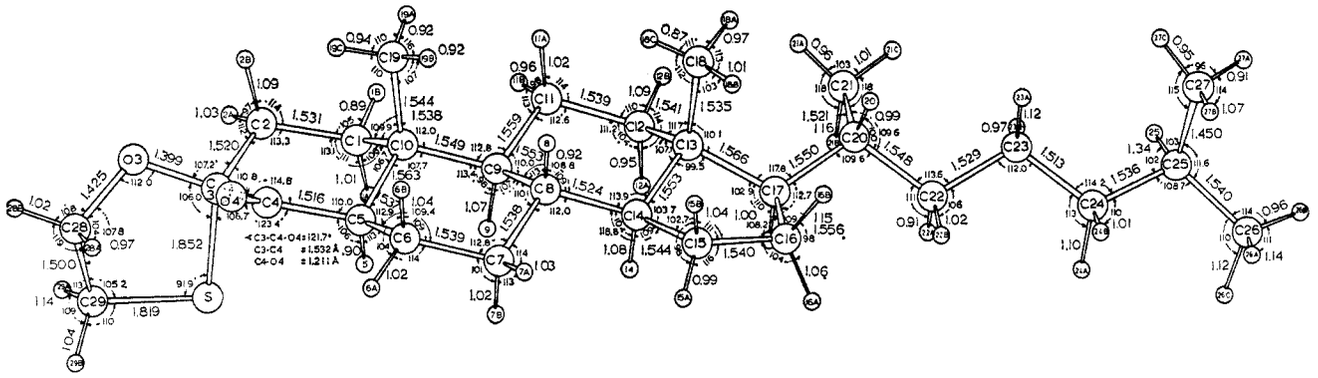


Figure 1.—Some interatomic distances and angles in the molecule. These values have been corrected for the effects of molecular libration.

TABLE I

POSITIONAL PARAMETERS FOR THE ATOMS, CORRECTED FOR LIBERATION OF THE MOLECULE

Atom	*x/a*	*y/b*	*z/c*	Atom	*x/a*	*y/b*	*z/c*
C-1	0.22650	0.43214	0.29102	H-7B	0.1428	0.0499	0.5227
C-2	0.18687	0.42394	0.17303	H-8	0.1116	0.4612	0.5533
C-3	0.13167	0.23942	0.14226	H-9	0.2437	0.2750	0.4747
C-4	0.07370	0.21163	0.21803	H-11A	0.2234	0.7295	0.5014
C-5	0.11556	0.21564	0.33402	H-11B	0.2973	0.6405	0.4710
C-6	0.05517	0.17204	0.40555	H-12A	0.3358	0.7179	0.6441
C-7	0.10252	0.16723	0.52141	H-12B	0.3516	0.4601	0.6401
C-8	0.15133	0.36394	0.55521	H-14	0.2480	0.2332	0.6628
C-9	0.20906	0.41009	0.47885	H-15A	0.1387	0.1551	0.7567
C-10	0.16339	0.42039	0.36153	H-15B	0.1047	0.3716	0.7552
C-11	0.26102	0.60466	0.51586	H-16A	0.2488	0.2245	0.9008
C-12	0.30939	0.58943	0.63098	H-16B	0.1898	0.4626	0.9014
C-13	0.25145	0.54727	0.70630	H-17	0.3379	0.3768	0.8175
C-14	0.20310	0.34961	0.66727	H-18A	0.2289	0.8433	0.7347
C-15	0.16016	0.29535	0.75778	H-18B	0.1614	0.6805	0.7639
C-16	0.22501	0.35602	0.85674	H-18C	0.1613	0.7534	0.6493
C-17	0.29400	0.47896	0.82074	H-19A	0.1400	0.7122	0.3414
C-18	0.19353	0.72751	0.71064	H-19B	0.0730	0.6032	0.3896
C-19	0.10413	0.60404	0.33923	H-19C	0.0699	0.5944	0.2716
C-20	0.33177	0.64683	0.90072	H-20	0.2869	0.7250	0.9213
C-21	0.39575	0.77686	0.86381	H-21A	0.3714	0.8525	0.8018
C-22	0.37186	0.54775	1.00772	H-21B	0.4456	0.6578	0.8581
C-23	0.40094	0.70188	1.09630	H-21C	0.4246	0.8864	0.9133
C-24	0.43022	0.59911	0.20208	H-22A	0.4170	0.4737	1.0021
C-25	0.47691	0.74049	1.28910	H-22B	0.3337	0.4491	1.0348
C-26	0.50623	0.61497	1.39054	H-23A	0.3483	0.8057	1.1007
C-27	0.43022	0.91800	1.30772	H-23B	0.4509	0.7626	1.0833
C-28	0.06545	0.07812	−0.01414	H-24A	0.4625	0.4547	1.1967
C-29	0.13742	−0.06473	0.01113	H-24B	0.3840	0.5282	1.2265
O-3	0.09018	0.26688	0.03728	H-25	0.5346	0.8208	1.2443
O-4	0.00004	0.19377	0.18636	H-26A	0.4490	0.5485	1.4124
S	0.19024	−0.00123	0.14519	H-26B	0.5386	0.6903	1.4477
H-1A	0.2653	0.3146	0.3122	H-26C	0.5345	0.4694	1.3710
H-1B	0.2511	0.5532	0.3012	H-27A	0.4619	1.0066	1.3535
H-2A	0.2272	0.4419	0.1237	H-27B	0.3809	0.8524	1.3368
H-2B	0.1475	0.5546	0.1451	H-27C	0.4169	1.0111	1.2505
H-5	0.1573	0.1249	0.3423	H-28A	0.0213	0.0309	0.0179
H-6A	0.0277	0.0372	0.3786	H-28B	0.0537	0.1026	−0.0932
H-6B	0.0062	0.2725	0.3979	H-29A	0.1852	−0.0350	−0.0380
H-7A	0.0580	0.1379	0.5634	H-29B	0.1227	−0.2192	0.0067

independent thermal motion would increase the bond lengths, but such corrections have not been made because the relatively large independent motions of these atoms result in a correction determined only as being in the range 0.001 to approximately 0.4 Å. All torsional angles in the side chain are within 3° of their expected values of 60 or 180°.

The steroid A ring and the oxathiolane ring (ring E) are both somewhat distorted. Torsional angles for these rings are given in Table II. A dipole interaction between atoms O-3 and O-4 (whose centers are separated by 2.737 Å) has flattened the A ring about atoms C-2, C-3, and C-4, so that the torsional angle ϕ (O-4–C-4–C-3–O-3) has been increased to +7.5°.[9] This also has the effect of producing a weak interaction between atoms O-4 and H-28A, which is further assisted by atom

(9) See Table II, footnote *a*.

TABLE II

TORSIONAL ANGLES IN THE RINGS[a,b]

Ring A		Ring B		Ring C		Ring D		Ring E	
Bond	ϕ (A–B), deg	Bond	ϕ (A–B), deg	Bond	ϕ (A–B), deg	Bond	ϕ (A–B), deg	Bond	ϕ (A–B), deg
C-1–C-2	−54.5	C-5–C-6	−57.9	C-8–C-9	−54.7	C-13–C-14	+48.2	C-3–O-3	+34.0
C-2–C-3	+47.1	C-6–C-7	+55.9	C-9–C-11	+54.9	C-14–C-15	−36.7	O-3–C-28	−46.3
C-3–C-4	−50.1	C-7–C-8	−54.3	C-11–C-12	−56.8	C-15–C-16	+10.8	C-28–C-29	+34.3
C-4–C-5	+57.4	C-8–C-9	+54.9	C-12–C-13	+56.4	C-16–C-17	+18.7	C-29–S	−13.5
C-5–C-10	−59.0	C-9–C-10	−55.3	C-13–C-14	−60.2	C-13–C-17	−40.0	S–C-3	−10.4
C-1–C-10	+58.7	C-5–C-10	+57.2	C-8–C-14	+59.9				

[a] The sign convention for torsional angles is that of W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960). [b] ϕ (A–B) is the torsional angle about the A–B bond, in which the other two atoms required to define the angle are those attached to either end of the bond and are in the ring in question.

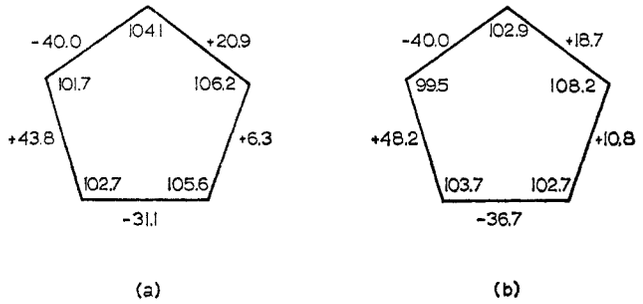


Figure 2.—Comparison of the interatomic and torsional angles calculated by Hendrickson[8] for a cyclopentane ring (a) with those observed for the D ring of this steroid (b).

C-28 lying 0.506 Å out of the plane of the remainder of the oxathiolane ring, and on the same side of this envelope shaped ring as is O-4.

The packing of the molecules in the crystal gives further evidence as to the distortion of the oxathiolane ring; however, it is impossible to say whether the packing plays the major part in the development of the distortion, or vice versa. Figure 3 gives a projection of the structure along the *b* axis of the unit cell. In the center of this figure, the close approach of oxathiolane rings of molecules related by the twofold screw axes, is evident. The sulfur atom of the molecule marked "b" is one-half a unit cell *b* edge (3.28 Å) above the sulfur atom of molecule "a" and the molecules lie in a widened V configuration. This places oxygen atom 3 of molecule a and hydrogen atom 28B of molecule b 2.54 Å apart, a separation which is 0.1 Å less than the sum of the van der Waals radii for the two atoms concerned.

Atom C-4 does not appear to have attained full sp^2 hybridization. This carbon atom lies 0.014 Å out of the plane of atoms C-3, C-5, and O-4 and, while the expected sp^2–sp^3 bond length is 1.505 Å,[10] both bonds C-3–C-4 and C-4–C-5 are longer than this. It may be seen that the side of C-4, which is away from the spiro junction at C-3, is more nearly normal, while the longer distance C-3–C-4 is as would be expected for an sp^3–sp^3 bond. The angle C-3–C-4–C-5 has also been reduced. This is partly due to C-4 lying out of the plane of the carbonyl group, but the reduction in the angle is not so much as appears at first sight, since, on the evidence accumulating in this laboratory, the intraring C–C–C angle for such a ketone system is generally observed to be 116°. On the other side of the spiro junction, the bond C-2–C-3 is 0.13 Å shorter than that expected.

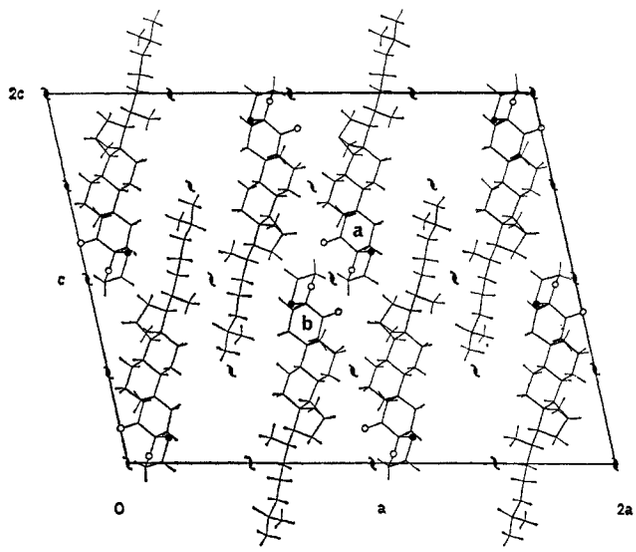


Figure 3.—Projection of the structure as viewed down the *b* axis of the unit cell. The closest intermolecular contacts are between the A, D, and E rings of molecules related by the 2_1 axes perpendicular to the projection. Shaded circles are sulfur atoms; open circles are oxygen atoms.

In the oxathiolane ring, the two C–S bonds differ quite significantly. The C-29–S length agrees with the accepted value of 1.82 Å for such bonds[11] but the C-3–S bond is 0.033 Å longer than this, which is a difference of six standard deviations. A similar, but opposite, effect is observed for the C–O bonds in the ring. Bond C-28–O-3 is normal, but C-3–O-3 is 0.026 Å shorter than it (four standard deviations). These differences may be due to the variation of electronegativities between the oxygen and sulfur atoms. The shortening of the C-28–C-29 bond may also be reflective of these electronegativity differences.

The methyl groups, C-18 and C-19, in the steroid nucleus are almost strictly oriented by their hydrogen atoms interacting with nearby nuclear axial hydrogen atoms. The methyl group at C-19 is rotated by approximately 12° from the staggered position to accommodate the interactions between H-11A and H-8 and the methyl hydrogen atoms H-19A and H-19B. However, the C-18 methyl group is not so severely restricted in its rotational position and it does in fact take up a staggered configuration about the C-18–C-13 bond. The torsional angles ϕ (H-18A–C-18–C-13–C-17) and ϕ (H-18B–C-18–C-13–C-17) of 71 and 48°, respectively

(10) L. S. Bartell and R. A. J. Bonham, *J. Chem. Phys.*, **32**, 824 (1960).

(11) S. C. Abrahams, *Quart. Rev.*, **10**, 407 (1956).

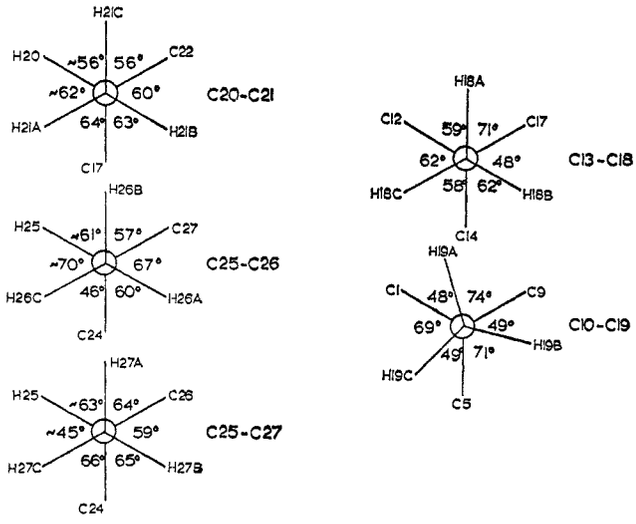


Figure 4.—Torsional angles for the five methyl groups in the molecule.

(see Figure 4), are due to the strained configuration at the C/D-ring junction. In the side chain, the three methyl groups have the expected staggered configurations, the only unexpected torsional angles being those involving H-25, the position of which, as has been pointed out previously, was not determined very precisely.

The side chain, with the exception of the C-21 and C-27 methyl groups, is planar to within 0.07 Å, and this plane lies at an angle of 120° to the plane through the steroid nucleus. The dihedral angle between the oxathiolane ring and the steroid nucleus is 82°.

Registry No.—Cholestan-4-one-3-spiro(2,5-oxathiolane), 17021-85-1.

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Di-5α-cholestan-3α-ylamine, a Diaxial Bis Steroidal Amine[1a]

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Ammonolysis of 5α-cholestan-3β-yl tosylate (**1**) in relatively small amounts of anhydrous ammonia leads to formation of the secondary diaxial amine **3** in addition to the major product, the primary axial amine **2**. The product amines have been characterized by pmr and mass spectrometry. As the minimum molar ratio of ammonia to **2** in a typical run is 75, it is clear that this highly hindered primary amine (**2**) is very much more effective at displacing tosylate anion from **1** than is ammonia. Attempts to prepare **3** from **1** and **2** in several solvents were not successful, while a low yield of **3** was obtained from a reaction conducted in the molten state. The uniqueness of the solvent liquid ammonia for this reaction is discussed.

Reaction of 5α-cholestan-3β-yl tosylate (**1**) with relatively small amounts of anhydrous ammonia has now been shown to furnish a new product, $C_{54}H_{95}N$, mp 165–166°, in addition to the major product,[2] 5α-cholestan-3α-ylamine (**2**). The new amine, which has been obtained in up to 16% yield, was assigned the structure of di-5α-cholestan-3α-ylamine (**3**) on the basis of its elemental analysis and molecular weight, the formation of an N-acetyl derivative lacking an N–H stretching vibration in the infrared spectrum, and on the basis of a pmr spectrum in deuteriochloroform. A signal at τ 7.22 with a half-band width (w) of ~7 cps (at 60 Mcps) for two equatorial 3β hydrogens clearly defines the stereochemistry.[3,4]

Compounds **2** and **3** showed molecular ions in their mass spectra at m/e 387 (Σ_{35} 1.19%) and m/e 757 (Σ_{35} 1.50%), respectively.[5] The two typical ions expected for a 3-amino- or 3-alkylamino-5α-cholestane are derived from carbons 1, 2, and 3 (less one hydrogen) and the amine function, and from carbons 3, 4, 5, 6, and 7 (less two hydrogens) and the amine function.[6] From

(1) (a) This investigation was supported in part by Grant No. AM-06419 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. (b) To whom correspondence should be addressed at the Medical Research Building, Boston University School of Medicine, Boston University Medical Center, Boston, Mass. 02118.

(2) J. L. Pinkus, G. Pinkus, and T. Cohen, *J. Org. Chem.*, **27**, 4356 (1962).

(3) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 77–85; (b) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4624 (1962); (c) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958), and **82**, 6427 (1960); (d) H. Feltkamp and N. C. Franklin, *Ann. Chem.*, **683**, 55 (1965); (e) H. Feltkamp, N. C. Franklin, K. D. Thomas, and W. Brügel, *ibid.*, **683**, 64 (1965); (f) H. Feltkamp, N. C. Franklin, W. Kraus, and W. Brügel, *ibid.*, **683**, 75 (1965); (g) H. Booth, N. C. Franklin, and G. C. Gidley, *Tetrahedron*, **21**, 1077 (1965).

(4) Results with model amine and alcohol compounds are consistent with the stereochemical assignment. Equatorial hydrogens show w = 7–10 cps; examples are (solvent, τ, w in cps) *trans,trans*-2-decalylamine ($CDCl_3$, 6.78, ~8), *trans,trans*-10-methyl-2-decalylamine (neat, 6.87, ~8), 5α-cholestan-3α-ylamine (**2**) ($CDCl_3$, 6.87, ~8), *trans,trans*-2-decalyl acetate (neat, 5.00, ~7), and *trans,trans*-2-decalol ($CDCl_3$, 5.88, ~9). Axial hydrogens show w = 19–33 cps; examples are *trans,cis*-2-decalylamine ($CDCl_3$, 7.42, ~21), *trans,cis*-2-decalyl acetate (neat, 5.42, ~29), and *trans,cis*-2-decalol ($CDCl_3$, 6.47, ~19). Our w values for those of the above model compounds whose band widths have been measured elsewhere[3e,f] are about 20–30% less than the band-width values (W) reported since the latter values are based on an approach where band widths are measured at different band heights depending on conformation equilibria.

The pmr signal for the equatorial 3β hydrogens of **3** would be expected to occur as found at higher field than that observed for the model compounds with equatorial hydrogens, since alkylation of nitrogen results in increased shielding of the tertiary α hydrogen.[3g] Unfortunately, data are not available[3g] to make a quantitative prediction of the upfield shift expected in going from **2** to **3** (0.35 ppm observed).

(5) These are nominal molecular weights, based on integral atomic mass units, and in the case of **3** is one atomic mass unit less than the actual molecular weight rounded off to the nearest integer.

(6) (a) L. Dolejš, V. Hanuš, V. Černý, and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 1584 (1963); (b) W. Vetter, P. Longevialle, F. Khuong-Huu-Laine, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1324 (1963); (c) Z. Pelah, M. A. Kielczewski, J. M. Wilson, M. Ohashi, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 2470 (1963).