CH_3; (*R,R*)-2,3-butanediol ketal), 97590-63-1; **11** (R = CH_3), 97551-96-7; *cis*-**11** (R = CD_3), 97551-82-1; *trans*-**11** (R = CD_3), 97590-74-4; **13**, 97551-83-2; **14**, 13368-65-5; **14** (6-bromide), 97590-65-3; **14** (2-bromide), 97590-66-4; **15a**, 97551-84-3; **15b**, 97590-64-2; **16a**, 97551-85-4; **16a** (α,α-dimethyl deriv), 97551-87-6; **16b**, 97551-86-5; **16b** (α,α-dimethyl deriv), 97551-88-7; **17**, 97551-89-8; **18**, 97551-90-1; **19**, 54307-74-3; **20**, 97551-91-2; **21**, 97590-67-5; (−)-**22**, 57287-85-1; (+)-**23**, 97590-69-7; (±)-**23**, 97551-92-3; **24**, 97590-68-6; **25**, 97551-93-4; *cis*-**25**, 97551-93-4; NaSEt, 811-51-8; HCOOEt, 109-94-4; *n*-BuSH, 109-79-5; EtSH, 75-08-1; PhSH, 108-98-5; 2,2-dimethyl-3-cyclohexen-1-one, 73374-47-7; (±)-2-methyl-2-(trideuteriomethyl)-3-cyclohexen-1-one, 97551-78-5; (−)-(2*R*,3*R*)-butanediol, 24347-58-8; (+)-pulegone, 89-82-7; (±)-3-(ethyl(thio)cyclohexanone, 97590-71-1; (±)-3-methoxycyclohexanone, 97551-94-5; (±)-3-methylenecyclohexanol, 97551-97-8; (±)-3-methoxy-1-methylenecyclohexane, 97551-98-9; (±)-3-methylenecyclohexyl acetate, 97551-99-0; (±)-3-(ethylthio)-7-methylenecyclohexane, 97552-00-6; (±)-3-methyl-1-methylenecyclohexane, 97590-72-2; cyclohexanol, 108-93-0; methyoxycyclohexane, 931-56-6; cyclohexyl acetate, 622-45-7; cyclohexyl fluoride, 372-46-3; cyclohexyl chloride, 542-18-7; cyclohexyl bromide, 108-85-0; (methylthio)cyclohexane, 7133-37-1; methylcyclohexane, 108-87-2; cinchonidine, 485-71-2; 2-cyclohexen-1-one, 930-68-7.

Conformational Analysis of Steroids in Solution: 17β-Hydroxy-19-nor-5α,17α-pregn-20-yn-3-one and Its 5β-Isomer Studied by Nuclear Magnetic Resonance

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The information obtained from two-dimensional NMR spectroscopy at 200 and 500 MHz allowed the complete assignment of the ^1H and ^{13}C NMR spectra of 17β-hydroxy-19-nor-5α,17α-pregn-20-yn-3-one and of its 5β-isomer. The conformation of these molecules in solution was probed by comparing the observed vicinal coupling constants in rings A, B, and C with the corresponding couplings calculated by means of a generalized Karplus relation using the proton–proton torsion angles derived from the steroid conformation in the solid state and/or the conformation calculated by general valence force field methods. The puckering and conformation of the five-membered ring D were determined directly by an analysis of the experimental vicinal couplings by using the generalized Karplus relation in combination with the concept of pseudorotation. It was thus found that the solution conformation of these molecules corresponds with the conformation determined by X-ray crystallography and/or molecular mechanics (MM2). This conclusion is important for establishing the structure–function relation of steroids. The chemical shift and coupling constant features displayed by the NMR spectra of the title compounds are correlated with the conformation of these steroids. For instance, the relatively small $^3J_{15\alpha-16\alpha}$ is explained by the through-space interactions between the carbon–hydrogen orbitals of the C_{15}–C_{16} fragment and the orbitals about the C_{13}-methylene bridge in the distorted $^{13}T_{14}$ envelope conformation of ring D.

Many physiological functions are directed by hormonal steroids, but the mechanism by which a biomolecular event is evoked by a particular steroid is not fully understood. In general, it is presumed that a steroid exerts its biological action after interaction with a protein, e.g., a receptor.[1] Since the physiological response to the distinct steroids appears to be highly specific, it may be deduced that, next to the chemical composition, the steroid conformation plays an important role in the physiological processes. Therefore conformational analysis of steroid molecules is clearly important for establishing the structure–function relation involved.

Most of the present knowledge about steroid conformations stems from X-ray crystallographic studies, but also molecular mechanics (force field calculations) as well as ^1H and ^{13}C NMR studies have contributed. Of course, the ^1H NMR technique is very advantageous to study the steroid conformation as it is able, at least in principle, to yield detailed information about the molecular structure *in solution*. However, the assignment of the ^1H NMR spectra involved is in that case a conditio sine qua non.

Until recently[2] the full analysis of ^1H NMR spectra of steroids has been seriously hampered by the fact that the greater part (>20) of the mutually coupled protons resonate within the 1–2.5 ppm region of the spectrum. The unraveling of the many overlapping signals in this small part of the spectrum presents an extremely difficult task. It was not until developments in NMR instrumentations, i.e., highly stable superconducting magnets interfaced to modern computer-controlled spectrometers, together with the rise of the so-called two-dimensional (2D) NMR techniques revolutionized the field that it was indeed possible to assign the complex ^1H and ^{13}C NMR spectra of steroid molecules.

Recently, a 2D NMR strategy was developed in our laboratories to identify 19-nor steroids.[3] This type of steroid has an even more extended and therefore more complicated network of coupled spins than the common

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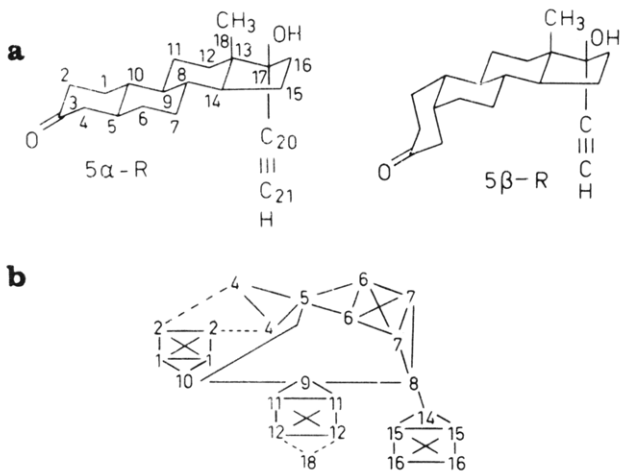

Figure 1. (a) Structures of the two steroids studied in this paper. (b) Diagram showing the coupling network in which the protons of 5α-R and 5β-R are involved; long-range couplings are indicated by dashed lines.

steroids possessing the C_{10}-methyl group. Our strategy is based on the combination of 2D *J*-resolved and 2D spin-echo *J*-correlated (SECSY) experiments. It was shown that these two techniques allow for a complete assignment of the NMR spectrum of a 19-nor steroid model compound, i.e., norethisterone.[3] In this paper we present the assignment of the ^1H and ^{13}C NMR spectra of 17β-hydroxy-19-nor-5α,17α-pregn-20-yn-3-one (5α-R, cf., Figure 1) and its 5β-isomer (5β-*R*, cf., Figure 1) utilizing the aforementioned strategy. The latter two steroids are products in the photodecomposition of norethisterone (a frequently used progestogenic steroid in the oral contraceptives). As such the analysis of the spectra formed a rigorous test for our assignment method since the NMR spectra involved are extremely complicated: 26 mutually coupled protons resonate within a spectral region spanning ca. 1.5 ppm; see also the coupling constant network diagrammed in Figure 1b. Next the extracted vicinal proton–proton coupling constants are used to determine the conformation of these steroids in solution. It will be shown for the first time that the steroid conformation in solution corresponds very well with the conformations inferred from solid state data and/or force field calculations.

Results and Discussion

Analysis of the NMR Spectra. The expected complicated network of coupled spins of 5α-R and 5β-R is schematized in Figure 1b. Figure 2a shows that even at 500 MHz the high-field region (0.9–2.4 ppm) of the steroid NMR spectrum is very crowded due to the 24 overlapping signals arising from 26 protons. In Figure 2b a simplified spectrum is presented, which is achieved by projecting the 2D *J* spectrum onto the f_2 axis (δ). Proton resonances were assigned by recording a SECSY spectrum of the steroid and by pursuing the same line of reasoning as described in a previous article.[3] A 2D ^{13}C–^1H hetero shift correlation experiment was performed to verify the attained ^1H NMR analysis.

For the precise assignment of proton signals in extremely crowded regions, e.g., the region 1.29–1.34 ppm in the ^1H spectrum of 5α-*R*, cross sections taken along the f_1 axis of the 2D hetero spectrum were used.

As far as relevant a good accordance is obtained with the data of norethisterone.[3] Table I summarizes the chemical shift data for the two steroids under study. Coupling constant data (Table II) were derived from the cross sections taken parallel to f_1 axis in the 2D *J*-resolved

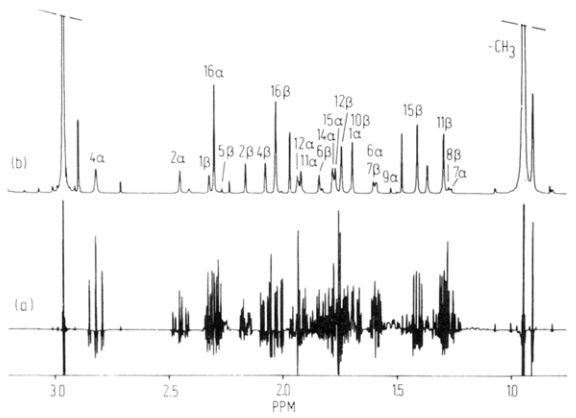

Figure 2. (a) Normal 1D 500-MHz ^1H NMR spectrum of 5β-R. (b) Projection of the 500-MHz 2D *J* spectrum of 5β-R (the so-called "broad-band proton-decoupled" ^1H NMR spectrum). Assignment of the resonances is indicated; nondescriptive resonances stem from impurities or artifacts.

Table I. Chemical Shift Data of 5α-R and 5β-R (δ)

C	5α-R	5β-R	H	5α-R	5β-R
1	32.1	29.2	1α	~1.33[a]	1.688
			1β	2.375	2.316
2	42.3	37.5	2α	2.390	2.444
			2β	2.479	2.157
3	214.9	216.0			
4	50.0	44.1	4α	2.270	2.815
			4β	2.270	2.069
5	45.5	40.4	5α	1.503	
			5β		2.260
6	35.3	32.1	6α	1.751	1.59[a]
			6β	1.299	1.834
7	31.8	26.5	7α	1.049	1.258
			7β	1.794	1.59[a]
8	43.3	43.9	8β	1.296	1.268
9	49.6	39.6	9α	0.793	1.520
10	47.2	41.7	10β	~1.33[a]	1.688
11	27.3	27.1	11α	1.955	1.913
			11β	1.309	1.292
12	34.2	34.3	12α	1.838	1.928
			12β	1.694	1.736
13	[b]	[b]			
14	51.0	50.9	14α	1.659	1.775
15	24.2	24.2	15α	1.739	1.763
			15β	1.398	1.405
16	40.2	40.2	16α	2.281	2.294
			16β	2.012	2.024
17	80.7	80.7			
18	13.6	13.6	18	0.938	0.942
20	89.1	89.2			
21	75.0	75.0	21	2.939	2.956

[a] Not resolved. [b] Not measured (signal hidden by the solvent signal).

spectra. However, not all coupling constants could be determined, since in each steroid some protons resonate at almost the same frequency, which leads to intermingled cross sections in the 2D *J* spectra. The chemical shift data are considered accurate to 0.001 ppm; the coupling constant data to ±0.5 Hz. Data concerning the protons at C_1 and C_2 could not be determined accurately (see above).

Conformational Analysis. As was mentioned in the introduction, most of our knowledge about steroid conformations stems from X-ray crystallographic studies. Moreover, in several cases it has been shown that force field calculations[4,5] may well reproduce the structural features observed for steroids in the solid state.[6,7] The

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(5) Allinger, N. L.; Yuh, Y. *QCPE* **1980**, *12*, 395.
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Table II. Observed and Calculated Coupling Constants in 5α-R and 5β-R (in Hz)[a]

H-H	5α-R		5β-R	
	J_{obsd}	J_{calcd}	J_{obsd}	J_{calcd}
1α-1β	−13.7		−11.2	
1α-2α	5.9	4.3	3.0	4.0
1α-2β	13.1	13.6	2.4	2.5
1α-10β	*b*	12.3	2.7	2.3
1β-2α	2.4	2.3	14.2	13.7
1β-2β	4.9	4.3	5.4	4.1
2α-2β	−13.2		−14.4	
2α-4α	0.8		1.7	
2α-4β			~1	
2β-4α			~0.5	
2β-4β	1.5		2.2	
4α-4β	*b*		−14.0	
4α-5α	3.5	3.7		
4α-5β			14.0	12.3
4β-5α	12.8	12.3		
4β-5β			4.3	3.8
5α-10β	10.5	12.0		
5β-10β			4.5	3.6
5α-6α	3.2	3.4		
5α-6β	11.7	12.3		
5β-6α			2.0	1.8
5β-6β			4.5	4.8
6α-6β	−12.7		−13.2	
6α-7α	3.4	3.6	4.3	4.0
6α-7β	3.0	2.7	*b*	2.4
6β-7α	13.0	13.3	13.6	13.1
6β-7β	3.4	3.6	4.4	4.1
7α-7β	−12.8		−13.5	
7α-8β	11.8	12.4	11.7	12.3
7β-8β	3.4	3.2	*b*	3.3
8β-9α	9.7	12.0	9.8	12.0
8β-14α	12.2	12.1	12.3	12.1
9α-11α	4.2	3.9	4.4	4.0
9α-11β	12.2	12.2	11.7	12.2
9α-10β	11.8	12.0	11.4	12.0
11α-11β	−13.5		−13.7	
11α-12α	4.4	4.2	4.4	4.2
11α-12β	2.8	2.3	2.4	2.3
11β-12α	13.1	13.2	13.7	13.2
11β-12β	3.9	4.2	4.2	4.2
12α-12β	−13.2		−12.7	
12α-18	1.2		1.0	
12β-18	~0.3		~0.3	
14α-15α	7.5		7.5	
14α-15β	11.2		11.7	
15α-15β	−12.2		−12.2	
15α-16α	9.8		9.4	
15α-16β	3.9		3.7	
15β-16α	5.5		5.5	
15β-16β	12.0		12.0	
16α-16β	−13.7		−13.7	

[a] The calculated couplings were computed from the proton–proton torsion angles taken from the MM2 structure by using a generalized Karplus equation.[6] [b] Not measured.

latter point may also be illustrated by the case of 5α-R. The solid-state structure of this compound is known,[8] and the structure was calculated by means of Allinger's MM2 force field program[4,5] (see Computational Methods). Perusal of the geometrical data describing the latter two structures of 5α-R shows a good correspondence in C–C bond lengths (root mean square deviation between observed and calculated distances 0.0086 Å) and C–C–C bond angles (root mean square deviation 0.79°). The endocyclic torsion angles for both structures are listed in Table III; again a good correspondence between the two structures is noted albeit ring A appears to be somewhat more flattened about C_3 in the X-ray structure than in the MM2 structure.

Table III. Endocyclic Torsion Angles Observed and Calculated by Molecular Mechanics (MM2) for 5α-R and 5β-R

torsion angle	5α-R		5β-R calcd, deg
	obsd,[8] deg	calcd, deg	
10-1-2-3	−55.0	−53.5	55.0
2-1-10-5	57.3	55.6	−58.4
1-2-3-4	49.1	52.3	−50.5
2-3-4-5	−46.4	−52.8	49.3
3-4-5-10	47.1	54.0	−51.6
10-5-6-7	−55.9	−55.9	−53.0
4-5-10-1	−52.3	−55.6	56.2
6-5-10-9	57.9	55.9	54.4
5-6-7-8	53.8	56.7	54.6
6-7-8-9	−53.3	−58.1	−57.2
7-8-9-10	56.1	58.4	58.5
14-8-9-11	−54.4	−51.6	−51.7
9-8-14-13	57.1	59.0	58.7
8-9-10-5	−58.4	−57.0	−57.3
8-9-11-12	55.0	50.6	50.9
9-11-12-13	−55.9	−53.7	−53.8
11-12-13-14	55.5	56.5	56.5
12-13-14-8	−58.1	−61.0	−60.9
17-13-14-15	47.1	46.4	46.4
14-13-17-16	−42.8	−41.6	−41.6
13-14-15-16	−33.2	−33.1	−33.2
14-15-16-17	5.6	6.5	6.5
15-16-17-13	23.7	22.2	22.2

For 5β-R such a comparison between crystallographic and MM2 data is not possible since the structure of 5β-R (or any other steroid having a 5β-configuration together with a 3-one function and no extra substituents) has not been studied by X-ray diffraction techniques.[9] The endocyclic torsion angles in 5β-R derived from the MM2 structure are given in Table III.

It is of considerable interest to determine whether the conformational features observed in the crystal and MM2 structures are preserved in solution. In principle, the conformation of 5α-R and 5β-R in solution may be derived from the observed vicinal NMR coupling constants since the latter are related to the proton–proton torsion angles in 5α-R and 5β-R via a so-called generalized Karplus relation.[10] However, seen in the light of the rather large experimental error in the observed coupling constants (~0.5 Hz) together with the notion that it is hazardous to extract an "accurate" value of a torsion angle from a single experimental coupling constant[10] this approach will undoubtedly rise to large uncertainties in the individual proton–proton torsion angles derived. Therefore, in this way it will be extremely difficult to obtain a consistent representation of the steroid conformation in solution.

Conformation of Rings A, B, and C. It was for this reason that we settled for an alternative approach: Starting from the solid-state or MM2 structure the *expected* coupling constants were calculated by means of a generalized Karplus relation.[10] The calculated couplings for ring A, B, and C were then compared with the observed coupling constants and probed for correspondence (see Table II).

On the whole, the calculated vicinal coupling constants in 5α-R and 5β-R reproduce accurately the observed ^3J's observed in the NMR spectra (root mean square deviation between the observed and calculated couplings in 5α-R,

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(9) We thank Dr. S. Gorter, (X-ray and Electron Diffraction Section, Gorlaeus Laboratory, Leiden), who performed a Bibser-Cambridge file search (author: S. Motherwell).
(10) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.

Table IV. Observed and Calculated Coupling Constants for Ring D in 5α-R and 5β-R

	5α-R					5β-R		
$^3J_{H-H}$	J_{obsd}[a]	ϕ_{HH}[b,c]	J_{calcd}[a,c]	ϕ_{HH}[b,d]	J_{calcd}[a,d]	J_{obsd}[a]	ϕ_{HH}[b,d]	J_{calcd}[a,d]
14α–15α	7.5	−36.3	7.1	−36.3	7.1	7.5	−37.6	6.8
14α–15β	11.2	−156.3	10.7	−156.3	10.7	11.7	−157.6	10.9
15α–16α	9.8	5.3	12.1			9.4		
15α–16β	3.9	−113.9	2.7	−115.1	2.9	3.7	−114.6	2.8
15β–16α	5.5	125.1	4.9	123.9	4.7	5.5	124.4	4.8
15β–16β	12.0	6.1	12.1	4.9	12.1	12.0	5.4	12.1
P		9.6		11.5			11.1	
Φ_m		40.4		41.8			43.5	
rms deviation J_{obsd} vs. J_{calcd}, Hz			1.13		0.67			0.71

[a] In Hz. [b] In decimal degrees. [c] Least-squares fit derived from all six observed proton–proton couplings in ring D. [d] Least-squares fit derived from five observed proton–proton couplings ($J_{15\alpha-16\alpha}$ was excluded from the calculations).

0.55 Hz, and in 5β-R, 0.54 Hz, compare with the estimated experimental error of ~0.5 Hz). This indicates that the conformation of rings A, B, and C as determined by X-ray and molecular mechanics is in good accordance with the solution conformation of these rings in both stereoisomers.

However, one coupling in Table II deserves some further comment: in both compounds $^3J_{8\beta-9\alpha}$ deviates noticeably (i.e., more than 3× root mean square deviation) from the overall accordance between the calculated and observed couplings in ring A, B, and C. As such, the observed coupling constant $^3J_{8\beta-9\alpha'}$, i.e., between the two bridgehead protons $H_{8\beta}$ and $H_{9\alpha'}$ is remarkably small considering the fact that it concerns an axial–axial coupling. The cause of the deviation of the observed $H_{8\beta}$–$H_{9\alpha}$ coupling is not clear but may originate from the convexity in the steroid skeleton together with a small helical deformation[11,12] (the C_1–C_{10}–C_9 moiety is bound somewhat upwards with regard to their respective positions in a regular conformation and the C_6–C_7–C_8 moiety is somewhat flattened[11]).

Conformation of Ring D. A noteable exception to the abovementioned approach, which started from the solid-state or MM2 structure, is formed by the five-membered ring D in the steroids: Since the five endocyclic torsion angles are intimately interrelated via the laws of the pseudorotation, the conformation of these five-membered rings can be derived from the observed coupling constants in an a priori way.

The conformational analysis of five-membered rings is thus greatly facilitated by using the concept of pseudorotation.[13,14] In terms of the formalism given by Altona and Sundaralingam[15] ring D can be described quantitatively by two parameters, i.e., the phase angle of pseudorotation (P) and the puckering amplitude (Φ_m). The five endocyclic torsion angles in ring D (Φ_0–Φ_4, cf. Figure 3) are interrelated via the pseudorotation eq 1. On basis of the ex-

$$\Phi_j = \Phi_m \cos (P + 4j\pi/5); j = 0\text{–}4 \quad (1)$$

tended pseudorotation equation[17] together with the correlation between the proton–proton torsion angles and the endocyclic torsion angles derived from the MM2 structure of 5α-R the following relations between the proton–proton

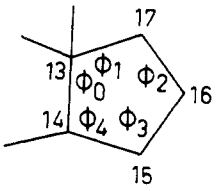

Figure 3. Convention for the numbering of the endocyclic torsion angles in ring D of steroid molecules. Following Altona et al.,[16] the torsion C_{17}–C_{13}–C_{14}–C_{15} is taken as the reference angle Φ_0.

torsion angles ϕ_{HH} and the pseudorotation parameters governing the conformation of ring D were established:

$$\phi_{14\alpha-15\alpha} = -7.6 + 1.001\Phi_m \cos (P - 144.8) \quad (2a)$$

$$\phi_{14\alpha-15\beta} = -127.6 + 1.001\Phi_m \cos (P - 144.8) \quad (2b)$$

$$\phi_{15\alpha-16\alpha} = -0.4 + 1.001\Phi_m \cos (P + 72.3) \quad (2c)$$

$$\phi_{15\alpha-16\beta} = -119.6 + 1.001\Phi_m \cos (P + 72.3) \quad (2d)$$

$$\phi_{15\beta-16\alpha} = 119.4 + 1.001\Phi_m \cos (P + 72.3) \quad (2e)$$

$$\phi_{15\beta-16\beta} = 0.4 + 1.001\Phi_m \cos (P + 72.3) \quad (2f)$$

The torsion angles ϕ_{HH} in eq 2a–f are linked to the corresponding proton–proton coupling constants via a generalized Karplus equation.[10] In other words, the observed proton–proton couplings in ring D are a function of the pseudorotation parameters P and Φ_m; hence the conformational analysis of ring D in 5α-R and 5β-R boils down to a least-squares fitting of the *two* independent parameters P and Φ_m to the *six* experimental coupling constants. This objective was realized by an iterative least-squares computer program; the results obtained for ring D in 5α-R are listed in the third and fourth column of Table IV.

The solution conformation of the five-membered ring D appears to be characterized by $P = 9.6°$ and $\Phi_m = 40.4°$, i.e., a distorted C_{13} β-envelope conformation ($^{13}T_{14}$). Comparison of this solution structure with the solid-state structure ($P = 11.0°$, $\Phi_m = 47.9°$) and the MM2 structure ($P = 9.7°$, $\Phi_m = 46.9°$) of ring D reveals a striking resemblance: The conformation of these five-membered rings are virtually identical although the solution conformation seems to be slightly less puckered than the other two.

Notwithstanding this good correspondence in pseudorotational parameters, the residual root mean square deviation between calculated and experimental coupling constants is very high (~1.1 Hz). Scrutiny of the individual couplings in Table IV (second and fourth column) reveals that it is especially $J_{15\alpha-16\alpha}$ that is responsible for this high root mean square deviation ($\Delta J = J_{exp} - J_{calcd} = -2.3$ Hz). At first sight this large discrepancy between experimental and calculated $H_{15\alpha}$–$H_{16\alpha}$ coupling is puzzling, the more so as the analogous $H_{15\beta}$–$H_{16\beta}$ coupling appears to be very well reproduced by our calculations. However,

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it occurred to us that our findings are consonant with the nonequivalence of the exo–exo and endo–endo vicinal coupling constants observed[18,19] in the bicyclo[2.2.1]heptane (norbornane) system. Semiempirical calculations indicated[19,20] that in the highly puckered envelope geometry of norbornanes, the through-space interactions between the carbon–hydrogen orbitals of the C_2–C_3 fragment and the orbitals about the C_7-methylene bridge in norbornane causes a relative decrease (in the order of 3 Hz) of the endo–endo (cis) coupling constant with respect to the exo–exo (cis) coupling. The same mechanism is likely to be operative in the ring D of the steroid 5α-R: in the near envelope conformation of this ring the C_{13} resides at the flap of the envelope and will therefore selectively reduce the $H_{15\alpha}$–$H_{16\alpha}$ coupling. Since this effect is not accounted for by the generalized Karplus relation it follows that the $H_{15\alpha}$–$H_{16\alpha}$ vicinal coupling constant cannot be reproduced correctly in the current pseudorotation analysis. Therefore, it is reasonable to exclude this coupling from the minimization procedure. A recalculation of the pseudorotation parameters from the observed coupling constants, but with $J_{15\alpha-16\alpha}$ eliminated from the input data set, yields (cf. Table IV, fifth and sixth column) virtually the same conformation for ring D in 5α-R as was obtained earlier ($P = 11.5°$, $\Phi_m = 41.8°$). Not surprisingly, the root mean square deviation between calculated and observed coupling constants has dropped significantly: The final root mean square value of 0.67 Hz is in good correspondence with the estimated experimental error in the observed coupling constants (ca. 0.5 Hz). Be this as it may, the two calculations presented above show that the minimization procedure does not hinge upon a single, outlying value in the input dataset (i.e., the vicinal coupling constants observed). Of course, this must be ascribed to the favorable ratio "observables" (5–6 J's) to "parameters" (2, i.e., P and Φ_m), but, nevertheless, it is encouraging that the pseudorotation analysis is capable of detecting (single) outlying observables.

Finally, we calculated the conformation of the D ring in 5β-R from the observed coupling constants. A $^{13}T_{14}$-like conformation was deduced for this five-membered ring, and again the calculated $H_{15\alpha}$–$H_{16\alpha}$ coupling constant was much larger than the observed $^3J_{15\alpha-16\alpha}$. Exclusion of this coupling from the input data set yielded the following pseudorotation parameters: $P = 11.1°$, $\Phi_m = 43.5°$ (cf. Table IV). In this case comparison with solid-state data is not possible; the correspondence of these solution pseudorotation parameters with those predicted by the MM2 force field calculations ($P = 9.7°$, $\Phi_m = 47.0°$) is excellent.

So, the pseudorotation analysis presented in Table IV shows that the solution conformation of the D ring of 5α-R and 5β-R is in good accordance with the conformations of the D ring deduced by other methods (X-ray and MM2 calculations). Moreover, the pseudorotation parameters obtained for 5α-R and 5β-R show that the conformation of the D ring is not influenced by an α–β isomerization at the C_5-position. The results presented in this section and the preceding one lead to the conclusion that the conformation of, at least, the steroids 5α-R and 5β-R as determined by X-ray crystallography and force field (MM2) calculations corresponds on the whole with the solution conformation of these stereoisomers.

NMR Spectroscopic Implications. A perusal of the chemical shift data in Table I and the structures of the steroids fairly elicits some shielding and deshielding phenomena. For instance, the ^{13}C signals belonging to C_1, C_2, C_{4-7}, C_9, and C_{10} in 5β-R resonate at higher fields with respect to those in 5α-R. These shielding effects arise from the difference in orientation of α-C, β-C, and/or γ-C alkyl substituents in both steroids.[21,22] So C_9 in 5β-R (δ 39.6) undergoes a twofold γ-C axial alkyl effect of about −5 ppm with respect to C_9 in 5α-R (δ 49.6). C_7 sustains the same effect once in 5β-R, whereas C_6 (δ 32.1) in 5β-R has a β-C axial alkyl substituent and C_6 in 5α-R (δ 35.3) a β-C equatorial alkyl substituent resulting in a difference in chemical shift of about 3 ppm.

From the chemical shifts of the protons one can also derive some shielding and deshielding phenomena. As is expected on basis of the diamagnetic anisotropy in saturated alicyclic compounds[23] the equatorial protons at C_6, C_7, and C_{11} are consistently found further downfield by 0.1–0.8 ppm than the axial proton at the same carbon. However, $H_{12_{eq}}$ absorbs at higher field than its geminal proton. Obviously, the reason for this aberrant behavior is that the axial H_{12} proton is deshielded by the acetylenic group nearby. By the same deshielding effect $H_{14_{ax}}$ has shifted downfield when compared with the 14_{ax} protons in two comparable steroids.[2,24] The changeover from a trans to a cis fusion of rings A and B in going from 5α-R to 5β-R gives rise to some conspicuous effects: The 7α- and 9α-protons in 5β-R are shifted downfield in comparison to the same protons in 5α-R; similarly, $H_{6\beta}$ resonates at δ 1.834 in 5β-R compared to δ 1.299 in 5α-R. Again, these observed chemical shift changes are qualitatively in correspondence with the shifts expected on basis of diamagnetic anisotropy considerations.[23] Moreover, $H_{9\alpha}$ will suffer a considerable deshielding due to the "flagpole" interactions with $H_{2\alpha}$ and $H_{4\alpha}$. The diaxial couplings in ring A, B, and C are larger than diaxial couplings involving bridgehead protons.[24]

The C_{18}-methyl group has the well-established long-range coupling (~1 Hz) with the 12α-proton. In 5α-R and 5β-R a not previously reported small long-range coupling (~0.3 Hz) of the C_{18}-methyl group with the 12β-proton is observed near the limit of detection, both in the 2D J-resolved spectra and in the SECSY experiments. The existence of the $J_{18-12\alpha}$ and $J_{18-12\beta}$ makes the absence of a long-range coupling between the methyl group and the methine 14α-proton the more remarkable.

Finally, the $H_{15\alpha-16\alpha}$ coupling is always smaller than the $H_{15\beta-16\beta}$, although the dihedral angles between the C–H bonds comprising the coupled protons are almost equal (Table II). The explanation for this effect is given in the preceding section.

Conclusions

A complete assignment of the ^1H and ^{13}C NMR spectra is obtained of two isomeric steroids, 5α-R and 5β-R, notwithstanding the complexity of the spectra due to their highly extended networks of coupled spins. Some general shielding and deshielding phenomena are observed for this type of steroids. A not previously observed long-range coupling between the C_{18}-methyl group and $H_{12\beta}$ is found.

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The relatively small $H_{15\alpha-16\alpha}$ coupling is explained by the through-space interactions between the carbon–hydrogen orbitals of the C_{15}–C_{16} fragment and the orbitals about the methylene bridge in the highly puckered envelope of ring D of the steroids. It is shown on basis of a comparison between the observed coupling constants and those calculated by means of a generalized Karplus equation[10] for rings A, B, and C and the application of the laws of pseudorotation for ring D, that the conformations derived from the solid-state data or MM2 calculations corresponds with the conformation of these steroids in solution.

Experimental Section

The steroids 17β-hydroxy-19-nor-5α,17α-pregn-20-yn-3-one (5α-R) and 17β-hydroxy-19-nor-5β,17α-pregn-20-yn-3-one (5β-R), generous gifts from Schering, A. G. (Berlin), were dissolved in CD_3OD (ca. 15 mg mL^{-1}).

NMR Spectroscopy. ^1H NMR spectra were recorded on a Bruker WM-500 NMR spectrometer interfaced to an ASPECT-2000 computer and a real-time pulser board. Chemical shifts (δ) were measured relatively to the residual methanol peak and converted to the standard Me_4Si scale by adding 3.38 ppm. ^{13}C NMR spectra were recorded on a Bruker WM-200WB spectrometer operating at 50.3 MHz also equipped with an ASPECT-2000 computer and a real-time pulser board. Chemical shifts were measured relatively to the central peak of the methanol multiplet and converted to the Me_4Si scale (δ_{CH_3OH} 49.3). For further experimental details see ref 3 and references cited therein.

Computation Methods. The structure of 5α-R and 5β-R were calculated by means of general valence force field methods using the computer program MM2.[4,5] For reasons described elsewhere,[10] the hydrogen atoms were removed from the minimized structure and their positions were recalculated from the remaining heavy atom skeleton by using standard methods[10,25] (i.e. methylene hydrogens have a local C_{2v} symmetry with a H–C–H bond angle of 107.6°; methine hydrogens on tertiary sp^3 carbon atoms are fixed in positions having equal bond angles to the other three non-hydrogen substituents; the C–H bond length is 1.105 Å).

The crystal structure data of 5α-R were taken from Rohrer et al.[8] Only the data pertaining to the heavy atoms were used since it is well-known that hydrogen atom coordinates from X-ray diffraction data are at least 1 order of a magnitude less precise than coordinates obtained for heavy atoms (due to the low scattering power and the noncoincidence of bonding electrons and nucleus in the case of hydrogens). The hydrogen atoms were fixed to the crystal structure skeleton following the guidelines given in the preceding paragraph.

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2-Bicyclo[3.2.0]heptyl and 7-Norbornyl Cations

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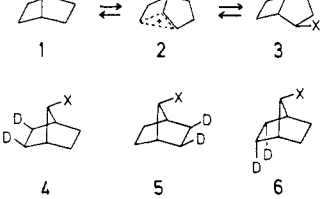
The structure and reactivity of 2-bicyclo[3.2.0]heptyl and 7-norbornyl cations have been probed with the aid of optically active, deuterium-labeled, and methyl-substituted precursors. Bicyclo[3.2.0]heptyl-6,7-d_2 and 6-methyl- and 7-methylbicyclo[3.2.0]heptyl substrates rearranged with >98% inversion at the migration origin to give *anti*-7-norbornyl products. Optically active 2-methylbicyclo[3.2.0]heptyl substrates afforded 1-methyl-7-norbornanol of >98% ee. Anti–syn leakage is characteristic of 7-norbornyl substrates and may be due to k_Δ,k_c competition. Several carbocations have been shown to undergo "same-side bridge-flipping" (**2a** ⇄ **2b**), leading to partial racemization of the parent system and to structural isomerization of others. Bridge-flipping has not been observed with 2-methylbicyclo[3.2.0]heptyl substrates, owing to stabilization of the carbocation by Me. The product distributions cannot be rationalized in terms of open (classical) ions. Bridged (nonclassical) intermediates provide an internally consistent interpretation of our data.

Considerable effort has been expended to explore the $C_7H_{11}^+$ manifold.[1] Controversy regarding the structure of the 2-norbornyl cation continues to receive much attention.[2] The 7-norbornyl cation, posing similar problems, has been studied less extensively. In 1958 Winstein et al.[3] observed that acetolyses of either 7-norbornyl brosylate (1-OBs) or *exo*-2-bicyclo[3.2.0]heptyl brosylate (3-OBs) led to similar product distributions (1-OAc: 3-OAc ≃ 95:5).



The bridged ion **2** was proposed as a common intermediate,

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