Steroidal Analogues of Unnatural Configuration. Part 14.[1] Conformational Analysis of 4,4,14α-Trimethyl-19(10→9β)*abeo*-5β,10α-pregnane-6,11-diols by *X*-Ray Crystallography and Force-field Calculations

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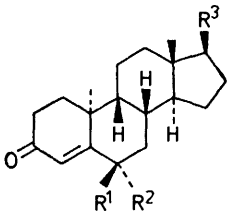
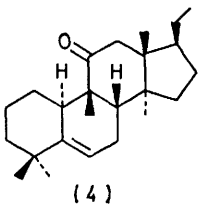
The *X*-ray structures of the 6α,11β- (6), 6β,11β- (7), and 6β,11α-diols (8) have been determined, and their conformations shown to be predicted accurately by the force-field method. The 6β,11α-diol (8) favours a flattener all-chair conformation, whereas rings B and C of (6) and (7) adopt non-chair conformations in response to served α-face interactions. The detailed conformational analysis of the 6,11-diols is discussed in terms of puckeinge parameters, and the steric energies of different conformers are compared. The 6α,11α-diol (9) for which *X*-ray crystallographic data could not be obtained is predicted by force-field calculations to prefer non-chair conformations of rings B and C, in apparent contradiction of spectroscopic findings.

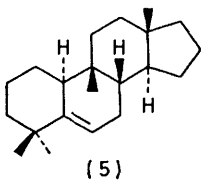
ALTHOUGH non-chair conformations of the cyclohexane rings in steroids have frequently been invoked in order to rationalise spectroscopic findings,[2] proven boat or twist conformers are relatively rare in this field.[3] Furthermore, many of those detected through *X*-ray crystallography owe their ring deformations to constraints imposed by additional rings[4] or ring-junction stereochemistry.[5]



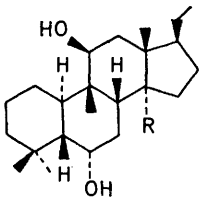
(1) $R^1 = CH_3$ $R^2 = F$ $R^3 = OAc$
(2) $R^1 = H$ $R^2 = CH_3$ $R^3 = Ac$
(3) $R^1 = F$ $R^2 = CH_3$ $R^3 = OAc$



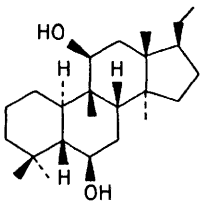
(4)



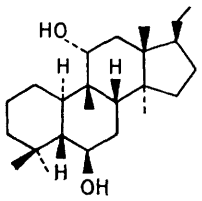
(5)



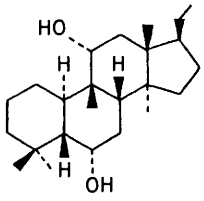
(6) $R = CH_3$
(10) $R = H$



(7)



(8)



(9)

Amongst the examples in which demonstrable boat or twist conformations are adopted by saturated steroidal rings in response to steric interactions alone, those affecting rings B and/or C are particularly uncommon. An investigation of a series of retro-steroids[6] has revealed that appropriate modifications of the substitution pattern at C(6) result in progressive deformation of the same parent system from the B-chair, C-chair conformer of (1) to the B-twist, C-chair of (2) and the B-boat, C-twist of (3); the adoption of these conformations in (2) and (3) may arguably be facilitated by the olefinic bond ' exocyclic ' to ring B.[7] However, a comparison of the reactions of 4,4,14α-trimethyl-19(10→9β)-*abeo*-10α-pregn-5-en-11-one (4)[8] and 4,4,9-trimethyl-9β,10α-estr-5-ene (5)[1] showed that it is necessary to invoke similarly drastic ring B and C deformations of the fully saturated derivatives (6)—(9) in order to rationalise spectroscopic and mechanistic anomalies. These deformations have been ascribed[1,8,9] to the influence of the 14α-methyl group upon the congested α-face of (6)—(9); this group may be regarded as part of an axial t-butyl residue attached by C(8)—C(14) to ring B. Dreiding models reveal (Figure 1) that the resultant interactions are aggravated in (6) and (9), as a result of the axial 6α-hydroxy-group, and that further 1,3-diaxial interactions between the 13β-methyl- and 11β-hydroxy-groups are present upon the β-face in (6) and (7). Lesser interactions involving *peri*-related groups in rings A and B of all the compounds (6)—(9) may also be contributory. The overall result is that much of the steric stress would be dramatically relieved by deformation of the central fused rings, possibly to the extent of their adopting boat-like conformations.[8] Dreiding models suggest, and force-field calculations (*vide infra*) appear to confirm that deformation of ring B or C separately in these compounds (6)—(9) results in sympathetic deformation of its *cis*-fused neighbour. Accordingly, the propensity for conformational change, based upon the relative severity of steric interactions,

may be deduced from Dreiding models as (6) > (9) > (7) > (8). However, such a comparison cannot predict whether any of the compounds does suffer deformation. Furthermore, earlier experimental evidence [8] has failed to reveal the precise nature and extent of deformations, and a more detailed study seemed to be justified by the rarity of the suspected conformational types and their possible interest as structure-activity models.[7]

The problem was approached with the aid of force-field calculations and *X*-ray crystallography of the 6,11-diols (6)—(9). The latter study was confined to the 6α,11β- (6), 6β,11β- (7), and 6β,11α-diols (8), since suitable crystals of the 6α,11α-diol (9) could not be obtained. Some aspects of the n.m.r. spectroscopy of (6)—(9) were also re-examined.[8]

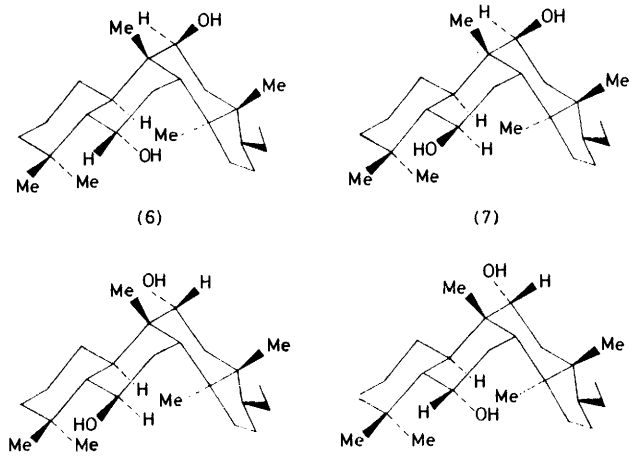


FIGURE 1 The all-chair conformers of diols (6)—(9) showing the sterically interacting groups (including hydrogen)

EXPERIMENTAL

X-Ray data for the compounds (6)—(8) were collected on a Philips PW 100 four-circle diffractometer at the National Physical Research Laboratory.

The MM1 programme of Allinger [10] was used for force-field calculations; input data for compounds (6)—(10) consisted of co-ordinates of idealised geometries as perceived on Dreiding models. Results are reported in the Discussion section, in terms of steric energies and puckering parameters. Atomic co-ordinates derived from force-field minimisations are given in Supplementary Publication No. SUP 22432 (35 pp., 1 microfiche).*

N.m.r. spectra were recorded on a Varian XL 100 spectrometer in FT mode using deuteriochloroform solutions with tetramethylsilane as internal standard. The signals for the 6- and 11-protons of (6), (8), and (9) were well-separated [8] and data were taken directly from the spectra, whereas those for (7) were obtained after mutual separation of the signals through the addition of $Pr(fod)_3$ (2.8 mol %).

Crystallographic Data.—Crystal data and details of the crystallographic analyses of compounds (6)—(8) are given in Table 1.

* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978, Index issue.

TABLE 1

Crystal data and details of crystallographic analyses of compounds (6)—(8)

Cpd.	(6)	(7)	(8)
Formula	$C_{24}H_{42}O_2$	$C_{24}H_{42}O_2$	$C_{24}H_{42}O_2 \cdot \frac{1}{2}(C_4H_8O_2)$
M	362.36	362.36	406.39
Cryst. solvent	Ethanol	Benzene	Dioxan
Space group	$P4_12_12$	$P2_12_12_1$	$P2_1$ *
a/Å	14.22(1)	20.30(1)	12.69(1)
b/Å		14.93(1)	15.26(1)
c/Å	21.76(1)	14.23(1)	12.78(1)
β/°			90.5(1)
U/Å^3	4 400	4 315	2 474
D_c/g cm^{-3}	1.09	1.11	1.09
F(000)	1 616	1 616	904
Z	8	8	4
μ(Mo-K_α)	0.35	0.36	0.37
Scanwidth/°	0.9	0.6	1.0
Scan time/s	30	20	40
Backgrd. count/s	30	20	40
Step size/°	0.03	0.03	0.025
$I_{obs.}$	881	1 571	2 023
F cut-off	2σ	2σ	1σ
R	0.084	0.098	0.205

* Pseudo-orthorhombic $P2_12_12$.

X-Ray Structural Determination.—The structures of the three isomers were solved by direct methods by use of the program system [11] SHELX 77. Figure 2 shows the atom numbering scheme used.

The structure of the tetragonal 6α,11β-diol (6) was developed by tangent refinement from the C(1)–C(10)–C(9)–C(11)–O(2) fragment which, together with a spurious peak, appeared as a six-membered ring on a multisolution *E* map. The solution for the dimeric 6β,11β-diol (7) was harder to find. It was eventually established on the basis of probabilities calculated by consideration of only half the cell content and omission of several prominent reflections of the {*h*00} type. The dioxan adduct of the 6β,11α-diol (8) is so close to being orthorhombic that the space group $P2_12_12$, which is consistent with the apparent absences, was assumed for solving the phase problem. The success with this approach becomes even more remarkable when it is considered that a solution was first obtained in the pseudo-centric (*hk*0) zone according to the method described [12] for centrosymmetric projections.

The structures of the 6α,11β- (6) and the 6β,11β-compounds (7) refined smoothly by full-matrix least-squares with unit weights, but the 6β,11α-structure (8) has still not been refined completely. Considered as an orthorhombic problem the occluded dioxan was found to be disordered with both oxygen atoms on the two-fold axis. Free refinement with inclusion of an averaged dioxan in the form of a twist ceased at *R* 0.30. Lowering of the symmetry to monoclinic somewhat facilitated refinement, but free refinement was still not meaningful. This is partially due to the fact that the two independent molecules in the monoclinic asymmetric unit both start refining from the average molecule of the orthorhombic unit cell. If all atoms are allowed to move independently their shifts are determined by improvement of the mathematical fit only, and not by meaningful molecular geometry. Such a refinement must perforce result in two wrong molecules, especially as far as bond lengths are concerned. The problem was to some extent overcome by applying bond-length constraints throughout both molecules during refinement. If, however, these constraints were relaxed at any stage, some bond lengths, particularly in ring A and around C(10), refined to

TABLE 2

Fractional atom co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses for compounds (6)—(8)

	x	*y*	*z*
(*a*) 6α,11β-diol (6)			
O(1)	9 184(8)	8 499(8)	9 204(5)
O(2)	6 810(9)	5 045(9)	7 827(5)
C(1)	8 661(13)	5 929(14)	7 709(9)
C(2)	9 467(13)	6 271(14)	7 312(9)
C(3)	10 221(16)	6 674(15)	7 699(10)
C(4)	9 912(13)	7 412(13)	8 176(8)
C(5)	9 042(12)	7 044(12)	8 562(8)
C(6)	8 635(12)	7 684(13)	9 054(8)
C(7)	7 695(13)	8 061(13)	8 849(9)
C(8)	6 970(10)	7 267(11)	8 838(8)
C(9)	7 340(11)	6 384(11)	8 482(7)
C(10)	8 238(11)	6 658(11)	8 129(7)
C(11)	6 613(11)	5 974(11)	8 015(7)
C(12)	5 544(13)	6 038(14)	8 201(9)
C(13)	5 266(10)	6 761(11)	8 644(7)
C(14)	6 002(11)	7 604(11)	8 617(7)
C(15)	5 518(15)	8 353(15)	9 036(10)
C(16)	4 476(15)	8 274(16)	8 888(10)
C(17)	4 331(13)	7 339(13)	8 540(9)
C(18)	5 213(15)	6 386(15)	9 311(10)
C(19)	7 606(13)	5 595(12)	8 958(8)
C(20)	3 387(14)	6 844(15)	8 724(11)
C(21)	3 158(24)	5 988(19)	8 380(15)
C(22)	10 804(17)	7 613(18)	8 567(11)
C(23)	9 626(16)	8 307(16)	7 822(9)
C(24)	6 060(16)	8 027(16)	7 965(11)
(*b*) 6β,11β-diol (7)			
	Molecule (i)		
O(1)	4 660(7)	4 095(9)	6 047(10)
O(2)	5 454(8)	7 605(7)	7 696(10)
C(1)	5 775(11)	6 929(12)	5 857(16)
C(2)	6 153(12)	6 873(12)	4 907(15)
C(3)	5 839(12)	6 205(12)	4 270(17)
C(4)	5 767(9)	5 258(12)	4 661(13)
C(5)	5 420(10)	5 278(13)	5 586(13)
C(6)	5 340(10)	4 352(13)	6 044(14)
C(7)	5 630(11)	4 324(14)	7 072(16)
C(8)	5 340(10)	5 004(12)	7 668(14)
C(9)	5 291(8)	6 006(10)	7 252(12)
C(10)	5 708(10)	6 007(14)	6 297(14)
C(11)	5 598(9)	6 691(11)	7 936(13)
C(12)	5 413(11)	6 598(14)	8 991(15)
C(13)	5 212(9)	5 666(12)	9 347(13)
C(14)	5 574(9)	4 968(12)	8 676(13)
C(15)	5 439(14)	4 104(17)	9 185(19)
C(16)	5 482(13)	4 352(16)	10 272(17)
C(17)	5 489(10)	5 363(14)	10 279(15)
C(18)	4 488(12)	5 506(19)	9 330(19)
C(19)	4 580(10)	6 277(14)	7 033(15)
C(20)	5 115(11)	5 713(14)	11 186(16)
C(21)	5 171(13)	6 690(16)	11 323(19)
C(22)	5 431(11)	4 664(14)	3 934(15)
C(23)	6 483(11)	4 865(16)	4 758(19)
C(24)	6 353(11)	5 103(16)	8 737(17)
	Molecule (ii)		
O(1)	6 493(7)	−1 054(10)	7 321(9)
O(2)	8 478(6)	418(9)	4 833(8)
C(1)	8 571(9)	−1 288(12)	5 829(13)
C(2)	8 892(11)	−2 118(14)	6 253(15)
C(3)	8 433(10)	−2 769(14)	6 712(16)
C(4)	7 997(10)	−2 323(14)	7 466(15)
C(5)	7 645(11)	−1 457(15)	7 032(16)
C(6)	7 162(10)	−995(13)	7 718(14)
C(7)	7 392(9)	−90(11)	7 935(12)
C(8)	7 429(9)	507(12)	7 096(13)
C(9)	7 783(9)	81(12)	6 226(12)
C(10)	8 139(8)	−811(11)	6 577(12)
C(11)	8 356(9)	684(12)	5 793(13)
C(12)	8 157(10)	1 743(13)	5 702(14)
C(13)	7 692(10)	2 062(13)	6 515(14)
C(14)	7 708(8)	1 437(11)	7 403(11)
C(15)	7 299(10)	1 963(13)	8 082(14)
C(16)	7 433(12)	2 984(15)	7 889(16)
C(17)	7 847(9)	3 008(12)	6 986(13)
C(18)	6 978(9)	2 159(13)	6 068(15)
C(19)	7 279(9)	−168(13)	5 465(14)
C(20)	7 722(12)	3 822(15)	6 332(16)
C(21)	7 947(10)	4 689(13)	6 856(15)
C(22)	7 451(9)	−3 026(13)	7 754(14)
C(23)	8 355(10)	−2 064(14)	8 333(15)
C(24)	8 399(10)	1 382(15)	7 828(15)
(*c*) 6β,11α-diol (8)			
	Molecule (i)		
O(1)	3 782(12)	4 339(12)	−1 007(13)
O(2)	6 752(14)	1 019(13)	651(15)
C(1)	6 003(28)	1 712(20)	−1 371(24)
C(2)	6 625(27)	2 077(25)	−2 303(27)
C(3)	5 908(30)	2 743(22)	−2 858(27)
C(4)	5 648(20)	3 523(18)	−2 160(19)
C(5)	5 077(17)	3 137(13)	−1 224(16)
C(6)	4 634(14)	3 886(13)	−540(13)
C(7)	4 192(20)	3 532(19)	498(18)
C(8)	4 874(17)	2 902(14)	1 153(17)
C(9)	5 316(15)	2 159(13)	448(14)
C(10)	5 764(18)	2 468(16)	−609(16)
C(11)	6 139(18)	1 668(16)	1 165(19)
C(12)	6 897(16)	2 119(16)	1 913(17)
C(13)	6 249(20)	2 764(16)	2 555(19)
C(14)	5 682(17)	3 417(15)	1 824(17)
C(15)	5 289(23)	4 076(20)	2 650(21)
C(16)	6 116(26)	4 106(25)	3 539(27)
C(17)	6 893(21)	3 353(17)	3 300(19)
C(18)	5 521(25)	2 302(25)	3 347(26)
C(19)	4 402(19)	1 517(18)	263(21)
C(20)	7 353(26)	2 925(22)	4 286(23)
C(21)	8 177(33)	3 472(32)	4 883(37)
C(22)	4 952(27)	4 077(23)	−2 887(27)
C(23)	6 577(24)	4 137(24)	−1 924(31)
C(24)	6 486(18)	3 978(17)	1 232(19)
	Molecule (ii)		
O(1)	−1 164(11)	660(11)	934(12)
O(2)	1 679(14)	3 954(13)	−859(14)
C(1)	823(25)	3 352(20)	1 131(22)
C(2)	1 532(27)	3 160(25)	2 082(25)
C(3)	943(28)	2 426(21)	2 667(26)
C(4)	677(21)	1 611(19)	2 012(19)
C(5)	82(17)	1 881(13)	1 018(15)
C(6)	−341(13)	1 079(12)	406(12)
C(7)	−805(18)	1 422(19)	−626(16)
C(8)	−55(15)	1 930(13)	−1 342(16)
C(9)	269(16)	2 782(13)	−746(16)
C(10)	705(21)	2 574(17)	363(17)
C(11)	1 065(16)	3 322(14)	−1 422(17)
C(12)	1 863(18)	2 783(17)	−2 037(20)
C(13)	1 287(18)	2 112(15)	−2 724(18)
C(14)	793(15)	1 445(14)	−1 973(15)
C(15)	385(21)	732(19)	−2 723(20)
C(16)	1 270(24)	697(23)	−3 552(25)
C(17)	2 003(22)	1 491(18)	−3 342(21)
C(18)	506(24)	2 595(23)	−3 440(24)
C(19)	−685(20)	3 390(19)	−557(22)
C(20)	2 461(25)	1 914(22)	−4 336(23)
C(21)	3 227(31)	1 321(28)	−4 929(32)
C(22)	110(33)	1 047(27)	2 838(29)
C(23)	1 712(23)	1 111(24)	1 821(30)
C(24)	1 584(20)	985(19)	−1 248(20)

ridiculous values. Furthermore, the dioxan still appeared to be disordered. It was possible to explain all electron density near the dioxan by superimposing four chair-like molecules in such a way that their oxygen atoms are coincident. In addition all atoms in rings A and D of both steroid molecules had unrealistically high thermal vibration parameters. These observations suggest that the true symmetry is even lower and/or the true unit cell is a multiple of the apparent cell of the monoclinic model.

A tentative attempt to refine the structure in $P1$ was soon abandoned when the fit did not improve materially and the irregular symptoms persisted. The only alternative is a *super cell which* could be either monoclinic or triclinic and with either four or eight formula units per asymmetric unit, as was found for anhydrous cholesterol.[13] Since no experimental evidence for the existence of such a cell could be found, this course was not pursued. The constrained monoclinic model with four dioxan molecules superimposed, and which refined to R 0.20, has consequently been accepted as the basis for the present discussion.

The refined co-ordinates of the various steroid moieties are in Table 2 and of disordered dioxan in Table 3. The

TABLE 3

Atomic fractional co-ordinates ($\times 10^4$) defining the disordered molecule of dioxan. The common thermal vibration parameter $a = 0.309$ (15)

	x	y	z
O(1)	7 173(41)	0	5 895(32)
O(2)	8 090(41)	−253(44)	4 266(33)
C(1)	7 905(75)	−698(57)	5 847(57)
C(2)	7 521(85)	−957(36)	4 734(66)
C(3)	7 725(71)	716(29)	5 458(61)
C(4)	7 443(79)	509(62)	4 307(56)
C(5)	6 575(58)	−376(68)	5 075(66)
C(6)	8 650(46)	124(70)	5 104(63)
C(7)	6 549(50)	140(105)	4 994(59)
C(8)	8 739(49)	−260(108)	5 155(57)
C(9)	7 058(54)	57(100)	4 093(59)
C(10)	7 889(82)	690(43)	5 749(86)

separate dioxan rings defined by these co-ordinates are: O(1)–C(1)–C(2)–O(2)–C(4)–C(3), O(1)–C(5)–C(2)–O(2)–C(6)–C(3), O(1)–C(1)–C(8)–O(2)–C(4)–C(7), and O(1)–C(5)–C(9)–O(2)–C(6)–C(10). Final observed and calculated structure factors, atom thermal parameters, and hydrogen atom positions are listed in Supplementary Publication No. SUP 22432.

All hydrogen co-ordinates in the 6β,11α-structure (8), have been calculated, but for compounds (6) and (7), most hydrogen atoms were located on difference maps.

RESULTS AND DISCUSSION

The three structures (6)—(8), determined by X-ray crystallography provided reference parameters for comparison with those obtained through force-field calculations. The latter method, applied also to (9) and the hypothetical substance (10), afforded the calculated steric energies and puckering parameters of the discrete conformational types, referred to in this discussion as (CCC)- and (CBB)-conformers. These three-letter designations signify chair-like (C) and boat-like (B) conformations for rings A, B, and C respectively. This ' shorthand ' nomenclature is used for convenience, and individual ring geometries are more accurately described throughout by adapting published systems for five-[14] and six-membered[15] rings to the steroid numbering illustrated in Figure 2.

X-Ray Structures.—The crystal structures of all three isomers (6)—(8) depend on the presence of intermolecular hydrogen bonds. Where these bonds are formed in a regular fashion, high-symmetry crystals of the tetragonal 6α,11β-isomer (6) are obtained. Hydrogen bonding is less regular in the 6β,11β-isomer (7), and the asymmetric unit contains two crystallographically independent, but chemically identical molecules. The 6β,11α-isomer (8) crystallises with clathrated dioxan; this further complicates the packing in the crystal, which already appears to contain two different, but related, conformers.

In the tetragonal crystal of (6) the maximum number of intermolecular hydrogen bonds of the types O(1)–H · · · O(2) and O(2)–H · · · O(1) is formed. The molecules are so arranged that all the hydroxy-groups cluster around the screw axes and consequently, all the molecules form part of a regular three-dimensional network. The hydrogen-bonded pairs of the 6β,11β-isomer (7), however, have no symmetry. Each pair constitutes an asymmetric unit which is further hydrogen-bonded to symmetry-related pairs. The situation is similar for the 6β,11α-isomer (8), except that a high degree of pseudosymmetry occurs.

It is emphasised that both of the two slightly different conformers determined for the 6β,11α-isomer (8) could be incorrect. It is likely that the asymmetric unit contains a number of identical molecules in slightly

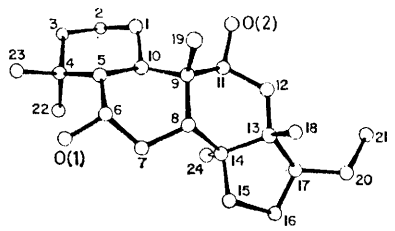


FIGURE 2 Numbering system illustrated on the X-ray structure of the 6α,11β-diol (6)

different orientations. To describe the structure in less than the actual number of orientations amounts to averaging over certain of these to yield a false geometry and high ' thermal motion '. This type of pseudosymmetry cannot however occur unless the different orientations are much alike; consequently the observed conformations should be equally close to reality.

No unusual bond parameters meriting detailed discussion were observed for (6)—(8) and, since the molecular conformations are best compared in terms of puckering parameters (*vide infra*) calculated directly from the fractional co-ordinates, the detailed data are not tabulated. Stereoscopic drawings of the structures are shown in Figure 3.

Steric Energies.—The steric energies derived from force-field minimisations[10] for various conformers of the compounds (6)—(9) are given in Table 4.

The 6α,11β-diol (6), in which both hydroxy-groups are axial in the (CCC)-conformer (Figure 1), is shown to favour the (CBB)-conformer by 4.5 kcal mol^{-1}. The energy difference favouring (CBB)-conformers is reduced to 0.2 and 1.0 kcal mol^{-1} respectively in those isomers, (7) and (9), having axial-equatorial 6,11-substituent pairs in the undeformed state (Figure 1), whereas the di-equatorial 6β,11α-isomer (8) favours the (CCC)-conformer

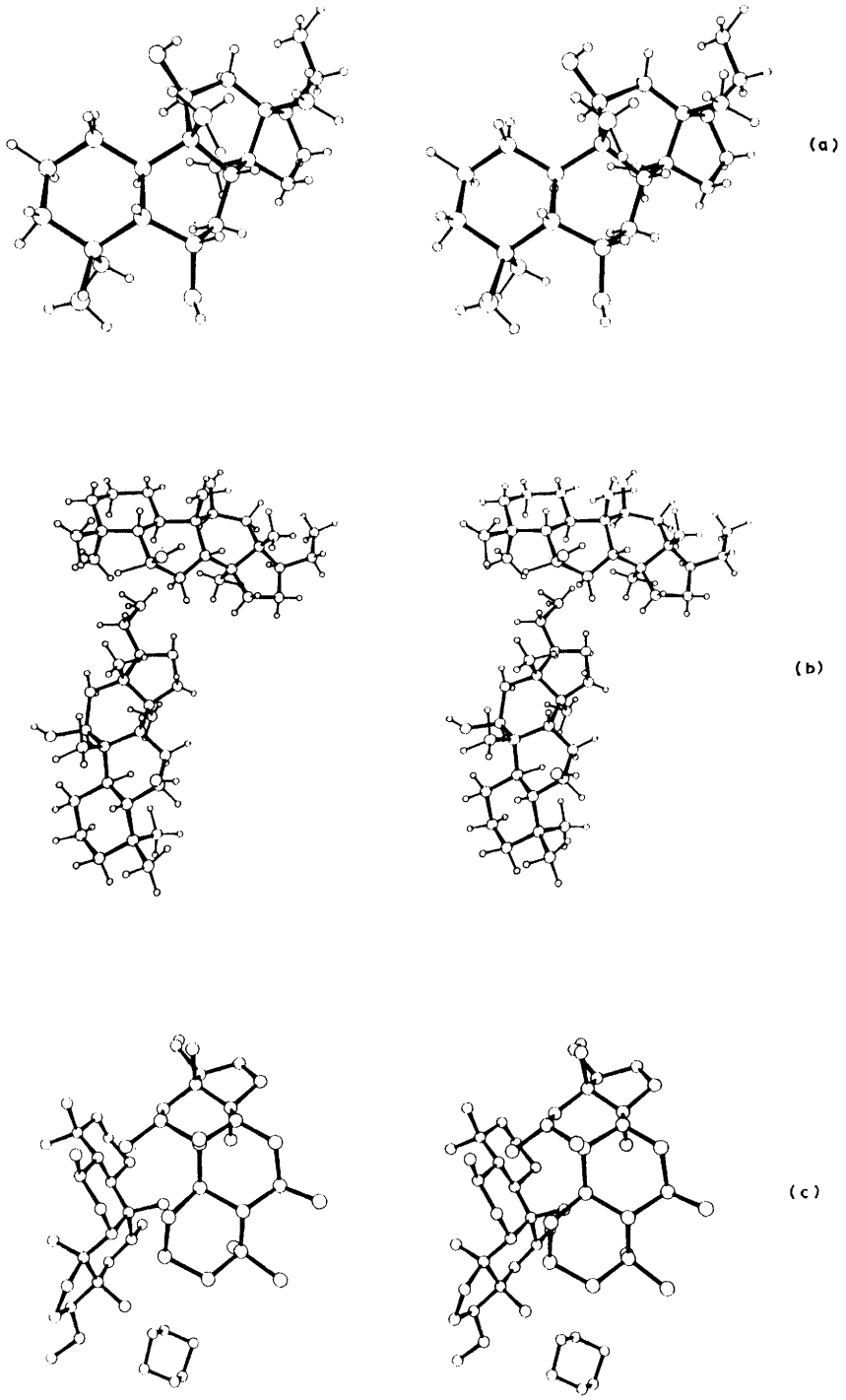


FIGURE 3 Stereorepresentations of the *X*-ray structures of diols (a) (6), (b) (7), and (c) (8)

by 2.0 kcal mol^{-1}. These results corroborate the intuitively derived order of preference for ring deformation (*vide supra*), and predict that all but one of the compounds must differ from the (CCC)-state. The results for (7) must be treated with caution since the small energy-difference calculated for the (CCC)- and (CBB)-conformers suggests an equilibrium slightly favouring the latter in the gas phase at 25 °C; however the difference is smaller than the error found between experimental and calculated energies in a related study.[16]

Other combinations of ring conformations were also examined in order to ascertain whether more stable structures were possible in certain likely examples. In the case of (7), the final energy and conformation of the (CCB)-form was equivalent to that of the (CCC)-form, *i.e.* despite different input conformers, the same mini-

mised (CCC)-conformation resulted, and is demonstrably that of lower energy. The (CBC)- and (BBB)-conformers of the 6α,11α-diol (9) were considered, but had appreciably higher energies than that of the (CBB)-form (Table 4) and can be disregarded.

The conformers of (6)—(8) favoured by force-field minimisations are also compatible with conclusions (Table 4) drawn from *X*-ray data (*vide infra*).

It was of interest to quantify the influence of the 14α-methyl group, as the experimentally proven [1,8] factor in promoting conformational change in the series. Accordingly, the steric energies of the (CCC)- and (CBB)-conformers of the hypothetical 24-nor-6α,11β-diol (10) were calculated. This example was chosen as the most likely to suffer deformation, even in the absence of the 14α-methyl group. However, the results (Table 4) revealed that the (CCC)-form of (10) would be favoured by 4.4 kcal mol^{-1} [*cf.* the 6α,11β-diol (6)], and confirm that the 14α-methyl group is indeed an essential steric requirement for promoting deformations in rings B and C of this series.

The nature of these deformations is illustrated (Figure 4) for a representative example; thus, a projection (a) of the 6α,11β-diol (6) derived from Dreiding models shows the severe non-bonded interactions present when rings A, B, and C assume 'ideal' chair conform-

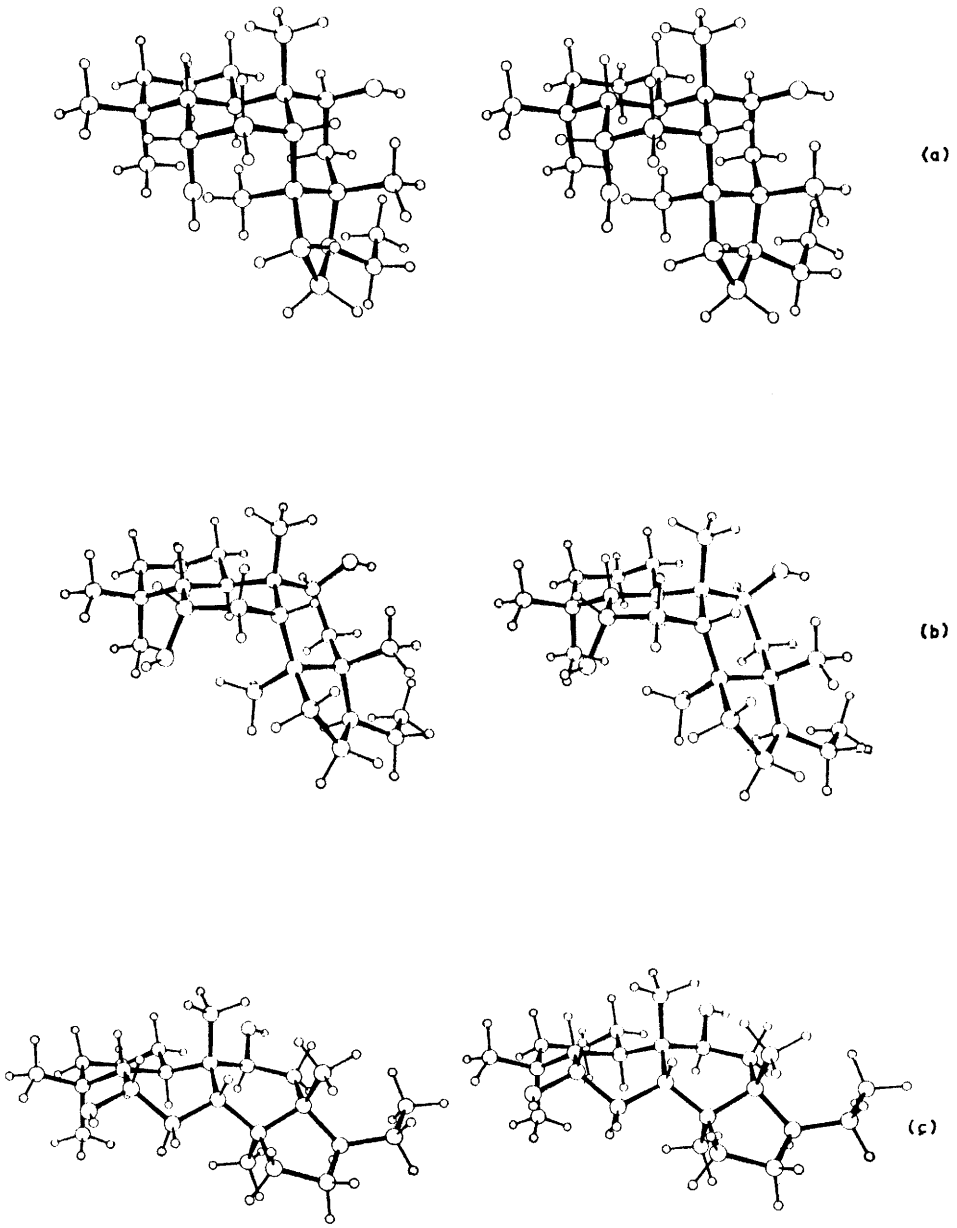


FIGURE 4 Stereo-representations of the 6α,11β-diol (6) in (a) the (CCC)-conformation as described by Dreiding models, (b) the (CCC)-conformation resulting from force-field minimisation of (a), and (c) the (CBB)-conformation resulting from force-field minimisation of conformation ($^1C_4$, $B_{7,10}$, $B_{11,14}$,$^{13}T_{14}$)

TABLE 4

Calculated steric energies and predicted conformations of 6,11-diols

Cpd.	Steric energies [a] (CCC)	(CBB)	Other	Favoured conformer Force field	X-Ray
(6)	73.3	68.8		(CBB)	(CBB)
(7)	67.8	67.6	67.7 (CCB) [b]	(CBB) ⇌ (CCC)	(CBB)
(8)	67.5	69.5		(CCC)	(CCC)
(9)	72.3	7.13	75.5 (CBC) [c] 82.4 (BBB) [d]	(CBB)	
(10)	53.3	5.77		(CCC)	

[a] Calculated by the force-field method and given in kcal mol^{-1}. Input co-ordinates used the following ideal (Dreiding) geometries: (CCC) $^1C_4$, $^5C_8$, $^8C_{12}$, $^{13}T_{14}$; (CBB) $^1C_4$, $B_{7,10}$, $B_{11,14}$, $^{13}T_{14}$; (CCB) $^1C_4$, $^5C_8$, $B_{11,14}$, $^{13}T_{14}$; (CBC) $^1C_4$, $^6T_{10}$, $^8C_{12}$, $^{13}T_{14}$; and (BBB) $B_{3,10}$, $^{5,8}B$, $^{9,13}B$, $^{13}T_{14}$. [b] Input data minimised to the (CCC)-conformation. [c] Final geometry *ca.* $^1C_4$, $^6T_{10}$, ($^{13}E + {}^{13}C_9$), $^{13}T_{14}$. [d] Final geometry *ca.* $^1T_3$, ($^8T_{10} + B_{7,10}$), $^9T_{14}$, $^{13}T_{14}$.

ations. The inadequacy of such a representation has been recognised,[17] and the force-field-minimised (CCC)-conformer (b) of (6) reveals that the α-face interactions may be considerably alleviated by flattening of rings B and C, despite the attendant increase in bond-angle strain. However, this does not represent the favoured conformer of (6), but merely that which would obtain if more drastic ring deformations were impossible. In the alternative, (CBB)-conformer (c), some of the residual van der Waals strain, as well as bond-angle strain associated with ring flattening is dissipated at the expense of added torsional strain. The energies calculated for these strains in Figure 4 (b) and (c) are: van der Waals 29.1 and 26.1, bond angle 25.1 and 21.4, and torsional 7.9 and 10.9 kcal mol^{-1}. These factors thus account for most of the 4.5 kcal mol^{-1} difference in total steric energy between (c) and (b).

Conformational Analysis.—The *X*-ray and force-field geometries of the diols (6)—(10), defined in terms of puckering parameters,[15] are grouped together as (CCC)-(Table 5) and (CBB)-conformers (Table 6). Discrete conformers of cyclohexane are similarly defined (Table 7) for comparison. Since ϕ is undefined for θ *0 and* 180°, it follows that large variations in ϕ have little geometrical significance when θ is close to the polar values.

In all the cases listed in Tables 5 and 6, ring A is close ($\theta \leqslant 9°$) to a perfect chair ($^1C_4$), with no evidence of excessive puckering or flattening; similarly ring D is close ($\phi = 242 \pm 8°$) to the ideal $^{13}T_{14}$ conformation.[14]

The (CCC)*-conformers.* A detailed comparison of the *X*-ray and force-field geometries of (8) is not meaningful [18] owing to the inadequacy in this case of the *X*-ray structural refinement (*R* 0.2) and its effect upon the derived puckering parameters. Nevertheless, the calculated parameters, θ and ϕ, reflecting modes of flattening for rings B and C show reasonable correspondence with those determined for molecule (ii) of (8), whereas the calculated degree of pucker (*Q*) for those rings is best compared with measurements made upon molecule (i) of (8) (Table 5). In the ensuing discussion, the puckering parameters derived from the force-field calculations are taken to represent the (CCC)-conformer of (8) most faithfully.

TABLE 5

Puckering parameters of (CCC)-conformers: θ, ϕ in degrees, *Q* in Å

	Ring A			Ring B			Ring C			Ring D	
Cpd.	θ	ϕ	*Q*	θ	ϕ	*Q*	θ	ϕ	*Q*	ϕ	*Q*
(6): Calc.	2	2	0.56	28	155	0.47	18	263	0.55	342	0.51
(7): Calc.	4	45	0.58	16	195	0.43	29	243	0.55	338	0.49
(8): Calc.	6	51	0.59	20	189	0.43	25	236	0.56	337	0.50
X-Ray, mol. (i)	2	344	0.65	3	235	0.47	18	266	0.56	350	0.45
X-Ray, mol. (ii)	9	28	0.62	16	212	0.53	22	239	0.59	349	0.51
(9): Calc.	3	27	0.58	15	183	0.43	28	236	0.56	336	0.49
(10): Calc.	1	267	0.56	16	185	0.49	4	268	0.54	345	0.47

TABLE 6

Puckering parameters of (CBB)-conformers; θ, ϕ in degrees, *Q* in Å

	Ring A			Ring B			Ring C			Ring D	
Cpd.	θ	ϕ	*Q*	θ	ϕ	*Q*	θ	ϕ	*Q*	ϕ	*Q*
(6): Calc.	3	358	0.56	91	84	0.74	76	288	0.67	344	0.49
X-Ray	7	52	0.54	93	76	0.79	77	288	0.67	342	0.47
(7): Calc.	5	298	0.54	89	79	0.73	78	288	0.68	343	0.49
X-Ray *	3	206	0.54	88	72	0.77	82	285	0.71	349	0.48
(8): Calc.	5	342	0.56	91	78	0.70	79	286	0.68	338	0.49
(9): Calc.	5	17	0.56	93	82	0.72	79	287	0.68	339	0.49
(10): Calc.	2	336	0.55	92	81	0.75	82	299	0.67	348	0.46

* Parameters averaged over the values obtained from the two molecules in the unit cell.

The steric interactions in the (CCC)-conformers of compounds (6)—(10) are most clearly manifested in the calculated deformations of rings B and C (θ 15—29°, see Table 5) towards envelope or half-chair conformations and, in the case of ring B, by further flattening (*Q* 0.43—0.49 Å, see Table 5 and *cf.* Table 7).

Ring B in the (CCC)-conformer of (6) is deformed towards a $^9H_8$ conformation [$\phi(^9H_8)$ 150°], whereas rings B of the (CCC)-conformers of (9) and (10) are deformed

TABLE 7

Puckering parameters of cyclohexane conformers *

Conformer	θ/°	ϕ/°	Q/Å
Chair (C)	0	Undefined	0.575
Half-chair (H)	50.8	$(2n + 1) \times 30$	0.541
Envelope (E)	54.7	$n \times 60$	0.547
Twist (T)	90.0	$(2n + 1) \times 30$	0.775
Boat (B)	90.0	$n \times 60$	0.734

* Cyclohexane was subjected to force-field minimisation with restricted motion of certain atoms to ensure retention of the desired conformational type.

towards E_8 conformations [$\phi(E_8)$ 180°]; evidently the 6α,14α- and 6α,10α-interactions present in these 6α-substituted cases (6), (9), and (10) would thereby most effectively be diminished. By contrast, the conformation of ring B in the (CCC)-conformers of the 6β-substituted compounds (7) and (8) reflects hybrid $E_8/^7H_8$ character [$\phi(^7H_8)$ 210°].

Ring C in the (CCC)-conformer of the hypothetical compound (10) is close to a perfect chair, reflecting the reduced effect of α-face interactions compared with the 14α-methyl compounds (6)—(9), whose (CCC)-conformers display appreciable ring C deformation ($\theta \geqslant 18°$) towards ^{13}E [for (7), (8), and (9)] or hybrid $^{13}E/^{13}H_{14}$ [for (6)] conformations [$\phi^{13}E$) 240° and $\phi(^{13}H_{14})$ 270°].

It is thus demonstrated that, in the absence of more drastic ring deformations, steric relief in the (CCC)-conformers may be achieved through ring flattening at C(5) and C(9) towards E_8 and ^{13}E conformations of rings B and C respectively, and about the C(5)–C(6), C(5)–C(19), and C(9)–C(11) bonds towards $^9H_8$, $^7H_8$, and $^{13}H_{14}$ conformations respectively in the appropriate rings. These results further illustrate [17] the deficiencies of Dreiding models for predicting the nature of subtle conformational changes; thus, C(6), C(7), C(11), and C(12) are the most flexible ring B and C positions in Dreiding models of compounds (6)—(10) and it would mistakenly be concluded that steric relief could most readily be achieved through deformations of rings B and C towards $^9H_{10}$ (ϕ 90°) and $^8H_{14}$ (ϕ 330°) conformations respectively.

The (CBB)*-conformers.* The (CBB)-conformers of compounds (6)—(10) display remarkably similar conformations of rings B and C (Table 6): those slight differences reflected by the puckering parameters may be ascribed to substituent effects. In each case, ring B of the *X*-ray and force-field structures is within 3° (θ value) of the boat-twist pseudorotational circle [15] and all have hybrid $B_{7,10}/^6T_{10}$ conformers [$\phi(B_{7,10})$ 60 and $\phi(^6T_{10})$ 90°]. The force-field-derived parameters reflect slightly more boat-like character for rings B of the 6β-hydroxy-compounds (7) and (8) [ϕ 78° (4)] than of the 6α-hydroxy-compounds (6), (9), and (10) [ϕ 81° (3)]; this is ascribed to the influence of the pseudo bow-stern interaction between the 6β- and 9β-substituents, which is greater in the $^6T_{10}$ than in the $B_{7,10}$ conformation. No appreciable ring B flattening is seen in any of the (CBB)-conformers of compounds (6)—(10).

Comparison reveals that the *X*-ray parameters for (6) and (7) display more $B_{7,10}$ character than those of the corresponding calculations ($\Delta\phi$ 7 and 8°). This may be due to a slight systematic error in the force field employed here or alternatively, it may reflect the incompletely relaxed character of the compounds (6) and (7) in the crystalline state as a result of intermolecular hydrogen bonding (*q.v.*).

Ring C in the (CBB)-conformers of all the 14α-methyl compounds (6)—(9) is deformed away from the boat-twist pseudorotational circle towards envelope or half-chair conformations by an average of θ −11°. Nevertheless, it is most accurately defined as a hybrid $B_{11,14}/^9T_{14}$ conformation [$\phi(B_{11,14})$ 300 and $\phi(^9T_{14})$ 270°]. This arrangement is a compromise which minimises the pseudo bow-stern interactions present in both conformational extremes; the pure $^9T_{14}$ conformation would result in equivalent orientations between an 11α-substituent and the 14α-methyl group on the α-face, and the 9β- and 13β-methyl groups on the β-face. The presumably greater steric demand of the latter groups must be responsible for the partial $B_{11,14}$ character, in which β-face congestion is slightly diminished. This argument is supported by the calculation for the (CBB)-conformer of the hypothetical 24-nor-compound (10), in which the absence of the 14α-methyl group results in further pseudorotation of ring C to the pure $B_{11,14}$ conformation.

N.m.r. Spectroscopy.—The calculated and observed widths of signals for the 6- and 11-protons of compounds (6)—(9) are given in Table 8 and other data in the

TABLE 8

Calculated and observed n.m.r. data for diols (6)—(9) *

Cpd.	Proton	Calc. signal width/Hz (CCC)	Calc. signal width/Hz (CBB)	Obs. signal width /Hz
(6)	6β	12.6	22.7	19.0
	11α	6.7	14.8	16.0
(7)	6α	23.5	9.1	7.0
	11α	6.6	14.9	16.0
(8)	6α	24.6	9.0	17.0
	11β	15.5	8.1	13.0
(9)	6β	11.4	22.7	15.5
	11β	15.5	8.1	15.0

* A more complete Table, listing individually calculated torsion angles and their derived coupling constants, is given in Supplementary Publication No. SUP 22432 (see text).

Supplementary Publication. The former values are based upon torsion angles defined by the force-field geometries of the (CCC)- and (CBB)-conformers, and derived coupling constants calculated from a modified [19] Karplus equation. As a result of the method of determination, the experimental signal widths in Table 8 are considered to be more reliable than those previously reported.[8] Since the earlier reservations concerning first-order treatment of the observed splittings still apply, the overall signal widths are taken as the most meaningful basis for comparisons.

With the exception of those for the 6α,11α-diol (9) the widths of the observed signals lie close to those calculated for the empirically determined and energetically favoured

conformers. However, both carbinol proton signals for (9) indicate a (CCC)-conformer, in direct conflict with the force-field prediction that the (CBB)-conformer should be energetically favoured by *ca.* 1 kcal mol^{-1}. This discrepancy may possibly be ascribed to a solvent effect. Thus, the force-field calculations simulate a totally relaxed and isolated molecule,[18] whereas the n.m.r. sample in chloroform solution may be subject to associative effects which influence the relative energies of the respective conformers. It is relevant that the difference in steric energies between the (CCC)- and (CBB)-conformers of the 6β,11β-diol (7) is only 0.2 kcal mol^{-1}, and yet the n.m.r. spectrum is entirely compatible with the exclusive existence of the latter conformer in solution, and not an equilibrium condition. It is possible that variable-temperature studies may clarify this detail.

Conclusion.—The correspondence of molecular geometries derived from *X*-ray data and from force-field calculations is particularly good in the two cases (6) and (7) where a meaningful comparison can be made. Consequently, the force-field results have been used with confidence for a precise description of the geometry of (8), in the absence of an adequate *X*-ray refinement. Furthermore, the relative steric energies derived from force-field calculations for different conformers of (6)—(8) are qualitatively compatible with experimental findings, despite the surprising absence of n.m.r. evidence of an equilibrium between the (CCC)- and (CBB)-conformers of (7). If this is a consequence of the force field rather than experimental factors, it implies that the calculation of relative steric energies may be in error by 1 kcal mol^{-1} or more.

In the case of the 6α,11α-diol (9), the direct conflict between n.m.r. data and the force-field calculations is more serious, particularly since corroborative *X*-ray data are unavailable. The calculations favour the (CBB)-conformer by 1 kcal mol^{-1}, whereas n.m.r. data suggest that the (CCC)-conformer is favoured by at least 1 kcal mol^{-1} (giving an equilibrium of at least 85% of that conformer). Further experiments may resolve these problems, but it is also possible that the force field [10] employed in this study has not evolved to a stage where small energy differences between highly strained conformers can be interpreted with absolute confidence. Indeed, it is possible that the discrepancies may reflect the ' hardness ' of hydrogen–hydrogen non-bonded interactions in Allinger's MM1 program,[10] compared with those of other force fields.[18] It will be interesting to re-examine the compounds (6)—(9) with the aid of the new set of force-field parameters for the MM2 program,[20] when it is extended to include functionalised systems.

It is concluded that the MM1 program accurately predicts the geometries of the different conformers of (6)—(9) but that their relative steric energies are not necessarily as accurate; it seems prudent to assume an estimated standard deviation of at least 0.7 kcal mol^{-1} when evaluating these data. It should be stressed however, that despite the complexity of the molecules examined here, the power of the force-field technique is amply demonstrated. The experimental results and calculations provide a satisfactory explanation for the mechanistic anomalies and stereochemical aberrations in this series of compounds.[1,8]

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