$(2.612)^2$ gives the magnitude of the moment (3.82 D.). This value is in excellent agreement with the observed moment of 16α-bromo-5α-androstan-17-one which we have measured in benzene solution at 25° and found to be 3.85 D.[15]

(15) Unpublished data of F. V. Brutcher, Jr., and F. J. Reynolds.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA 4, PENNA.]

The Conformations of Substituted Cyclopentanes. III. Ring D in the Steroids[1,2]

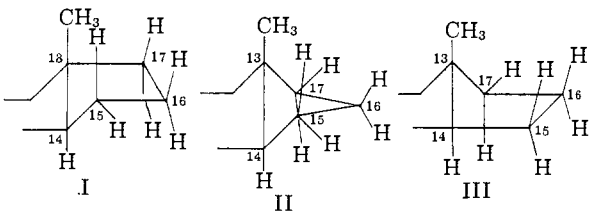
BY FREDERICK V. BRUTCHER, JR., AND WILLIAM BAUER, JR.

RECEIVED AUGUST 30, 1961

The previously-described,[1] maximally-puckered models for the symmetrical forms of cyclopentane have been applied to the description of three possible conformations of ring D in the steroids. Calculation of bond-bending and torsional energies as well as interaction energies for 1,3-substituents has suggested general stability relationships for these conformations on substitution of the ring. Infrared data on steroid haloketones and glycols have been utilized in assignment of conformation to several steroids. Some of the chemistry of ring D is discussed in the light of the conformations of the ring.

The most famous relative of the simple cyclopentane ring is certainly the five-membered ring D of the steroids.[3-7] In a previous paper we have constructed by vector analytical techniques[1,8] models of maximally puckered cyclopentane rings such as would be found in the *trans*-locked C/D ring system. In this paper we apply these models to ring D and interpret some of its chemistry.

As a first step, the three symmetrical conformations of ring D were constructed (I, II, III). Conformations I and II have been previously recorded in the literature while III has been hitherto neglected. Envelope conformation I[2] is that which has earlier been generally used by chemists having had its birth in Barton's original drawing of the steroid molecule.[9] Envelope I has C_{14} below the plane of C_{13}, C_{15}, C_{16}, C_{17}. Half-chair II is an arrangement which has been discussed in detail for simple cyclopentanes[2]; it has C_{13} above and C_{14} an equal distance below the C_{15}, C_{16}, C_{17} plane. Finally there is the previously neglected envelope III. This last conformation has C_{14}, C_{15}, C_{16} and C_{17} in a single plane while C_{13} lies above the plane.[10]



The next step in our analysis was to compare these three conformations with regard to their torsional (V_t) and angle-strain (V_B) energies, their electron-correlation energies (E_c) (London or dispersion energies) and any significant 1,3-interactions of a repulsive nature (van der Waals repulsive forces). In view of the laborious mathematical operation of summing up all C–C, C–H and H–H non-bonded London interactions, it was convenient to assume that the London force difference between envelope I (or III) and half-chair II is essentially the same as in the parent, unsubstituted, maximally-puckered models. Here[1] the envelope (E_c −47.95 kcal./mole) is stabilized 0.66 kcal./mole more than the half-chair (E_c −47.29 kcal./mole) or, in other words, the half-chair has 0.66 kcal./mole more energy than the envelope due to the London force effect. We therefore add 0.66 kcal./mole to the half-chair II when bond-bonding and torsional energies are being calculated.

For cases where interior angle strain energy and also correlation energy can be taken to be the same as in the parent conformations a new correction factor of 0.33 kcal./mole is of use. Substitutions of the type such as methyl, halogen or hydroxyl which change only the torsional energy would lead to this situation. This correction factor is derived by noting that the difference in bond-bending energies between the envelope (9.68 kcal./mole) and the half-chair (8.69 kcal./mole) favors the half-chair by 0.99 kcal./mole When this quantity is combined with the correlation energy difference (−0.66 kcal./mole) one arrives at the factor 0.33 kcal./mole favoring the half-chair; this energy is then added to envelope conformations I and III.

Another important factor does exist. In addition to the above energy terms the axial methyl group on C_{13} has the potentiality of strong interaction of repulsive, van der Waals type with the hydrogens at C_{15} and C_{16}. The earlier calculations for our unsubstituted models did not require in-

(1) Paper II, F. V. Brutcher, Jr., and W. Bauer, Jr., *J. Am. Chem. Soc.*, **82**, 2233 (1962); see also F. V. Brutcher, Jr., and W. Bauer, Jr., *Science*, **132**, 1489 (1960).

(2) F. V. Brutcher, Jr., T. Roberts, S. J. Barr and N. Pearson, *J. Am. Chem. Soc.*, **81**, 4915 (1959).

(3) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959.

(4) Eliel and Pillar[5] as well as Dauben and Pitzer[6] have considered the distortion in a cyclohexane ring arising upon fusion to a cyclopentane ring. They conclude that in the *trans* isomer the distortion is toward a more severe chair conformation. In hydrindane this causes crowding of the axial hydrogen atoms. When one of these is replaced by a methyl group as in the steroids, distortion of the cyclohexane ring in this fashion is, hence, exceedingly costly energywise and one expects it to be at a minimum. Eliel has presented experimental data which verify the existence of these distortions and at the same time indicate that they are, indeed, small.[5] With regard to the five-membered ring in the hydrindanes, Allinger and Coke (*J. Am. Chem. Soc.*, **82**, 2553 (1960)) have found that the *cis* isomer has a larger entropy and point out that this may be due to a larger partial pseudorotation (*cf.* J. P. McCullough, *J. Chem. Phys.*, **29**, 966 (1958)) in the *cis* isomer.

(5) E. L. Eliel and C. Pillar, *J. Am. Chem. Soc.*, **77**, 3600 (1955).

(6) W. G. Dauben and K. S. Pitzer in M. S. Newman, "Steric Effects in Organic Chemistry," J. Wiley and Sons, Inc., New York, N. Y., 1956, p. 37.

(7) For a discussion of several steroidal hydrindanones, see Fieser and Fieser, ref. 3, page 211 ff.

(8) K. S. Pitzer and W. N. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959).

(9) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(10) These three conformations may be considered to arise through a partial pseudorotation, the ring fusion preventing the full pseudorotation cycle from taking place.

clusion of 1,3-repulsive energies because no atoms approached each other within distances which would lead to interpenetration of their electron clouds such as might be the case in ring D. Our calculations (see Experimental section) must now, therefore, include these repulsions.[11]

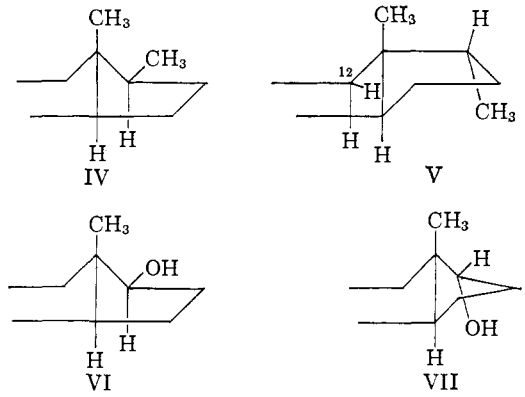
Androstane.—The relative stabilities for the three conformations of androstane are now given by summation of the torsional energies about the ring, addition of 0.33 kcal./mole to the envelope conformations (constant correlation and bond-bending energies) and addition of corrections for the 1,3-interactions between the C_{18}-methyl group and the β-hydrogens at C_{15} and C_{16}. These calculations show that the energy (relative) for I of 10.04 kcal./mole, due mainly to the very-unfavorable angular methyl interaction with C_{15}-hydrogen, bespeaks a large destabilizatiom of this conformation relative to the others. Both conformations II and III, however, are so close in energy that it is unlikely that the molecule would "freeze" in conformation III, but rather than in solution a highly restricted form of pseudorotation between II and III would probably occur. It must be noted, however, that only in III is the troublesome, angular methyl group symmetrically placed with regard to the β-hydrogens at C_{15} and C_{16}. If our calculated, repulsive interactions were on the low side in contrast to the real situation, then we would favor conformation III as that single structure which best represents the unsubstituted ring D in the androstane series.

TABLE I

ENERGY FOR CONFORMATION (ANDROSTANE)

	I	II	III
Correction	0.33	..	0.33
Torsion	5.01	4.81	4.86
1,3-Interaction	4.7	3.4	2.8
Total	10.04	8.21	7.99
17β-Methylandrostane			
Correction	0.33	..	0.33
Torsion	5.59	5.27	5.06
1,3-Interaction	4.6	3.4	2.8
Total	10.52	8.67	8.19
17α-Methylandrostane			
Correction	0.33	..	0.33
Torsion	5.59	5.27	5.06
1,3-Interaction	5.3	6.1	7.5
Total	11.22	11.37	12.89

17-Substituted Steroids.—Most steroids of general interest bear a substituent in the 17β-position. Employing the methyl group as a typical substituent, the energies of the three conformation are as shown in Table I. In this case, too, the envelope III is the form of lowest energy; further, the differences in energy have become greater than in androstane. If one now considers the 17α-substituted steroids, it is seen that a severe repulsion between the 17α-substituent with the hydrogen at the 14α-position in the conformation III drives such a material toward conformation I.[12] One concludes that a 17β-methyl steroid prefers the conformation III (IV) and its 17α-epimer the conformation I (V).[12] In addition it is noted that the 17β-material is more stable than the 17α-compound by about 3 kcal./mole. Analogous calculations for the 17-hydroxysteroids have also been carried out. The results again indicate the conformation III (VI) as the preferred form for the β-substituted material. The epimeric, 17α-substituted material is, however, only driven from III (VI) to II (VII) as the alcohol function interacts with the hydrogens at $C_{14}\alpha$ and $C_{12}\alpha$ somewhat less strongly than does the methyl group. The energy difference between the 17β-hydroxysteroid and the 17α-hydroxysteroid is found to be near 2.4 kcal./mole with the former (VI) favored over the latter (VII). This is in agreement with the fact that reduction of a 17-ketone with sodium in alcohol gives only the 17β-alcohol.[13] These calculations are also in complete accord with the well-known equatorial character of 17β-substituents in the steroid series as this position is, indeed, equatorial in the conformation III. Such data must, nevertheless, be employed with caution (especially since the most significant terms appear to be the van der Waals repulsions which at the same time are the least accurately known), but they provide a background against which experimental data may be viewed to advantage.



17-Ketosteroids.—The literature does not reveal a great deal of information of use in elucidating the conformations of ring D. However, it was found that infrared studies of 16-halo-17-ketosteroids using the method of Jones[14] and Corey[15] had been performed in several laboratories, but that the re-

(11) See T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948); **16**, 955 (1948).

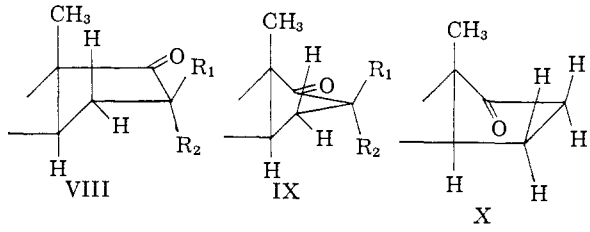
(12) In conformation III a 17α-substituent is repelled equally by the protons on $C_{14}\alpha$ and $C_{12}\alpha$. Approximate evaluation of distances from the 17α-position to the 12α-position shows that in conformation II the interaction between these latter positions is reduced to about one half of that between $C_{17}\alpha$ and $C_{14}\alpha$ and that in conformation I we may neglect the interactions involving the 12 α-proton. These interactions have not been included in the calculations above as they, in each case, merely serve to make the conformation III less attractive in cases where it is already excluded by the interaction with the 14α-proton. Further, although the C_{13}-methyl–C_{15}-β-hydrogen interaction in I appears to be an *n*-butane-type interaction similar to an axial methyl–hydrogen interaction in a cyclohexane system, it must be pointed out that the less than tetrahedral interior angles in ring D of I shorten these intramolecular distances and increase the unfavorable van der Waals repulsive forces.

(13) Reference 3, pp. 465–468, and references cited therein.

(14) R. N. Jones, D. A. Ramsey, F. Herling and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

(15) E. J. Corey, *ibid.*, **75**, 2301, 3297 (1953), and later papers.

ported data were in conflict.[16-18] In order to check on this we prepared several such materials and measured their infrared spectra.[19] These data (Table II), in agreement with Fishman and Djerassi,[18] confirm the fact that introduction of either a 16α- or a 16β-bromo substituent into a 17-keto-steroid gives rise to the same identical shift (12 cm.$^{-1}$) in the carbonyl-stretching frequency.



This clearly demonstrates that the angle between the 17-carbonyl group and each of the 16-bromo substituents is identical. Further, the projected angle between the carbonyl group and the bisectional[2] bromine substituent is within the bisectional range (θ = 60°) found in the α-bromocamphors. Since only the envelope conformation VIII fulfills these requirements it, then, is the preferred conformation for these 16-bromo-17-ketosteroids. Reynolds has confirmed this by measuring the dipole moment of 16α-bromo-5α-androstan-17-one.[1] Shoppee has previously suggested that these steroids perfer the half-chair conformation II (C_{17} = C = O)[16]; however, this cannot be the case[1] as $\theta_{16,17}$ for a β-substituent in this conformation (II) is about 79°, while $\theta_{16,17}$ for an α-substituent is only 41°. These orientations would give rise to different shifts of a magnitude such that the difference could readily be detected as has been the case with α-bromocyclopentanone and α-bromo-*trans*-hexahydroindan-2-one.[2] While the parameters involved in calculating the energies of cyclopentanones are less exact than those used above for cyclopentanes, it is instructive to consider these energies at this point. The results for androstan-17-one (Table III) suggest that II may be slightly favored over I, but even a small readjustment of geometry could reverse this order. The lesser stability of 17-ketone in envelope conformation X is a result of the unfavorable torsional energy of this conformation as well as its inability to accommodate trigonal hybridization at position 17. These factors more than outweigh the lower 1,3-interactions present in it. The shift from the calculated form IX of lowest energy for a 17-ketone to the conformation I (VIII) in the 16β-bromo-17-ketone permits the angular methyl–bromine repulsion to be minimized as well as presenting the lowest torsional energy at C_{15}–C_{16}. These two factors apparently are more important than any influence of dipole–dipole interaction which is expected to be least favorable in the observed envelope conformation VIII. The observed conformation VIII (R_1 = H, R_2 = Br) for 16α-bromo-17-ketosteroids also reflects a shift from the tentative parent conformation IX. Since there are no large van der Waals interactions with the bromine when it is in the 16α-position, the more favorable torsional energy of VIII at C_{15}–C_{16} is conformation determining (for this case the dipole–dipole interactions also favor VIII over IX and X).

TABLE II

INFRARED SHIFTS OF α-BROMOKETOSTEROIDS

	ν_{CCl_4}, cm.$^{-1}$	$\Delta\nu$
Estrone acetate	1742	..
16α-Bromoestrone acetate	1754	12
16β-Bromoestrone acetate	1754	12
5α-Androstan-17-one	1739	..
16α-Bromo-5 α-androstan-17-one	1751	12

TABLE III

ENERGY FOR CONFORMATION

	17-Ketosteroids			16-Ketosteroids		
Correction	...	0.66	...	...	0.66	...
Bond bending	11.73	11.05	13.56	11.73	11.05	11.73
Torsion	2.36	3.34	4.32	2.82	2.26	2.66
1,3-Interaction	4.7	3.4	2.8	4.8	3.5	1.4
	18.79	18.45	20.68	19.35	17.47	15.79

The 16β-bromo-17-ketones are thermodynamically more stable than their 16α-epimers.[17] The equilibrium may readily be determined by measurement of molar rotation in the presence of a small amount of alkali. We find that the β-epimer VIII (R_1 = Br, R_2 = H) with a bisectional bromine is present to the extent of about 78% at equilibrium at 21° in 3:1 methanol–chloroform. This is in agreement with similar data reported by Fajkŏs.[17] Since both materials exist in the envelope conformation VIII, the difference in stability is determined by 1,3-interactions alone. We calculate a favoring of the β-material by about 0.4 kcal./mole as compared to the experimental value of 0.79 kcal./mole. This result presents an indication of the essential correctness of the models as all of the distances involved are close to the sums of van der Waals radii of the interacting groups and the potential functions employed are most accurate in this region.

16-Ketosteroids.—In an earlier paper[2] it was found that α-halogen derivatives of *trans*-2-hexahydroindanones preferred the half-chair conformation and it was suggested that 16-keto steroids might behave similarly. Due mainly to the efforts of Fishman[18,19] at the Sloan Kettering Institute, very interesting 15- and 17-halo-16-ketosteroids have been synthesized, their spectra recorded and their conformations discussed. Fishman and Djerassi,[18] by techniques including optical rotatory dispersion measurements, report that a 17α-bromo-

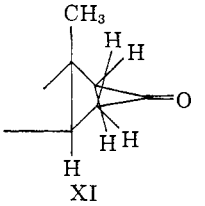
(16) C. W. Shoppee, R. H. Jenkins and G. H. Summers, *J. Chem. Soc.*, 3048 (1958).

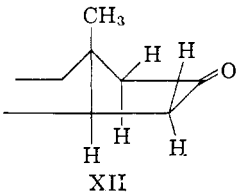
(17) J. Fajkŏs, *ibid.*, 3966 (1959); *Coll. Czech. Chem. Comm.*, **20**, 312 (1955).

(18) J. Fishman and C. Djerassi, *Experientia*, **15**, 138 (1960); J. Fishman and W. R. Biggerstaff, *J. Org. Chem.*, **23**, 1190 (1958).

(19) J. Fishman, *Chemistry & Industry*, 1078 (1961). See also the 17-halo-16-ketosteroids and their infrared shifts reported by J. Fajkŏs and J. Joska, *ibid.*, 872 (1960). It is also interesting to compare the relative stability of 16-keto- *vs.* 17-ketosteroids. Fishman (*J. Am. Chem. Soc.*, **82**, 6143 (1960)) has recently reported data on the relative stabilities of the four possible 16,17-hydroxy ketones (*cf.* W. S. Johnson, B. Gastambede and R. Pappo, *J. Am. Chem. Soc.*, **79**, 1991 (1952)). He found that the 16-hydroxy-17-ketones readily rearrange to the 17-hydroxy-16-ketones. From Table III this is not unexpected since the parent 16-ketone is more stable (15.79 *vs.* 18.48 kcal./mole) than the 17-ketone by calculation.

16-ketosteroid prefers the half-chair conformation XI. In a later report Fishman[19] finds that the 15β-bromo-16-keto steroid also prefers the half-chair. It is therefore of considerable interest to note that our calculated energy (Table III) for the parent 16-ketone leads to the prediction that envelope conformation XII may well be the preferred form for the parent as a result of the removal of steric interference between the axial methyl group[20] and the 16β-proton on introduction of the sp^2-hybridized carbonyl group at C_{16}. Substitution of halogen at C_{15} would lead to a twist at C_{14}–C_{15} toward the half-chair to decrease the torsional energy at this position. C_{17}-Substitution in the α-position would destabilize XII due to the C_{14}-proton interaction, while the β-substituent would, except for the dipolar repulsion with the carbonyl, be easily accommodated in XII. Indeed, the biggest shift (most equatorial) for the four bromo-16-ketosteroids was found for the 17β-bromo material.[19]

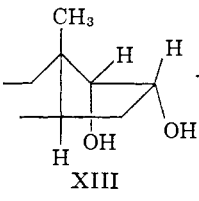

XI

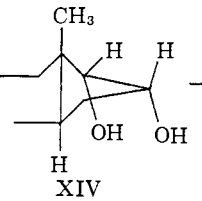

XII

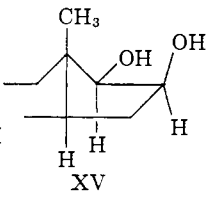
Steroidal Glycols.—Another experimental approach to the determination of conformations is suggested by the fact that the shift in O–H stretching frequency which is observed on formation of a hydrogen bond (H-bond) in a glycol can be correlated with the geometry of such a glycol.[21,22] A great number of such shifts for 1,2- as well as 1,3-diols have been reported. Kuhn has presented a correlation of this shift with the length of the OH. . .O bond.[21] His correlation has led to a number of interesting conclusions, but as was usual then it assumed a planar structure for cyclopentanediol. We have, therefore, modified Kuhn's analysis to fit the following data. The shift (102–103 cm.$^{-1}$) observed for the two *cis*-1,2-bicycloheptanediols is the appropriate value we must use for a completely eclipsed glycol.[23] Further, the minimum internuclear separation OH. . .O should not be taken to be less than about 1.4 Å. as observed in the very strongly H-bonded dimethylglyoximes.[24] Since the projected angle by electron diffraction[25] for ethylene glycol is 74°, and the $\Delta\nu$ is known, the derived —OH. . .O distance is incorporated also in our equation. The resulting correlation (the form suggested by Kuhn is retained) of these data as incorporated in eq. i yields projected angles for *meso*- and *d,l*-butane-2,3-diols of 60 and 68°, respectively, based upon available $\Delta\nu$'s.[21] The projected angle in butane itself has been reported as 63 ± 8° and it is not unreasonable to expect the dipole–dipole interaction between the C–O bonds to open this angle slightly. This correlation should prove of some utility to others in the series of cycloalkane-1,2-diols. Observed H-bond shifts and approximate projected angles between the alcohol functions of several sterols are recorded in Table IV. The projected angles were approximated by combination of the distances of closest approach of OH. . .O as measured on a scale model with the correlation given for shift with this distance.

$$\Delta\nu = 42.5/(r\ \mathrm{O}\ldots\mathrm{H} - 1.4) - 3.5 \qquad \text{(i)}$$

16,17-Glycols.—The data above for *meso*- and *d,l*-butane-2,3-diols as well as for ethylene glycol indicate that glycols which internally hydrogen bond prefer a projected angle near 60°. Therefore in interpreting our *cis*-glycols' conformations we look for that conformation which will allow the adjacent alcohol functions to be as far removed as possible in ring D and somewhat near 60°. Indeed no *cis*-16,17-glycol can be further apart than a θ of 36.5° (Table I, ref. 1). Since $\theta_{16,17}$ for the envelope conformation XIII is 36.5°, 16α,17α-diols might be expected to prefer this conformation. However, the previously mentioned interference between the 17α-hydroxyl and the C_{14}-hydrogen might be expected to destabilize XIII and to favor half-chair XIV where less interaction occurs. In XIV the $\theta_{16,17}$ is 19.0°. Our observed values for the two steroids 16α,17α-glycols in Table IV are 15° and 18°, confirming the half-chair as the preferred conformation for 16α,17α-glycols.


XIII


XIV


XV

With regard to the 16β,17β-glycols, envelope conformation XV with $\theta_{16,17}$ at 36.5° ought to be the preferred conformation if the angular methyl–C_{16} interaction is too feeble to force a movement toward eclipsing of the *cis*-glycol as in envelope I. The maintenance of an angle near 36.5° seems to win out and conformation XV is preferred since the glycols in Table IV have angles of 31° and 34°. Since both are on the low side of 36.5° a slight angular methyl–C_{16} hydroxyl repulsion may be involved. We have already noted that a single 17β-substituent would favor this conformation on the basis of energy calculations.

Cholesterol.—In conclusion, it is of interest to comment on the single most famous steroid, cholesterol. On the basis discussed above for the methyl and hydroxyl functions it is seen that the side chain of cholesterol (17β) will result in envelope conformation III being favored for this material. We may note that the X-ray analysis of Carlisle

(20) Since the axial methyl group is not present in *trans*-hexahydroindan-2-one this material, like cyclopentanone itself, will prefer the conformation II.

(21) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952); **76**, 4323 (1954); **80**, 5950 (1958).

(22) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, Chapt. 3, 5.

(23) H. Kwart and W. G. Vosburgh, *J. Am. Chem. Soc.*, **76**, 5400 (1954); H. Kwart and G. C. Gatos, *ibid.*, **80**, 881 (1958).

(24) G. C. Pimentel and C. H. Sederholm, *J. Chem. Phys.*, **24**, 639 (1956).

(25) See G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 715.

TABLE IV

H-BOND SHIFTS OF SOME GLYCOLS

	Free OH $\nu_{max}^{CCl_4}$, cm.$^{-1}$	Bonded O-H $\nu_{max}^{CCl_4}$, cm.$^{-1}$	$\Delta\nu$[a]	θ°
Estriol 3-methyl ether	3623	..	..	..
16-Epiestriol 3-methyl ether	3634	3559	75	31
17-Epiestriol 3-methyl ether	3639	3545	94	15
Androstan-17β-ol	3627	..	..	..
Androstan-16β, 17β-diol	3638	3568	70	34
3β-Acetoxyandrostan-16α,17a-diol	3634	3543	91	18
cis-Cyclopentane-1,2-diol[b]	3633	3572	61	42
trans-Cyclopentane-1,2-diol[b]	3620	..	..	..
cis-Cyclohexane-1,2-diol[b]	3626	3587	39	68
trans-Cyclohexane-1,2-diol[b]	3634	3602	32	$\geq$70
cis-Bicycloheptane-1,2-diols[c]	3644	3541	103	0

[a] Cole has emphasized the point that the significant shift is that of the bonded peak from the position of the same alcohol function when not H-bonded.[26] He also finds that axial alcohols show a free peak at slightly higher frequency than their equatorial isomers. If this is the case, our spectra lead to the assignment of axial peaks at 3639 cm.$^{-1}$, equatorial at 3627 cm.$^{-1}$ and quasi axial (quasi equatorial) peaks at 3634 cm.$^{-1}$. Such correction serves in each case to reduce the shifts quoted above, and, hence, strengthen our arguments. [b] Quoted from Kuhn, ref. 21. [c] Reported by Kwart and confirmed in this Laboratory.[23]

and Crowfoot[27] definitely rules out conformation I, and favors III. While II cannot be definitely excluded on the basis of the X-ray analysis, III seems to be most reasonable when calculated energies are also considered.

We wish to acknowledge the generosity of Drs. J. Fishman and T. F. Gallagher of the Sloan Kettering Institute for Cancer Research as well as that of Dr. L. H. Sarett of Merck Sharp and Dohme in providing us with some of the compounds employed in this study. Thanks are due to Dr. Morton Kramer for his painstaking measurement of the spectra of the materials supplied by Dr. Fishman. Thanks are also due to the Armstrong Cork Co. for a predoctoral fellowship (W. B., Jr.) and to the Committee for the Advancement of Research of the University of Pennsylvania for its support.

Experimental

Measurement of Spectra.—The spectra of the alcohols and glycols reported in this work were recorded employing a Beckman DK-1 instrument. Samples were of the order of 0.005 *M* and measured in a pair of matched 1-cm. fused silica cells. Precision of the measurements is considered to be better than ±2 cm.$^{-1}$. All peaks quoted are calibrated against the unbonded peak of ethylene glycol taken as 3644 cm.$^{-1}$.[21] The infrared spectra of the ketones were measured as previously reported.[2]

16-Bromoestrone Acetates.—The 16α- and 16β-bromoestrone acetates were prepared by the methods of Fishman and Biggerstaff[18] and had properties identical with those of authentic samples subsequently made available to use by Dr. Fishman.

Equilibration of 16-Bromoestrone Acetate.—A 6-ml. aliquot of 16α-bromoestrone acetate in 2:1 methanol–chloroform ([α]^{21}D +120°) was treated with 2 ml. of methanol containing 189 mg. of potassium hydroxide. The rotation of the resulting solution was constant by the time that a measurement could be made (less than 2 minutes); [α]^{21}D +148. From the rotations of the pure epimers[18] and this last datum the percentage of β-epimer at equilibrium is given as 78%.

Estriol Methyl Ethers.—Three-milligram samples of the free phenols from Dr. T. F. Gallagher (S.K.I.) were treated with methanolic potassium hydroxide followed by methyl iodide. The resulting solutions were diluted with water, extracted with ether and the ether removed at reduced pressure. After drying *in vacuo* the residues were extracted into dry carbon tetrachloride (in which the free phenols were negligibly soluble), but were not crystallized. The resulting solutions showed the peaks recorded. Since the peaks recorded are near those of our crystalline glycols (see below), these data were used in Table IV.

Dihydrotestosterone Semicarbazone.—A solution of 5 g. of testosterone in 60 ml. of ethyl ether and 60 ml. of dioxane was added dropwise over 10–15 min. to 1 g. of lithium in 500 ml. of ammonia. After 1 hour the still blue solution was treated with 13 g. of ammonium chloride after which the ammonia was allowed to evaporate. The ethereal residue was diluted with chloroform, washed with several portions of water and evaporated at the water-pump to a sirup. The sirup was taken up in 100 ml. of hot ethanol. A solution consisting of 2 g. of semicarbazide hydrochloride and 3 g. of sodium acetate in 15 ml. of hot water was added to the ethanolic ketone solution. Digestion at water-bath temperature for a few minutes yielded a solid which was removed by filtration after cooling in an ice-bath. The solid was washed with ethanol and then with ether. After drying, the product weighed 5.05 g. (87%), m.p. 253–254.5°, lit.[28] m.p. 249–251°.

Androstan-16β-ol.[28]—A mechanically stirred dispersion of 5.00 g. of the above semicarbazone and 3.30 g. of potassium hydroxide in 35 ml. of bis-(β-hydroxyethyl) ether and 5.5 ml. of 99% hydrazine hydrate was heated slowly to 210–215°. After 45 minutes the mixture was allowed to cool to 180° after which it was poured with rapid stirring into a 100-ml. portion of ice and water. The precipitated solid was collected by filtration and washed with water until neutral to litmus. The dried solid, 3.16 g. (77%), had m.p. 165.5–167.5°, lit.[28] m.p. 164–166°.

Androstan-17-one.—A solution consisting of 1.60 g. of chromic anhydride in 15 ml. of water and 15 ml. of concentrated sulfuric acid was added dropwise with caution to a hot solution of 1.60 g. of androstan-17β-ol in 150 ml. of acetone. The solution was diluted to a volume of 500 ml. with water and cooled in an ice-bath. The fine platelets of ketone were removed by filtration and washed with water. The dry product weighed 1.40 g. (89%), m.p. 114–118°, lit.[16] m.p. 119–121°. This material was used without further purification in the following reactions.

Androstan-17-one enol acetate, prepared as described by Fajkós,[17] had m.p. 76–80°, lit. 84–85°.

16β-Acetoxyandrostan-17-one.—A solution of the enol acetate (0.60 g.) in 20 ml. of glacial acetic acid containing 0.5 ml. of acetic anhydride was treated with approximately 1 g. (wet with acetic acid) of lead tetraacetate. The mixture had become homogeneous after an hour, but excess oxidant was still present after 19 hr. (orthophenanthroline test solution). The solution was diluted with 150 ml. of ether and 75 ml. of water. The ether layer was removed and washed with water, sodium bicarbonate, and water until neutral. The ethereal solution was filtered through a cone of sodium sulfate and evaporated to dryness. The resulting pale yellow crystals, 0.34 g. (54%), were recrystallized from absolute ethanol to give material, m.p. 149–153°. The analytical sample obtained from petroleum ether had m.p. 154–155°, [α]^{22}D chf. +86.0°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.87; H, 9.70. Found: C, 75.95; H, 9.9.

Androstan-16β,17β-diol.—A solution of 16β-acetoxyandrostan-17-one, 88.1 mg. in 30 ml. of diethyl ether, was stirred overnight with an excess, 0.1 g., of lithium aluminum hydride. The usual work-up yielded 19.9 mg. (26%) of material with m.p. 175.5–178° after recrystallization from petroleum ether. The analytical sample had m.p. 177–178°, and also had a strong internal hydrogen bond in the infrared.

Anal. Calcd. for $C_{19}H_{32}O_{2\cdot1/2H_2O}$: C, 75.70; H, 11.03. Found: C, 76.05; H, 11.01.

16α-Bromoandrostane-17-one was prepared by bromination of the enol acetate as described in the literature.[16,17] After several recrystallizations from absolute ethanol the

(26) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956).

(27) H. Carlisle and D. Crowfoot, *Proc. Roy. Soc.* (*London*), **184A**, 81 (1945).

(28) W. V. Ruyle, A. E. Erickson, A. Lovell and E. M. Chamberlin, *J. Org. Chem.*, **25**, 1260 (1960).

material had m.p. 197°, $[\alpha]^{22}D$ +56°, lit.,[17] m.p. 197°, $[\alpha]D$ +58°.

3β-Acetoxyandrostan-16α,17α-diol.—3β-Acetoxy-Δ^{16}-androstene,[17] 55.6 mg., was treated with an excess of osmium tetroxide in 10 ml. of ether containing 0.1 ml. of pyridine. A flocculent tan precipitate immediately formed which darkened on standing. After 3 hours, 20 ml. of petroleum ether was added and the straw-colored supernatant fluid decanted. The solid was dissolved in 50 ml. of absolute ethanol. The solution was treated with a rapid stream of hydrogen sulfide until precipitation was complete. Filtration yielded a colorless solution which was evaporated to dryness under reduced pressure. The residue was crystallized from aqueous ethanol to yield 24.3 mg. (40%) of triol monoacetate, m.p. 149–151°, $[\alpha]^{22}D$ −0.089°. The analytical sample from petroleum ether had m.p. 153.5–154°, and had a strong internal hydrogen bond in the infrared.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.03; H, 10.36.

Theoretical Calculations, Torsional Barriers.—The van der Waals interactions of 1,2-substituents are determined from the barrier to rotation about the C–C bond of an appropriately substituted ethane. This is convenient both because of the availability of these barriers in the literature and because several interactions are thus determined by a single calculation. The barriers employed in the present work are tabulated below. The barriers for use at the 17,13-position of the steroids are estimated. Thus, the barrier for rotation about the 2,3-bond of 2-methylbutane is desired for the 17,13-position in the 17-methylsteroids. The ratio of the barrier in 2-methylpropane to that of 2,2-dimethylpropane was assumed to be the same as that of the desired barrier to the barrier in 2,2-dimethylbutane. (Similarly, the barrier in 2-methylpropanol was estimated by increasing the barrier in ethanol in the ratio of the barriers in propane and 2-methylbutane.) The barriers for rotation against the carbonyl group for which the position of lowest potential is known to be that of eclipsing were assumed to be diminished from that of acetaldehyde. The barrier in α-methylpropionaldehyde may then be estimated as (V_0 ethane) (V_0 acetaldehyde)/(V_0 2-methylpropane).

1,3-Interactions.—The energy, E_{vw}, of the van der Waals interactions of a pair of functional groups is given by[29]

$$E_{vw} = \frac{-2.25\epsilon^* r^{*6}}{r^6} + 8.28 \times 10^5 \epsilon^* \exp. -r/0.0736r^*$$

where r is the distance between the interacting functions, r^* is the *effective* sum of the van der Waals radii of these groups and ϵ^* is a function of the types of interacting groups. The values of ϵ^* in kcal./mole where hydrogen is interacting with the second function are: hydrogen, 0.042; methyl, 0.117; hydroxyl, 0.103; bromine, 0.139. For methyl interacting with the second group; methyl, 0.326; hydroxyl, 0.286; bromine, 0.380. The values of ϵ^* have been chosen such that the usually accepted values for the energy of an axial methyl group (1.8 kcal./mole),[6] alcohol (0.8 kcal./mole)[6] and bromine (0.73 kcal./mole),[30] are twice the potential given by the above functions (two axial hydrogens interacting) when applied to the ideal chair form of cyclohexane.

(29) T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948).

Potential barriers to rotation (V_0 in kcal./mole)

Ethane[a]	2.800
Propane[b]	3.400
2-Methylpropane[c]	3.850
2,2-Dimethylpropane[c]	4.400
2-Methylbutane[d]	~3.760
2,2-Dimethylbutane[c]	4.300
Ethanol[e]	3.000
2-Methylpropanol[d]	~3.320
Bromoethane[f]	3.570
1-Bromo-2-methylpropane[d]	~3.950
Acetaldehyde[g]	1.150
α-Methylpropionaldehyde[d]	~0.850

[a] K. S. Pitzer, *Diss. Faraday Soc.*, **10**, 66 (1951). [b] K. S. Pitzer, *J. Chem. Phys.*, **12**, 310 (1944). [c] K. Ito, *J. Am. Chem. Soc.*, **75**, 2430 (1953). [d] See text for method of estimation. [e] S. C. Schumann and J. G. Aston, *J. Chem. Phys.*, **10**, 559 (1942). [f] D. R. Lide, *ibid.*, **30**, 37 (1958). [g] R. W. Kelb, C. C. Lin and E. B. Wilson, *ibid.*, **26**, 1695 (1957).

Bond lengths, Å.		Parameters employed	van der Waals radii, Å.	
C–C	1.54	—C–C–O 109.5°	H	1.20
C–H	1.10	—C–O–H 105° (adjusted	OH	1.86
C–Br	1.91	slightly for H-bonding)	CH_3	2.00
C–OH	1.43		Br	1.95
O–H	0.96			

(30) E. L. Eliel and R. G. Haber, *J. Am. Chem. Soc.*, **81**, 1249 (1959).

[CONTRIBUTION FROM THE JAMES BRYANT CONANT LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

The Cleavage of *cis*- and *trans*-1,2-Dimethyl-1,2-cyclopentanediol by Chromic Acid

BY JAN ROČEK AND F. H. WESTHEIMER

RECEIVED OCTOBER 2, 1961

Chromic acid in water oxidizes *cis*-1,2-dimethyl-1,2-cyclopentanediol to 2,6-heptanedione 17,000 times faster than the *trans* isomer; in 90% acetic acid, the factor is 800. These data suggest that the *cis*-diol (and open-chain diols by analogy) rapidly and reversibly form a cyclic ester with chromic acid; the rate-determining step of the oxidation process is then the decomposition of this ester with cleavage of the C–C bond. The *trans* isomer is presumably oxidized by a non-cyclic mechanism. The energetics of the fission of glycols is compared to that for the oxidation of secondary alcohols, and the selection of oxidants for cleavage *vs.* simple formation of ketone is discussed.

In a recent paper on the oxidation of pinacol to acetone,[1] one of us proposed a mechanism for the process in which a cyclic ester of chromic acid is formed, and then decomposes to cleavage products. The evidence in favor of this mechanism consisted chiefly of two facts: pinacol is oxidized much more rapidly than is its monomethyl ether, and the solvent isotope effect, k_{D_2O}/k_{H_2O} is 2.7. However, despite the advances which have recently been made[2] in the quantitative estimate of solvent deuterium isotope effects, the prediction for complex reactions involving several protonations is still uncertain. The present work was undertaken to investigate further the mechanism of the cleavage of glycols by chromic acid.

We have therefore measured the rates for the chromic acid oxidation of the two isomeric 1,2-

(1) Y. W. Chang and F. H. Westheimer, *J. Am. Chem. Soc.*, **82**, 1401 (1960).

(2) C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 42, 3207, 3214 (1961); C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182 (1960); C. G. Swain, R. F. W. Bader and E. R. Thornton, *ibid.*, **10**, 200 (1960).