Stereochemistry of Some Steroidal Ketones

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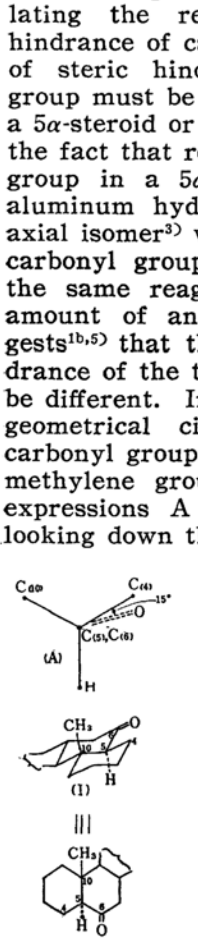
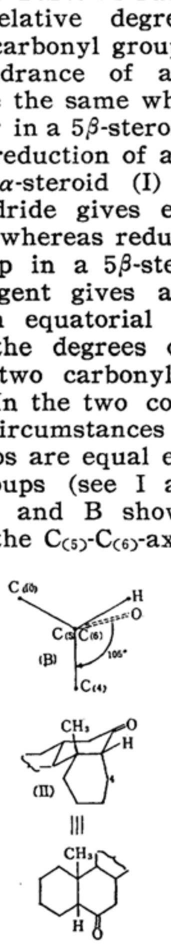
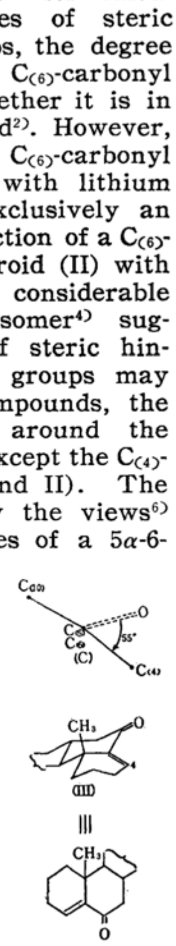
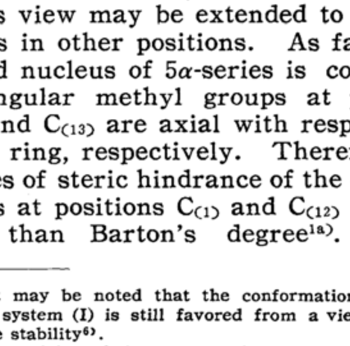
According to Barton's rule[1a] for calculating the relative degrees of steric hindrance of carbonyl groups, the degree of steric hindrance of a $C_{(6)}$-carbonyl group must be the same whether it is in a 5α-steroid or in a 5β-steroid[2]. However, the fact that reduction of a $C_{(6)}$-carbonyl group in a 5α-steroid (I) with lithium aluminum hydride gives exclusively an axial isomer[3] whereas reduction of a $C_{(6)}$-carbonyl group in a 5β-steroid (II) with the same reagent gives a considerable amount of an equatorial isomer[4] suggests[1b,5] that the degrees of steric hindrance of the two carbonyl groups may be different. In the two compounds, the geometrical circumstances around the carbonyl groups are equal except the $C_{(4)}$-methylene groups (see I and II). The expressions A and B show the views[6] looking down the $C_{(5)}$-$C_{(6)}$-axes of a 5α-6-ketone (I) and a 5β-6-ketone (II), respectively. The angle between the $C_{(6)}$-oxo-group and the $C_{(4)}$-methylene group is much greater in II than in I. The interaction between the oxo-group and the $C_{(4)}$-methylene group may be smaller in II than in I. Thus the oxo-group in II must be less hindered[7]. This postulation is well in line with the results of the hydride reduction, if we accept the generalization[1b,5] that the more hindered ketone gives the more axial hydroxyl group by lithium aluminum hydride reduction.







This view may be extended to carbonyl groups in other positions. As far as the steroid nucleus of 5α-series is concerned, the angular methyl groups at positions $C_{(10)}$ and $C_{(13)}$ are axial with respect to A and C ring, respectively. Therefore the degrees of steric hindrance of the carbonyl groups at positions $C_{(1)}$ and $C_{(12)}$ may be less[8] than Barton's degree[1a]. If we



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[1] D. H. R. Barton, *J. Chem. Soc.*, **1953**, 1027, (a) p. 1034, (b) p. 1029 footnote 23.

[2] Barton has stated that systems having cis-fused rings may prove more complex.

[3] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, **1952**, 3361.

[4] Y. Urushibara and K. Mori, This Bulletin, in press.

[5] Cf. W. G. Dauben, E. J. Blanz, Jr., J. Tin and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

[6] W. Klyne, *Experientia*, **12**, 119 (1956).

[7] It may be noted that the conformation of 5α-6-ketone system (I) is still favored from a viewpoint of relative stability[6].

[8] An axial methyl group attached at α-carbon atom may have less hindering effect than an axial methyl group attached at β-carbon atom, and steric effect by these axial methyl groups seems to be important in the intermediates. The expression D shows the necessary intermediates for the reactions with reagents like lithium aluminum hydride[9], semicarbazide, phenylhydrazines[10], and so on.

[9] L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949).

[10] See, e. g., Hammett, "Physical Organic Chemistry", McGraw-Hill Book Co., p. 333 (1940).

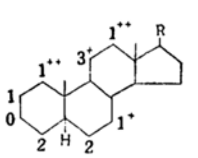
TABLE I

REDUCTION OF STEROIDAL KETONES WITH LITHIUM ALUMINUM HYDRIDE

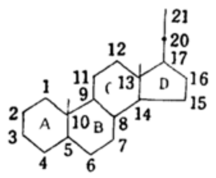
Compounds	Position of carbonyl groups*	Relative degrees of steric hindrance		Products	Composition of products		Ref.
		Barton's degree	Modified degree		Equatorial (%)	Axial (%)	
cholestan-1-one	1	2^+	1^{++}	cholestan-1-ol	35	65	11
cholestan-2-one	2	1	1	cholestan-2-ol	37	52	5
cholestan-3-one	3	0	0	cholestan-3-ol	90	10	12, 13, 14
coprostan-3-one	3(5β)	0	0	coprostan-3-ol	94	4	12
cholest-5-en-3-one	3(5-ene)	0	0	cholest-5-en-3-ol	90	5	12
cholestan-4-one	4	2	2	cholestan-4-ol	7	86	15
cholest-5-en-4-one	4(5-ene)	—	less than 2	cholest-5-en-4-ol	main	—	16, 15
cholestan-6-one	6	2	2	cholestan-6-ol	6	93	3
coprostan-3, 6-dione	6(5β)	2	1^+	coprostan-3, 6-diol	considerable amount of 6α(equatorial)-compd.		4
cholest-4-en-6-one	6(4-ene)	—	less than 2	cholest-4-en-6-ol	main	—	16, 15
cholest-4-en-3β-ol-6-one acetate	6(4-ene)	—	less than 2	cholest-4-en-3β, 6-diol	75(crude)	—	17
cholestan-3β-ol-7-one acetate	7	1^+	1^+	cholestan-3β, 7-diol	45	55	5
4-chloro-17α-hydroxy-3,20-bisethylenedioxy-pregnan-11-one	11	3^+	3^+	4-chloro-11, 17α-dihydroxypregnane-3, 20-dione bisethylene-ketal	trace	90	18
25D, 5α-spirostan-3β-ol-12-one acetate	12	2^+	1^{++}	25D, 5α-spirostane-3β, 12-diol	50	50	19

* In 5α-steroids unless otherwise stated

arbitrarily indicate the degree of the steric effect by an axial substituent attached at α-carbon atom by the + sign, indicating a positive magnitude less than one unit, Barton's degrees may be modified as shown in IV (see also Table I). The results of reduction of steroidal ketones with lithium aluminum hydride (Cf. Table I) suggest[20] that the sum (indicated by the ++ sign)



IV



of the steric effect by the γ-carbon atom which is bent round so as to hinder the carbonyl group and the steric effect by the axial substituent attached at α-carbon atom may be smaller than one unit in magnitude. If it is true, the order of relative degrees of steric hindrance of the $C_{(1)}$- or $C_{(12)}$-carbonyl group and of those of the $C_{(4)}$- or $C_{(6)}$-carbonyl group reverses in the two estimations.

Becker et al.[1,6] and Jones et al.[15] recorded that reduction of cholest-4-en-6-one with lithium aluminum hydride gave mainly cholest-4-en-6α-ol. Urushibara and Mori[17] reported that reduction of cholest-4-en-3β-ol-6-one acetate with lithium aluminum hydride gave mainly cholest-4-en-3β, 6α-diol. These facts are of interest in connection with the foregoing discussion.

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[11] H. B. Henbest and R. C. L. Wilson, *J. Chem. Soc.*, **1956**, 3289.

[12] C. W. Shoppee and G. H. R. Summers, ibid., **1950**, 687.

[13] H. R. Nace and G. L. O'Connor, *J. Am. Chem. Soc.*, **73**, 5824 (1951).

[14] W. G. Dauben, R. A. Micheli and J. F. Eastham, ibid., **74**, 3852 (1952).

[15] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, **1955**, 2876.

[16] E. J. Becker and E. S. Wallis, *J. Org. Chem.*, **20**, 353 (1955).

[17] Y. Urushibara and K. Mori, This Bulletin, in press.

[18] R. H. Levin et al., *J. Am. Chem. Soc.*, **76**, 546 (1954). Cf. L. H. Sarett et al., ibid., **73**, 1777 (1951).

[19] R. Hirshmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, ibid., **76**, 4013 (1954).

[20] It may be necessary to study the relative degrees of steric hindrance of these carbonyl groups by using carbonyl reagents such as ethyleneglycol, ethanedithiol, semicarbazide and the phenylhydrazines, etc., since the degrees of steric hindrance of the carbonyl groups may not exactly be reflected redution with lithium aluminum hydride[21].

[21] Cf. K. D. Hardy and R. J. Wicker, ibid., **80**, 640 (1958).

Cholest-4-en-6-one and cholest-4-en-3β-ol-6-one acetate exhibit the maximum absorption bands at 243 mμ (ε=6,360)[22] and 236 mμ (ε=6,300)[23] in the ultraviolet region, respectively. A method of calculating the principal absorption band of α,β-unsaturated ketones was devised by Woodward[24] and was extended by Fieser and Fieser[25]. The calculated value of the absorption maximum for the 4-ene-6-ketone system is 242mμ, which is in agreement with the observed wavelengths within 6 mμ. In Woodward-Fieser-Fieser's method of calculation no steric factor is considered. We may thus assume[26] that the steric hindrance involved in the system does not cause an abnormal change in wavelength but causes a decrease in absorption intensity and is associated with the transition between the non-planar ground state and the near-planar excited state[27]. Hence, the interplanar angle θ between the $C_{(6)}$-carbonyl double bond and the 4,5-ethylenic bond in the ground state may be calculated[30] from Braude-Sondheimer's equation[26] as roughly 55°[31], if the value of intensity for the unhindered system is arbitrarily taken as 18,000[33]. The expression C shows the view looking down the $C_{(5)}$-$C_{(6)}$-axis of the 4-ene-6-ketone (III). The interaction between the carbonyl group and the $C_{(4)}$-methylene group may be smaller in III than in I; it means that the carbonyl group in III is less hindered, and then may be reduced to the stable form in a more proportion. The result of the hydride reduction corroborates the assumption. Jones et al.[15] reported that reduction of cholest-5-en-4-one, $\lambda_{\max}$ 242 mμ (calculated value; 242 mμ), ε=5,900, with lithium aluminum hydride gave mainly the 4α (equatorial)-hydroxy compound. This phenomenon may also be explained in a similar way ($\theta \simeq 55°$). Another example was recorded by Shapiro et al.[34] who reduced 5,16-pregnadien-3β-ol-20-one acetate with lithium aluminum hydride, obtaining the 20α-hydroxy compound (stable form). 16,17-Saturated $C_{(20)}$-ketones are exclusively reduced to 20β-isomers[35].

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22) H. Reich, F. W. Walker and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1951).

23) E. R. H. Jones et al., *J. Chem. Soc.*, **1937**, 801; ibid., **1940**, 659.

24) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 76 (1942).

25) L. F. Fieser and M. Fieser, "Natural Products related to Rhenanthorene", 3rd. ed., Reinhold Publishing Corp., (1949) p. 190.

26) E. A. Braude and F. Sodheimer, *J. Chem. Soc.*, **1955**, 3754.

27) It should be noted that the wavelengths of the absorption maxima of the semicarbazone (253 mμ; ε, 7,050) and of the 2, 4-dinitrophenylhydrazone (375 mμ; ε, 24,900) of cholest-4-en-6-one are abnormally low[22,28,29] with low intensity. Steric hindrance involved in the systems seems to be strong, because of bulkiness of $=NNHCONH_2$ and $=NNHC_6H_3(NO_2)$-2,4 moieties, and to be associated with transitions between non-planar ground states and non-planar excited states.

28) L. Dorfman, *Chem. Revs.*, **53**, 86 (1953).

29) K. Hirayama, "Zikken Kagaku Koza", 1,I, Maruzen, Tokyo, (1957), p. 91, 97.

30) The rough interplanar angles for other α,β-unsaturated ketosteroids may also be calculated.

31) Turner and Voitle[32] ascribed the fact that compounds having the s-cis configuration exhibit diminished absorption intensity to the decrease in the distance separating the ends of the conjugated system.

32) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 1403 (1951).

33) Cf. K. Morita, This Bulletin, **31**, 379 (1958); see also Idem., *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **78**, 1581 (1957).

34) E. L. Shapiro, D. Gould and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 2912 (1955).

35) *Inter al.*, W. Klyne and E. Miller, *J. Chem. Soc.*, **1950**, 1972; H. Hirschmann et al., *J. Biol. Chem.*, **192**, 115 (1951); R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 2283 (1951).