(potassium bromide) at 1712 (3-one) and 1675 cm.$^{-1}$ (Δ^8-11-one), no hydroxyl band; lit.[21] m.p. 210–212°, λ_{max} 253 mμ (ε 9300).

Lithium–Ammonia Reduction of 5α,25D-Spirost-8-ene-3,11-dione (XXII).—A solution of 30 mg. of the diketone XXII in 10 cc. of ether was added to a stirred solution of 1 cc. of methanol in 30 cc. of liquid ammonia. Lithium (60 mg.) was added in small pieces, and the mixture was stirred for 10 min. Ammonium chloride (1 g.) was then added, the ammonia was allowed to evaporate, water was added to the residue, and the product was isolated with chloroform. Chromatography on 2 g. of alumina and crystallization from methanol yielded 9 mg. of 5α,25D-spirostane-3β,11α-diol (XXIII), m.p. 216–218°. This compound was identical with an authentic sample (m.p. 217–219°)[19,22] through infrared comparison and nondepression of the m.p. on admixture.

Hydration of 5α-Cholesta-7,9(11)-dien-3β-ol (XVIa).—5α-Cholesta-7,9(11)-dien-3β-ol [m.p. 110–112°, $[\alpha]_D$ +40°; λ_{max} 235, 243, and 251 mμ (ε 13,500, 15,600, and 10,100)] was prepared by dehydrogenation of 5α-cholest-7-en-3β-ol with mercuric acetate, as described by Fieser and Herz.[33] The diene (500 mg.) was hydrated by method a; the product was acetylated and then chromatographed on 20 g. of alumina. Elution with pentane–benzene (9:1) yielded 55 mg. (10%) of 5α-cholest-7-en-3β-ol acetate (XVIII), m.p. 116–118°, identified by direct comparison with an authentic sample. Elution with pentane–benzene (1:1) afforded 375 mg. (59%) of 5α-cholest-7-ene-3β,11α-diol diacetate (XVIIb), m.p. 146–148°, which after crystallization from ether–methanol showed m.p. 150–151°, $[\alpha]_D$ −20°. The compound gave a yellow color with tetranitromethane and a positive Fieser selenium dioxide test.[32]

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.17; H, 10.39.

(33) L. F. Fieser and J. E. Herz, *J. Am. Chem. Soc.*, **75**, 121 (1953).

Saponification of the diacetate XVIIb with methanolic potassium hydroxide (1-hr. boiling), followed by crystallization from ether–methanol, yielded 5α-cholest-7-ene-3β,11α-diol (XVIIa), m.p. 161–162°, $[\alpha]_D$ +3°.

Hydration of 5α-Ergosta-7,9(11)-dien-3β-ol (XVIa).—5α-Ergosta-7,9(11)-dien-3β-ol [m.p. 142–144°, $[\alpha]_D$ +32°; λ_{max} 236, 243, and 252 mμ (ε 13,200, 14,900, and 9600)] was prepared by dehydrogenation of 5α-ergost-7-en-3β-ol with mercuric acetate, as described by Fieser and Herz[33] for 5α-cholest-7-en-3β-ol. The diene (500 mg.) was hydrated by method a; the product was acetylated and then chromatographed on 20 g. of alumina. Elution with pentane–benzene (4:1) furnished 65 mg. (12%) of 5α-ergost-7-en-3β-ol acetate (XVIII), m.p. 155–157°, identified by direct comparison with an authentic sample. Elution with pentane–benzene (4:1) yielded 425 mg. (68%) of 5α-ergost-7-ene-3β,11α-diol diacetate (XVIIb), m.p. 137–140°, which after crystallization from ether–methanol showed m.p. 143–145°, $[\alpha]_D$ −17°. The substance gave a yellow color with tetranitromethane and a positive Fieser selenium dioxide test.[32]

Saponification of the diacetate XVIIb through 1-hr. boiling with methanolic potassium hydroxide and subsequent crystallization from ether–methanol led to 5α-ergost-7-ene-3β,11α-diol (XVIIa), m.p. 171–173°, $[\alpha]_D$ +2°.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.35; H, 11.56.

Acknowledgment.—We are indebted to Dr. L. Caglioti and Dr. G. Cainelli (Istituto de Chimica Generale del Politecnico, Milano) for sending us an advance copy of the paper referred to in ref. 14, as well as to Dr. B. A. Hems (Glaxo Ltd., Greenford, Middlesex, England) for a gift of 7-dehydrocholesterol.

Nuclear Magnetic Resonance Studies on Steroids. III.[1] Steroidal Epoxides and Episulfides

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Received August 30, 1963

Proton magnetic resonance spectra of steroidal epoxides and episulfides were investigated to evaluate chemical shifts of the angular methyls and of the epoxidic or episulfidic protons due to the orientation of α and β isomers. The epoxidic or episulfidic proton signal of α isomers is generally found at a higher field than that of β isomers, and their patterns are characteristic of the locations and configurations. Even though the coupling constants obtained from those signals by first-order approximation were considerably smaller than the values calculated from the Karplus equation with the dihedral angles measured in Dreiding models, they allowed the estimation of a $\cos^2$ dependence of the coupling constants on dihedral angles in the epoxide or episulfide systems. A revised Karplus equation is proposed for the 1,2-epoxycyclohexane system. Furthermore, the relationship between the magnitudes of the coupling constants and electronegativities is discussed briefly.

In regard to the proton magnetic resonance (n.m.r.) spectra of steroidal epoxides, Zürcher[2] has reported the chemical shift of the 19-methyl group in several compounds. More recently, Cross[3] has published the n.m.r. spectra of many steroidal 5,6-epoxides, with a discussion on the signal of the epoxidic and 19-methyl protons. On the other hand, the n.m.r. spectra of ethylene oxide, ethylene sulfide,[4] and their monosubstituted derivatives[5–7] have been reported in detail.

This paper presents the n.m.r. spectra of 33 steroidal epoxides and episulfides, and the relationships of the angular methyl and epoxidic (episulfidic) proton signals to the location and configuration of the epoxy (epithio) group. Further, correlation of the coupling constant of the epoxidic (episulfidic) proton with the dihedral angle is discussed in connection with the electronegativities of the participating atoms.

Results and Discussion

Table I lists the n.m.r. spectral data obtained, and Fig. 1 shows typical examples of the signal patterns of epoxidic and episulfidic protons.

Recent studies have shown that geminal and vicinal proton spin-coupling constants are of the opposite sign in various systems.[6,8] In a series of ethylene oxides, geminal couplings (J_{gem}) and vicinal couplings (J_{trans}

(1) Part II: K. Tori and K. Kuriyama, *Chem. Ind.* (London), 1525 (1963).

(2) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961).

(3) A. D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962).

(4) F. S. Mortimer, *J. Mol. Spectry.*, **5**, 199 (1960).

(5) H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959); C. A. Reilly and J. D. Swalen, *ibid.*, **32**, 1378 (1960); **34**, 980 (1961); J. I. Musher, *Mol. Phys.*, **4**, 311 (1961).

(6) C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **35**, 1522 (1961).

(7) J. I. Musher and R. G. Gordon, *ibid.*, **36**, 3097 (1962).

(8) For example, R. Freeman, K. A. McLauchlan, J. I. Musher, and K. G. R. Pachler, *Mol. Phys.*, **5**, 322 (1962); R. R. Fraser, *Can. J. Chem.*, **40**, 1483 (1962).

and J_{cis}) between epoxidic protons appear to be of the same signs; whereas in the same series geminal couplings of a methylene group attached to an epoxy ring and vicinal couplings (J_{vic}) between the methylene and the epoxidic protons are of opposite signs, and J_{vic} has the same sign as that of J_{trans}.[5-7] This is clearly demonstrated in the spectrum of epichlorohydrin.[6] However, in spectra of steroidal epoxides (episulfides), it is difficult to assign the signals of methylene groups attached to the epoxy (epithio) ring. Therefore, analyses of the epoxidic (episulfidic) proton signals in the present work were carried out mainly by first-order approximation. Thus, the coupling constants shown in Table I are given without signs. All of these are J_{cis} and J_{vic}, and there are no J_{gem} and J_{trans} in these systems.

Signal Shifts of the Angular Methyl Groups Due to an Epoxy or Epithio Group.—In the n.m.r. spectra of steroids, it is well-known that the substituent effect of various functional groups on the position of the angular methyl signal shows additivity.[2,9] This substituent effect, or the additivity value, is given by the shift in the angular methyl signal due to introduction of a functional group to the steroidal nucleus. The additivity value is fairly large when the substituent is in a 1,3-diaxial relationship to the angular methyl group, and the value for a polar substituent at a β-position of the methyl group is relatively large.[1,2,9-12] However, the additivity in steroids having a functional group that causes alterations in the relative positions of the angular methyls to it is difficult to realize, because of the mutual interactions with other substituents and of the change in ring conformation.[3,11,13]

On the assumption that the additivity rule would hold in the steroids examined, substituent effects due to epoxy (epithio) groups on the angular methyl signals were obtained as shown in Table II, by using the reference compounds listed in Table I. In order to obtain the values for 5β,6β-,[14] 9β,11β-, and 14β,15β-epoxy (epithio) groups in Table II, 5α-H, 9α-H, and 14α-H steroids were respectively used as reference compounds in accordance with Zürcher's view.[2] Zürcher used 9α-H and 14α-H steroids as references for 9β,11β- and 14β,15β-epoxides, respectively.[2] This treatment is believed to be reasonable because the 1,2-epoxycyclohexane ring takes a half-chair form like the cyclohexene ring, as has been demonstrated by Ottar[15] with the electron diffraction method.

Table II gives the following conclusions: (i) in general, an epithio group gives larger shifts than does the corresponding epoxy group; (ii) in the effects of 2,3-epoxy (epithio) and 11,12-epoxy group on the 19-methyl, β isomers show larger values than do α isomers; (iii) a large shift is effected even by an α isomer when the substituent is located at a β,γ-position of the angular methyl group [for example, the 5α,6α-epoxy (epithio) group to the 19-methyl and the 11α,12α-epoxy (epithio) group to the 18-methyl group].

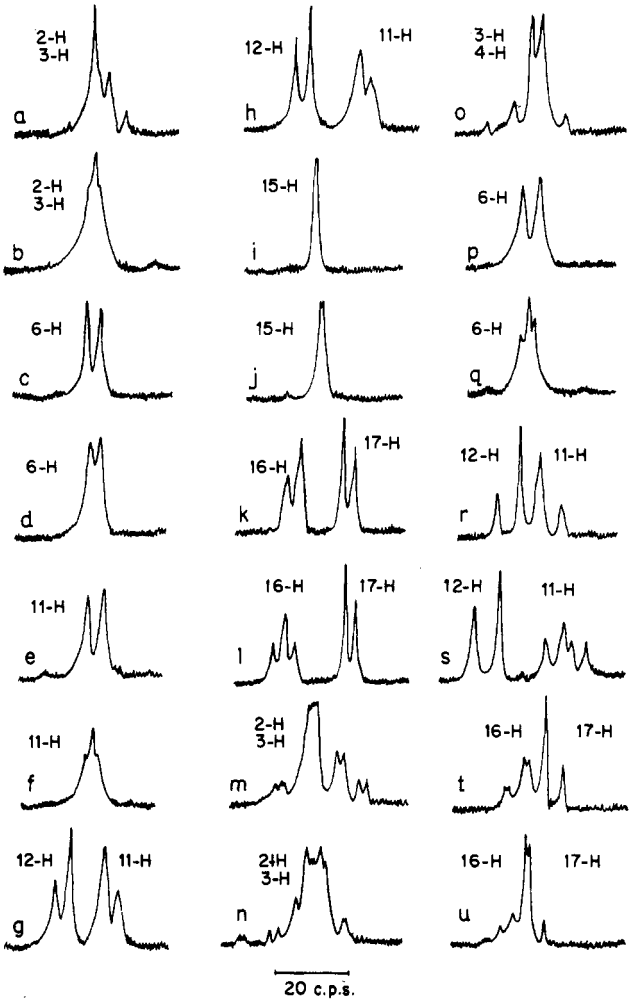

Fig. 1.—Signal pattern of epoxidic or episulfidic protons, at 60 Mc./sec., in 10–15% solutions, in chloroform at room temperature: a, 2α,3α-epoxide; b, 2β,3β-epoxide; c, 5α,6α-epoxide; d, 5β,6β-epoxide; e, 9α,11α-epoxide; f, 9β,11β-epoxide; g, 11α,-12α-epoxide; h, 11β,12β-epoxide; i, 14α,15α-epoxide; j, 14β,15β-epoxide; k, 16α,17α-epoxide; l, 16β,17β-epoxide; m, 2α,3α-episulfide; n, 2β,3β-episulfide; o, 3β,4β-episulfide; p, 5α,6α-episulfide; q, 5β,6β-episulfide; r, 11α,12α-episulfide; s, 11β,12β-episulfide; t, 16α,17α-episulfide; and u, 16β,17β-episulfide.

In facts i and ii, the size of the substituent and its spatial proximity to the angular methyl group can be considered as a major contributing factor. However, for fact iii, the inductive effect may also contribute to the shift.[11] In Table II, the shift value of the 9β,11β-epoxy group obtained from IX and XXXVIII is large when compared with the value obtained by Zürcher,[2] who examined methyl 3β-acetoxy-9β,11β-epoxy-5β-etianate. Examination of Dreiding models shows that this difference can result from the Δ^4-3-ketone grouping in IX which causes the 19-methyl group to come closer to the 9β,11β-epoxy group. Similarly, the large shift value for the 16α,17α-epoxy group, obtained in the cases of XV and XVII, may be due to the change in spatial relation between the 18-methyl group and the 17-methyl ketone with an introduction of the epoxy group into the D ring.

As seen from the results in Table II, it is difficult to differentiate the isomers only from the shift of angular

(9) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); J. S. G. Cox, E. O. Bishop, and R. E. Richards, *J. Chem. Soc.*, 5118 (1960); J. C. Jacquesy, J. M. Lehn, and J. Levisalles, *Bull. soc. chim. France*, 2444 (1961).

(10) G. Slomp and B. R. McGarvey, *J. Am. Chem. Soc.*, **81**, 2200 (1959).

(11) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

(12) K. Tori and E. Kondo, *Tetrahedron Letters*, **No. 10**, 645 (1963).

(13) K. Tori and T. Komeno, to be published.

(14) In this case Cross[3] has used 5β-H steroids as the references, contrary to Zürcher's view.[2]

(15) B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947).

TABLE I

N.M.R. DATA OF STEROIDAL EPOXIDES, EPISULFIDES, AND REFERENCE COMPOUNDS[a]

No.	Compound	Chemical shift (τ)[b] 19-H	18-H	O<H or S<H	Coupling constant, J (c.p.s.)
	Steroidal epoxide				
I	2α,3α-Epoxy-5α-cholestane[c]	9.23	9.35	~6.85 (center)	
II	2α,3α-Epoxy-5α-androstan-17β-ol acetate[d]	9.24	9.24	~6.85 (center)	
III	2β,3β-Epoxy-5α-cholestane[c]	9.15	9.36	~6.87 (center)	
IV	5α,6α-Epoxy-5α-cholestan-3β-ol[e]	8.84	9.38	7.11	$J_{6,7}$ = 3.8
V	5α,6α-Epoxy-5α-androstane-3,17-dione 3,17-bisethylene ketal	8.92	9.21	7.18	$J_{6,7}$ = 3.5
VI	5β,6β-Epoxy-5β-cholestan-3β-ol acetate[e]	8.98	9.35	6.93	$J_{6,7}$ = 2.5
VII	5β,6β-Epoxy-5β-androstane-3,17-dione 3,17-bisethylene ketal	9.00	9.18	6.93	$J_{6,7}$ = 2.5
VIII	Methyl 3α-acetoxy-9α,11α-epoxy-5β-cholanate[f]	8.87	9.26	6.85	$J_{11,12}$ = 4.5
IX	9β,11β-Epoxy-17α-hydroxy-21-acetoxypregn-4-ene-3,20-dione[g]	8.60	9.17	6.54	$J_{11,12}$ = 1.5
X	Methyl 3α-acetoxy-11α,12α-epoxy-5β-cholanate[h]	9.00	9.23	7.09 (11-H) 6.88 (12-H)	$J_{11,12}$ = 4.0 $J_{9,11}$ ~0
XI	Methyl 3α-carbethoxy-11α,12α-epoxy-5β-cholanate	9.00	9.23	7.10 (11-H) 6.89 (12-H)	$J_{11,12}$ = 4.0 $J_{9,11}$ ~0
XII	11β,12β-Epoxy-5α-pregnane-3β,20β-diol diacetate[i]	9.00	9.28	6.91 (11-H) 6.63 (12-H)	$J_{11,12}$ = 3.8 $J_{9,11}$ ~1.5
XIII	3β-Acetoxy-14α,15α-epoxy-5β,14α-card-20(22)-enolide[j]	9.00	9.22	6.46	$J_{15,16}$ ~0.3
XIV	3β-Acetoxy-14β,15β-epoxy-5β,14β-card-20(22)-enolide[j]	8.98	9.06	6.50	$J_{15,16}$ ~0.7
XV	16α,17α-Epoxypregn-4-ene-3,20-dione[k]	8.80 (8.81)[s]	8.93	6.28	$J_{15,16}$ ~0
XVI	2β,3α-Diacetoxy-16α,17α-epoxy-5β-pregnan-20-one[l]	9.00	8.98	6.33	$J_{15,16}$ ~0
XVII	3β-Acetoxy-16α,17α-epoxy-5α-pregnan-20-one[m]	9.17	8.98	6.34	$J_{15,16}$ ~0
XVIII	16α,17α-Epoxyandrostan-3β-ol acetate[n]	9.17	9.28	6.68 (16-H) 6.91 (17-H)	$J_{16,17}$ = 3.0 $J_{15,16}$ ~0
XIX	16β,17β-Epoxyandrostan-3β-ol acetate[n]	9.19	9.19	6.54 (16-H) 6.84 (17-H)	$J_{16,17}$ = 3.0 $J_{15,16}$ = 2.7
	Steroidal episulfide				
XX	2α,3α-Epithio-5α-cholestane[o]	9.20	9.36	6.72 6.95 (2- or 3-H)	$J_{2,3}$ = 7.0
XXI	2β,3β-Epithio-5α-cholestane[o]	9.09	9.36	~6.78 (center)	
XXII	2β,3β-Epithio-5α-androstan-17β-ol acetate[p]	9.10	9.24	~6.77 (center)	
XXIII	3β,4β-Epithio-5α-androstan-17β-ol acetate[p]	9.02	9.24	6.81 6.91 (3- or 4-H)	$J_{3,4}$ = 6.5
XXIV	5α,6α-Epithio-5α-cholestan-3β-ol acetate[q]	8.80	9.39	6.95	$J_{6,7}$ = 5.0
XXV	5α,6α-Epithio-5α-cholestan-3β-ol[q]	8.81	9.39	6.95	$J_{6,7}$ = 5.0
XXVI	5β,6β-Epithio-5β-cholestan-3β-ol[p]	8.85	9.36	6.72	$J_{6,7}$ = 2.0
XXVII	11α,12α-Epithio-5α-pregnane-3β,20β-diol diacetate[r]	9.08	9.09	7.10 (11-H) 6.93 (12-H)	$J_{11,12}$ = 7.0 $J_{9,11}$ ~0
XXVIII	Methyl 3-oxo-11β,12β-epithio-5β-cholanate[r]	8.83	9.17	7.03 (11-H) 6.68 (12-H)	$J_{11,12}$ = 7.0 $J_{9,11}$ = 5.0
XXIX	Methyl 3α-acetoxy-11β,12β-epithio-5β cholanate[r]	8.92	9.21	7.10 (11-H) 6.73 (12-H)	$J_{11,12}$ = 7.0 $J_{9,11}$ = 5.0
XXX	11β,12β-Epithio-5β-cholane-3α,24-diol diacetate[r]	8.91	9.21	7.10 (11-H) 6.73 (12-H)	$J_{11,12}$ = 7.0 $J_{9,11}$ = 5.0
XXXI	16α,17α-Epithio-5α-androstan-3β-ol acetate[p]	9.17	9.11	6.83 (16-H) 6.98 (17-H)	$J_{16,17}$ = 4.8 $J_{15,16}$ = 1.5
XXXII	16β,17β-Epithio-5α-androstan-3β-ol acetate[p]	9.19	9.19	6.77 (16-H) 6.83 (17-H)	$J_{16,17}$ = 5.2 $J_{15,16}$ = 3.4
XXXIII	16β,17β-Epithioandrost-4-en-3-one[p]	8.82	9.12	6.75 (16-H) 6.82 (17-H)	$J_{16,17}$ = 5.5 $J_{15,16}$ = 3.4
	Reference compound				
XXXIV	5α-Cholestane	9.22	9.35		
XXXV	5α-Cholestan-3β-ol	9.20	9.36		
XXXVI	5α-Cholestan-3β-ol acetate	9.18	9.35		
XXXVII	Methyl 3α-acetoxy-5β-cholanate	9.07	9.35		
XXXVIII	17α-Hydroxy-21-acetoxypregn-4-ene-3,20-dione	8.82[t]	9.28[t]		
XXXIX	5α-Pregnane-3β,20β-diol diacetate	9.17	9.37		
XL	3β-Acetoxy-5β,14α-card-20(22)-enolide[j]	9.01	9.37		
XLI	Pregn-4-ene-3,20-dione	8.81 (8.808)[s] (8.79)[u]	9.32 (9.31)[u]		
XLII	Methyl 3-oxo-5β-cholanate	8.98	9.31		
XLIII	3β-Acetoxy-5α-pregnan-20-one	9.17 (9.177)[s]	9.40		

[a] *Chloroform solution [10–15% (w./v.)] at room temperature.* [b] Signal positions of the side chain of cholestane derivatives are always τ 9.09 and 9.18, and that of the COOMe group of cholanate derivatives is always τ 6.33 ~ 6.34. [c] A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949). [d] J. Fajkos and F. Šorm, *Collection Czech. Chem. Commun.*, **24**, 3115 (1959). [e] T. Westphalen, *Ber.*, **48**, 1064 (1915); J. Hattori, *Yakugaku Zasshi*, **60**, 334 (1940); P. A. Plattner, T. Petrzilka, and W. Lang, *Helv. Chim. Acta*, **27**,

513 (1944). [f] E. Seebeck and T. Reichstein, *ibid.*, **26**, 536 (1943). [g] J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957). [h] J. Press and T. Reichstein, *Helv. Chim. Acta*, **25**, 878 (1942); A. Fürst and R. Scotoni, Jr., *ibid.*, **36**, 1410 (1953). [i] R. K. Callow and V. H. T. James, *J. Chem. Soc.*, 4744 (1956). [j] P. Hofer, H. Linde, and K. Meyer, *Helv. Chim. Acta*, **45**, 1041 (1962); H. Ishii, T. Tozyo, and D. Satoh, *Chem. Pharm. Bull.* (Tokyo), **10**, 645 (1962), kindly supplied by Dr. Ishii. [k] O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953). [l] Derived from "Yonogenin"; *cf.* K. Takeda, T. Okanishi, and A. Simaoka, *Chem. Pharm. Bull.* (Tokyo), **6**, 532 (1958). [m] B. Camerino, C. G. Alberti, and A. Vercellone, *Gazz. chim. ital.*, **83**, 795 (1953). [n] J. Fajkos, *Collection Czech. Chem. Commun.*, **20**, 312 (1955). [o] D. A. Lightner and C. Djerassi, *Chem. Ind.* (London), 1236 (1962); K. Takeda and T. Komeno, *ibid.*, 1793 (1962). [p] K. Takeda and T. Komeno, to be published. [q] T. Komeno, *Chem. Pharm. Bull.* (Tokyo), **8**, 672 (1960). [r] K. Takeda, T. Komeno, and J. Kawanami, *ibid.*, **8**, 621 (1960). [s] Ref. 2. [t] Ref. 12. [u] Ref. 11.

TABLE II

SUBSTITUENT EFFECT DUE TO AN EPOXY OR AN EPITHIO GROUP ON THE POSITION OF THE ANGULAR METHYL SIGNALS[a]

Substituent	Site of substituent	α 19-H	α 18-H	β 19-H	β 18-H
	2, 3	+0.01	0.00	−0.07	+0.01
	3, 4			(−0.042)[b]	
	5, 6	−0.26	+0.02	−0.20	0.00
		(−0.25)[c]		(−0.042)[c,d]	
Epoxy group	8, 9				
		(−0.100)[b]			
	9, 11	−0.20	−0.09	−0.22	−0.11
		(−0.200)[b]		(−0.125)[b,e]	
	11, 12	−0.07	−0.12	−0.17	−0.09
		(−0.067)[b]		(−0.192)[b]	
	14, 15	−0.01	−0.15	−0.03	−0.31
		(−0.017)[b]		(−0.100)[b]	
	16, 17	−0.01	−0.42		
Epithio group	2, 3	−0.02	+0.01	−0.13	+0.01
	5, 6	−0.385	+0.035	−0.35	0.00
	11, 12	−0.09	−0.28	−0.15	−0.14

[a] Values are given in p.p.m.; plus sign represents upfield shift. [b] Zürcher's value.[2] [c] Cross' value.[3] [d] This discrepancy is due to the use of 5β-H steroids as references.[3,14] The same value as ours can be obtained if 5α-H steroids were used as references. [e] See text.

TABLE III

DIFFERENCE IN SIGNAL POSITIONS OF EPOXIDIC OR EPISULFIDIC PROTONS BETWEEN α AND β ISOMER, $\Delta\tau_{\alpha,\beta}$ (P.P.M.)

Substituent	Site of proton	$\Delta\tau_{\alpha,\beta}$	Compound to be compared
	2, 3	−0.02	I, III
		(center)	
	6	0.18	IV, VI
Epoxy group	6	0.25	V, VII
	15	−0.04	XIII, XIV
	16	0.14	XVIII, XIX
	17	0.07	
	2, 3	0.06	XX, XXI
		(center)	
Epithio group	6	0.23	XXV, XXVI
	16	0.06	XXXI, XXXII
	17	0.05	

methyl signals, even though some of the α isomers can be distinguished from the β isomers.

Signal of Epoxidic or Episulfidic Proton.—Signal peaks of epoxidic (episulfidic) protons in the steroids examined appear at around τ 6.5–7.1, and at about τ 6.3 when the epoxy (epithio) group is conjugated with a carbonyl group, as shown in Table I. These chemical shifts of the epoxidic proton are close to those observed in simple monosubstituted ethylene oxides.[5-7] It should be noted that the epoxidic proton resonates at a considerably higher field than does an ordinary proton attached to an oxygen-bearing carbon atom. This fact can be explained by a possible small ring-current effect in three-membered rings, analogous to the case of the cyclopropyl ring.[16]

It is a known fact that an axial proton in a cyclohexane ring is more shielded than its equatorial counterpart.[17] In the present case of steroidal epoxides (episulfides), however, an epoxidic (episulfidic) proton in a 1,2-epoxycyclohexane (1,2-epithiocyclohexane) ring, regardless of α or β configuration, forms almost the same angle to the cyclohexane ring and is equatorial-like. However, as seen from Table I, the signal of an epoxidic (episulfidic) proton of α isomers generally appears at a higher field than that of β isomers. This difference in signal shift ($\Delta\tau_{\alpha,\beta}$) is listed in Table III. Although this fact is of considerable interest, a satisfactory explanation for this difference is not apparent at present.

The signal pattern of the epoxidic (episulfidic) proton, as shown in Fig. 1, has a characteristic form with regard to the location and configuration of the epoxy (epithio) group. It is not surprising that this signal pattern is always the same, so long as other substituents are not introduced into the same ring bearing the epoxy (epithio) group. For example, the episulfidic protons in XXVIII, XXIX, and XXX (11β,12β-episulfides) show the same signal pattern shown in Fig. 1 (s). Therefore, by comparing the signal pattern of an epoxidic (episulfidic) proton in a steroid with the patterns shown in Fig. 1, one can determine the location and configuration of this epoxy (epithio) group.[18]

Coupling Constant of Epoxidic or Episulfidic Proton.—In recent years, n.m.r. studies of ethylene oxide and and its monosubstituted derivatives[4-7] showed that this system is of an essentially different type from olefins, and its coupling constants are consistent with the Karplus correlation[19] because J_{cis} should be larger than J_{trans}.[4-7] For further confirmation of this view, systematic experiments on disubstituted ethylene oxides and epoxy groups in ring systems are required. Recently, Cross[3] has obtained the J_{vic} value between the epoxidic proton on the C-6 atom and the two protons on the C-7 atom in many steroidal 5,6-epoxides and has compared the observed values with those calculated by applying the Karplus equation (1)[19] to the dihedral angles measured in Dreiding models. However, J_{trans} and J_{cis} can not be obtained from these compounds. Thus,

$$\begin{cases} J = k_1 \cos^2\theta - c; & 0° \leq \theta \leq 90° \\ J = k_2 \cos^2\theta - c; & 90° \leq \theta \leq 180° \end{cases} \quad (1)$$

(16) J. D. Graham and M. T. Rogers, *J. Am. Chem. Soc.*, **84**, 2249 (1962); K. B. Wiberg and B. T. Nist, *ibid.*, **83**, 1226 (1961).

(17) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p. 115.

(18) In the cases of XV, XVI, and XVII, the signal patterns of the epoxidic protons appear, as a singlet, different from that of XVIII shown in Fig. 1 (k), because another substituent (17β-acetyl group) is introduced into the epoxy ring. The location and configuration of an epoxy (epithio) group, of course, can not be estimated in such cases as above.

(19) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

TABLE IV

COUPLING CONSTANTS IN THREE-MEMBERED RING SYSTEMS

Substance	—Coupling constants, J (c.p.s.)— J_{cis}	J_{trans}	J_{gem}	$J_{C^{13}-H}$	Ref.
Cyclopropane	7.5			161	21
Substituted cyclopropanes[a]	8.67	5.71	−6.65		20
Ethylene oxide	4.45	3.1		175.8	4
Propylene oxide	4.5	2.5	5.5		7
Monosubstituted ethylene oxides[a]	4.3	2.3	5.7		5, 6
1,2-Epoxycyclohexane deriv.[a]	3.9				This work
1,2-Epoxycyclopentane deriv.[a]	3.0				This work
Ethylene sulfide	7.15	5.65		170.5	4
Propylene sulfide	6.3	5.4	$\lesssim$0.4		7
1,2-Eipthiocyclohexane deriv.[a]	6.9				This work
1,2-Epithiocyclopentane deriv.[a]	5.6				This work
Ethylene imine	6.3	3.8		168.1	4

[a] Coupling constants are shown in mean values, as data for a series of derivatives are cited in the reference.

J = coupling constant in a >CH–CH< fragment

k_1, k_2, c = constants ($k_1 = 8.5$, $k_2 = 9.5$, $c = 0.28$ c.p.s.)

θ = dihedral angle between a respective pair of protons

it is not yet clear whether the Karplus correlations hold in the ethylene oxide system over the whole range of the dihedral angle. On the other hand, Hutton and Schaefer[20] have concluded from studies on the spectra of cyclopropane derivatives that J_{cis} is larger than J_{trans} and that both couplings are in good agreement with those calculated from the Karplus equation. Furthermore, the nonolefinic type of this coupling is supported by the fact that introduction of an electronegative substituent into the ring influences the coupling constants only a little,[20] although it is well-known that the cyclopropane ring has a π-character.

As can be seen from Table I, the magnitudes of J_{cis} (about 3.0 ~ 4.5 c.p.s., corresponding to dihedral angle 0°) between the epoxidic protons of various steroidal epoxides are in good agreement with those of ethylene oxide systems.[4-7] Similarly, good agreement with that of the ethylene sulfide system[4,7] is obtained in the case of steroidal episulfides (about 5.0 ~ 7.0 c.p.s.). These facts confirmed the previous conclusion that J_{cis} is larger than J_{trans}.

The coupling constants in three-membered ring systems are summarized in Table IV. Table IV shows that the magnitudes of J_{cis} and J_{trans} increase in the following order, ethylene oxide < ethylene sulfide $\lesssim$ ethylene imine < cyclopropane system, whereas $J_{C^{13}-H}$ determined by C^{13} satellites decreases in the above order.[4,21] Microwave studies showed that the H–C–H angles and accordingly the H–C–C–H dihedral angles in both ethylene oxide and ethylene sulfide are equal within a fraction of a degree, and also that the C–C bond lengths are almost equal.[22] The data on ethylene imine are not very different from those in the above two

TABLE V

CALCULATED AND OBSERVED COUPLING CONSTANTS FOR STEROIDAL EPOXIDIC AND EPISULFIDIC PROTONS, J (C.P.S.)

Site of substituent	Proton (H)	Dihedral angle[a]	J_{calcd}[b]	Epoxidic proton J_{obsd}	J_{calcd}[c]	Episulfidic proton J_{obsd}
5α, 6α	6β-7α	92°	0.3	~0	0.1	~0
		(94 ± 4°)[d]	(0.28-0.1)[d]	(~0)[d]		
	6β-7β	28°	6.4	3.8, 3.5	4.0	5.0
		(28 ± 4°)[d]	(5.8-6.8)[d]	(3.3-4.1)[d]		
5β, 6β	6α-7α	72°	0.5	~0	0.5	~0
		(75 ± 4°)[d]	(0.03-0.62)[d]	(~0)[d]		
	6α-7β	48°	3.5	2.5	2.3	2.0
		(49 ± 4°)[d]	(2.8-4.0)[d]	(2.1-2.7)[d]		
9α, 11α	11β-12α	98°	0.1	~0	0.1	
	11β-12β	22°	7.0	4.5	4.4	
9β, 11β	11α-12α	58°	2.1	~1.5	1.4	
	11α-12β	62°	1.6	~1.5	1.2	
11α, 12α	11β-9α	90°	0.3	~0	0.0	~0
11β, 12β	11α-9α	50°	3.2	~1.5	2.1	5.0
14α, 15α	15β-16α	74°	0.4	~0		
	15β-16β	46°	3.8	~0.3		
14β, 15β	15α-16α	38°	5.0	~0.7		
	15α-16β	82°	0.1	~0		
16α, 17α	16β-15α	62°	1.6	~0		~0
	16β-15β	58°	2.1	~0		1.5
16β, 17β	16α-15α	15°	7.6	2.7		3.4
	16α-15β	105°	0.4	~0		~0

[a] These values were measured in Dreiding models (accuracy about ±2°). [b] Calculated from Karplus equation 1.[19] [c] Calculated from a revised Karplus equation (2) for 1,2-epoxycyclohexane ring system proposed in the present work. [d] Cross' value.[3]

systems.[23] Therefore, as has already been pointed out, molecular geometry does not appear to contribute to the coupling constants in these systems.[4,7] Recent studies indicated that coupling constants in vinyl systems decrease with the increase in electronegativities of substituents.[24] This is also the case with the $-CH_2-CHX-$ fragment, although the effect of electronegativity of the substituent X on the coupling constant is much weaker.[25] Further, it has been shown that $J_{C^{13}-H}$ increases when an electronegative atom is bonded to the carbon.[26] The variation in the coupling constants in three-membered ring systems is, therefore, attributable to the electronegativity of the third atom of these ring systems, as already quoted by Williamson.[25] This consideration also gives a clear explanation for the difference in J_{vic} values of epoxides and episulfides from theoretical values, as quoted later. Table IV also shows that the coupling constants are somewhat smaller in a 1,2-epoxycyclopentane ring system (an epoxide on the steroidal D-ring) than those in a 1,2-epoxycyclohexane ring system. This point is discussed later.

In order to examine the applicability of the Karplus correlation[19] to J_{vic} between the epoxidic (episulfidic) proton and the proton on the adjacent carbon atom, we compared the observed J_{vic} values with those calculated from the Karplus equation 1 by using the dihedral angles between the respective pair of protons directly measured in Dreiding models, as shown in Table V. The dihedral angles obtained for the epoxides were adopted for the episulfides, because there may be no significant difference in C–C bond lengths and bond

(20) H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **41**, 684 (1963).
(21) N. Muller and D. Pritchard, *J. Chem. Phys.*, **31**, 768 (1959).
(22) G. L. Cunningham, A. W. Boyd, R. J. Myers, W. D. Guinn, and W. I. LeVan, *ibid.*, **19**, 676 (1951).
(23) T. E. Turner, V. C. Fiova, and W. M. Kendrick, *ibid.*, **23**, 1966 (1955).
(24) For example, T. Schaefer, *Can. J. Chem.*, **40**, 1 (1962).
(25) K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963).
(26) J. N. Shoolery, *J. Chem. Phys.*, **31**, 1427 (1959); E. R. Malinowski, *J. Am. Chem. Soc.*, **83**, 4479 (1961).

angles between epoxy and epithio groups as shown by the microwave studies mentioned above.[22] Figure 2 shows the plots of J_{vic} against dihedral angles together with the curve calculated from the Karplus equation 1. As clearly seen from Fig. 2, although the coupling constant of the epoxides has considerably smaller values than the calculated values, the J_{vic} is apparently a function of the dihedral angle. In the case of episulfides, this discrepancy is not so pronounced as in the case of the epoxides. As already mentioned, these discrepancies from the Karplus curve can be explained by the electronegativities of oxygen and sulfur atoms. The discrepancy is even larger when an epoxy or epithio ring is attached to the D-ring, that is, in the case of the 1,2-epoxy- or 1,2-epithiocyclopentane ring system. This fact was also seen in J_{cis} in Table IV. In the rigid ring system, the magnitudes of these couplings appear to be affected by the ring size also. Probably, these are due to the distortion of the normal bond angles of the epoxy (epithio) ring induced by the rigid ring system.

In the theoretically derived Karplus equation (1),[19] the values for the coefficients, k_1, k_2, and c, can be replaced by other values which vary with the nature of substituents on the >CH–CH< fragment and of the environments around it.[25,27] Several sets of the coefficients have been proposed from the experimental results for several systems.[27] From the results in Table V, we have deduced an approximate k_1 value for the 1,2-epoxycyclohexane ring system. Because there should be some difference in contribution of electronegativity of the oxygen atom, J_{cis} can not be discussed on the same basis as J_{vic}. The following revised Karplus equation (2) is proposed for the system.

$$J = 5.1 \cos^2 \theta \qquad 0° \leq \theta \leq 90° \qquad (2)$$

Calculated values of J_{vic} from this equation are also shown in Table V, and the calculated curve is shown in Fig. 2 by the broken line. Although the k_2 value is believed to be small as compared with that in the Karplus equation 1, the twin equation (2) for the dihedral angle 90–180° can not be obtained from the steroidal epoxides employed in the present study. Similarly, more experimental data will be required to derive revised Karplus equations for 1,2-epoxycyclopentane or epithio ring systems.

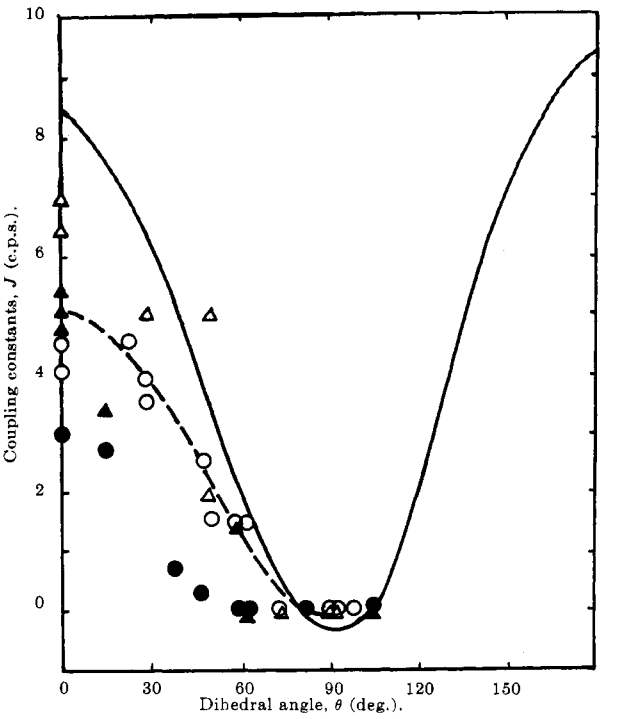

Fig. 2.—Plots of the coupling constants of steroidal epoxidic and episulfidic protons against the dihedral angles measured in Dreiding models: ○, observed in 1,2-epoxycyclohexane ring system; △, observed in 1,2-epithiocyclohexane ring system; ●, observed in 1,2-epoxycyclopentane ring system; ▲, observed in 1,2-epithiocyclopentane ring system; ———, calculated curve from the Karplus equation (1); – – – –, calculated curve from the revised Karplus equation (2) for 1,2-epoxycyclohexane ring system proposed in the present work.

Experimental

The spectra were taken with a Varian A-60 analytical n.m.r. spectrometer system on 10–15% (wt./v.) solutions of the samples in purified chloroform containing 1% tetramethylsilane as an internal standard. All the chemical shifts are expressed in τ-units, and coupling constants are in c.p.s. The calibration of the spectrometer was checked by using the signal peaks of pure *p*-anisaldehyde in 4.0% (wt./v.) solution in carbon tetrachloride.[28] Accuracy limits are about τ ±0.02 for chemical shifts and about ±0.3 c.p.s. for coupling constants. All the samples employed (see Table I) were synthesized by authentic methods in this laboratory.

Acknowledgment.—We are greatly indebted to Dr. H. Ishii for supplying us with the compounds (XIII, XIV, and XL), and also to Dr. K. Takeda, Director of this laboratory, and Dr. H. Minato for their helpful advice on this work.

(27) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961); R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 806 (1963).
(28) G. V. D. Tiers and D. R. Hotchkiss, *J. Phys. Chem.*, **66**, 560 (1962).