(0.0065 mol, 63.3%) of an orange oil which solidified on cooling, mp 57–60°. Three recrystallizations from hexane gave 0.62 g of a white powder, mp 72–73°.

Anal. Calcd for $C_{23}H_{44}N_2O_3$: C, 69.65; H, 11.18; N, 7.06. Found: C, 69.74; H, 11.38; N, 6.69.

B.—Oxalyl chloride (4.5 g, 0.355 mol) was added dropwise over 45 min to **9** (1.0 g, 0.0029 mol) in benzene (5 ml). The mixture was stirred for 1 hr as gases evolved and then warmed in a hot-water bath for 15 min in order to effect complete solution and an end to the evolution of gases. The excess oxalyl chloride was evaporated under vacuum, and the tan-orange crude acid chloride was added along with a small amount of benzene to a precooled solution of 25% aqueous dimethylamine (15 ml) maintaining a temperature of 5–10°. The solid was extracted with benzene. The combined extracts were washed with water, dried over potassium carbonate, and evaporated to leave an oil which quickly solidified on cooling. Recrystallization from hexane (200 ml) gave 0.84 g (0.00212 mol, 72%) of a white powder, mp 72–73°. This material was spectrally identical with the solid made in part A and a mixture melting point was determined at 71–73°.

Dimethyl 10-Oxononadecanedioate (10).—A mixture of crude **9** (0.4 g), methanol (25 ml), and concentrated sulfuric acid (1 drop) was refluxed for 48 hr. The cooled reaction mixture was diluted with aqueous sodium carbonate, and the precipitated beige solid was extracted with ether. The ether solution was dried with sodium sulfate and the ether was evaporated, leaving a gummy white solid. Four recrystallizations, two from hexane (30 ml) plus DARCO and two from 30–60° ligroin (10 ml), gave 70 mg of a white powder, mp 57–58° (lit. mp 50–52°[28] and 63–64°[29,30]).

Nonadecanedioic Acid (11).—A mixture of mossy zinc metal (10 g, 0.153 g-atom), mercuric chloride (1.0 g, 0.00369 mol), water (20 ml), and concentrated HCl (1 ml) was prepared in a 250-ml flask. Compound **9** (1.0 g, 0.0029 mol) was added followed by a mixture of glacial acetic acid (10 ml) and concentrated HCl (10 ml). The mixture was heated to reflux with good stirring, and an additional amount of concentrated HCl (30 ml) was added portionwise over the next 24 hr. After another 24 hr of reflux, the cooled reaction mixture was diluted with water. The precipitated white solid was collected and washed with water. Recrystallization from acetonitrile (75 ml) gave 0.55 g (0.00166 mol, 58%) of white crystals, mp 115–117° (lit. mp 118–119°[24,36]).

Registry No.—**3**, 818-88-2; **4**, 38312-53-7; **7**, 38312-54-8; **8**, 38312-55-9; **9**, 18197-46-1; **10**, 29263-75-0; **11**, 6250-70-0.

Acknowledgment.—The authors are grateful to the Witco Chemical Corporation for a research grant and to the Pennwalt Corporation for a very generous supply of sebacic acid.

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Determination of C-22 Epimers in Steroids Using Nuclear Magnetic Resonance Spectroscopy[1]

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In a recent publication the stereospecific syntheses of (20*S*,22*R*)- and (20*S*,22*S*)-17α,20,22-trihydroxycholesterol were described.[2] The determination of configuration at C-22 was secured from an examination of the ORD/CD spectra of the 22-benzoate esters of derivatives of these compounds.

The present communication reports a method based on nmr analyses of the hydroxy compounds which achieves the same result. Table I presents the 60-MHz nmr chemical shift data for cholesterol and a number of related compounds, obtained from $CDCl_3$ solutions. The pertinent signals are those for the C-21 methyl and the C-22 proton(s), although the signals for the C-18 and C-19 methyls are also listed for reference.

The C-21 methyl signal of cholesterol (I) occurs as a doublet, centered at *ca.* 55.2 Hz ($J \cong 5.0$ Hz), partially obscured by the doublet from the C-26,27 methyls. In (20*S*)-hydroxycholesterol (II) the C-21 methyl signal is shifted 21.8 Hz downfield. In neither spectrum is a unique signal for the C-22 protons discernable.

In the spectra of both (22*R*)- and (22*S*)-hydroxycholesterol (III and IV, respectively) the signals for the C-22 proton is shifted downfield to *ca.* 215 Hz, and hence are not useful for isomer identification. As seen from Table I, the signals for the C-18, C-19, and C-21 methyls likewise do not differentiate the isomers. A similar situation is observed for the spectra of the two isomeric (22*R*)- and (22*S*)-3α,5-cyclo-5α-cholestane-6β,22-diol 6-methyl ethers (V and VI, respectively).

When the spectra of the two epimeric (20*S*,22*R*)- and (20*S*,22*S*)-3α,5-cyclo-5α-cholestane-6β,20,22-triol 6-methyl ethers (VII and VIII, respectively) are compared, two pronounced differences are discerned. After assigning the signals for the C-18, C-19, C-26, and C-27 methyls, a singlet is observed at 72 Hz for the 22*R* isomer and at 77 Hz for the 22*S* isomer, which can only be assigned to the C-21 methyl protons. In addition, for the 22*R* isomer a triplet corresponding to one proton ($J = 7$ Hz) is observed at 222 Hz, while for the 22*S* isomer a broadened signal, also corresponding to one proton, is observed at *ca.* 195 Hz. These signals must be assigned to the C-22 protons of the isomers.

From the data cited for the two isomeric (22*R*)- and (22*S*)-hydroxycholesterols, it is to be noted that the conformation of the C-22 hydroxyl group, by itself, has no appreciable effect on the chemical shift of the C-21 methyl protons. Yet the above data show that when hydroxyl functions are present at *both* C-20 and C-22 a 5-Hz difference is observed between the chemical shifts of the C-21 methyl protons of the two isomers. The simplest explanation consistent with these observations is that factors influencing the chemical shift of the C-21 methyl protons differ in the two isomers. Through-bond contributions to these factors should be essentially identical for both isomers. Hence a steric or through-space explanation appears reasonable. In order for this explanation to be valid, when the C-20 hydroxyl group is present some functional group which contributes to the chemical shift of the C-21 methyl protons must adopt a different steric relationship to the C-21 methyl group in the (22*R*)-hydroxy isomer than it does in the (22*S*)-hydroxy isomer.

Molecular models show that the (20*S*)- and 22-hydroxyl groups are well situated for intramolecular hydrogen bonding. That this is indeed occurring in these compounds is confirmed by the chemical shifts of the hydroxyl protons, which are observed at *ca.* 120 Hz for both compounds. Both spectra were obtained from

(1) This work was supported by funds from the U. S. Public Health Service, RR05528, and institutional funding from the Worcester Foundation for Experimental Biology.

(2) R. C. Nickolson and M. Gut, *J. Org. Chem.*, **37**, 2119 (1972).

TABLE I

CHEMICAL SHIFTS OF SELECTED RESONANCES OF CHOLESTEROL AND SOME OF ITS DERIVATIVES[a]

No.	Compd	18 CH_3	19 CH_3	21 CH_3	22 H
I	Cholesterol	41.0	60·5	55.2	?
II	(20*S*)-Hydroxycholesterol	52.0	61.0	77.0	?
III	(22*R*)-Hydroxycholesterol	42.0	60.5	*ca.* 53.5	*ca.* 215
IV	(22*S*)-Hydroxycholesterol	41.5	60.0	*ca.* 53.5	*ca.* 215
V	(22*R*)-3α,5-Cyclo-5α-cholestane-6β,22-diol 6-methyl ether	44.5	61.5	*ca.* 54.5	*ca.* 215
VI	(22*S*)-3α,5-Cyclo-5α-cholestane-6β,22-diol 6-methyl ether	44.0	61.5	*ca.* 54.5	*ca.* 215
VII	(20*S*,22*R*)-3α,5-Cyclo-5α-cholestane-6β,20,22-triol 6-methyl ether	56.0	60.5	72.0	222
VIII	(20*S*,22*S*)-3α,5-Cyclo-5α-cholestane-6β,20,22-triol 6-methyl ether	58.0	60.5	77.0	*ca.* 195
IX	(20*S*,22*R*)-3α,5-Cyclo-22,23-epoxy-24-nor-5α-cholane-6β,20-diol 6-methyl ether	54.0	61.0	75.0	177.5
X	(20*S*,22*S*)-3α,5-Cyclo-22,23-epoxy-24-nor-5α-cholane-6β,20-diol 6-methyl ether	54.5	62.0	83.0	*ca.* 172
XI	(20*S*,22*R*)-3α,5-Cyclo-24-nor-5α-cholane-6β,20,22,23-tetrol 6-methyl ether	54.0	61.0	73.0	217
XII	(20*S*,22*S*)-3α,5-Cyclo-24-nor-5α-cholane-6β,20,22,23-tetrol 6-methyl ether	54.0	61.0	78.0	210

[a] In hertz, downfield from internal TMS. All spectra were recorded on a Varian Associates DA-60 IL spectrometer, from $CDCl_3$ solutions.

ca. 0.2–0.3 *M* solutions (in $CDCl_3$). At such concentrations of steroids, when only *intermolecular* hydrogen bonding occurs, the hydroxyl signals are observed at higher field. For example, the hydroxyl signal for a solution of comparable concentration of (22*R*)-3α,5-cyclo-5α-cholestane-6β,22-diol 6-methyl ether occurs at 91 Hz. It has previously been shown that even at infinite dilution the signal of an intramolecularly hydrogen bonded hydroxyl will occur at lower field than that for a hydroxyl which does not undergo intramolecular hydrogen bonding.[3]

From molecular models, it is observed that when intramolecular hydrogen bonding occurs between the (20*S*)- and (22*R*)-hydroxyls the C-22 proton is situated cis to the C-21 methyl. For the similar situation between the (20*S*)- and (22*S*)-hydroxyls the C-22 proton is *trans* to the C-21 methyl. Conversely, the remainder of the side chain (carbons 23 through 27) is situated trans to the C-21 methyl in the 22*R* isomer and cis in the 22*S* isomer. This is illustrated in Figure 1.

From the spectra of testosterone and epitestosterone it is observed that the C-17 proton cis to the C-18 methyl (in epitestosterone) gives a signal some 5 Hz further downfield than does the C-17 proton trans to the C-18 methyl (in testosterone). With the formation of an intramolecular hydrogen bond, as shown in Figure 1, a similar situation might be expected to be observed for the signals of the C-22 protons of the two isomers under discussion.

As mentioned earlier, this is indeed observed for the C-22 proton, the difference being *ca.* 7 Hz.

It thus follows that a likely explanation for the observed difference in chemical shifts for the C-21 methyl protons of the two isomers arises from the different steric orientation of carbons 23–27 with respect to the C-21 methyl group in the two isomers (*cf.* Figure 1). The hydroxyl groups of the two isomers are situated in sterically equivalent positions with respect to the C-21 methyls, and are not *per se* responsible for the difference in chemical shifts.

(3) T. A. Wittstruck and J. F. Cronan, *J. Phys. Chem.*, **72**, 4243 (1968).

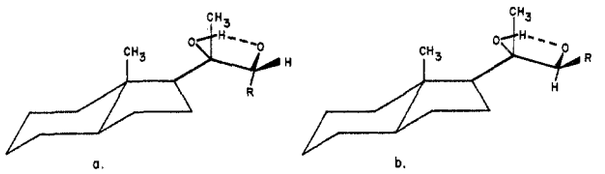

Figure 1.—Conformations adopted upon intramolecular hydrogen bonding between (a) (20*S*)-hydroxyl and (22*R*)-oxygen function, (b) (20*S*)-hydroxyl and (22*S*)-oxygen function in steroids. Only rings C and D of steroid are shown.

The fact that a sharp triplet is observed for the C-22 proton in the 22*R* compound but not in the 22*S* compound probably reflects freedom of rotation about the C-22–23 bond in the former but not in the latter.

The spectra of several other pairs of isomers containing the (20*S*)-hydroxyl function as well as an oxygen function of C-22 were examined in the light of the above interpretation. Thus, the lower melting isomer of (20*S*)-3α,5-cyclo-22,23-epoxy-24-nor-5α-cholane-6β,-20-diol 6-methyl ether (IX) gives its C-21 methyl signal at 75 Hz, whereas its higher melting isomer (X) gives the C-21 methyl signal at 83 Hz. The spectrum of the former shows a triplet ($J \cong 3$ Hz) at 177.5 Hz for the C-22 proton. For the latter isomer the C-22 signal occurs further upfield and in fact merges with the signals from the C-23 protons, giving an ABC pattern. (This multiplet has not been analyzed by exact analysis; hence the precise values of the chemical shifts for these protons are not available.) On the basis of the above interpretation the lower melting isomer must be assigned the 22*R* configuration, while the higher melting isomer is assigned the 22*S* configuration.

The two isomers of (20*S*)-3α,5-cyclo-24-nor-5α-cholane-6β,20,22,23-tetrol 6-methyl ether (XI and XII) give similar results. For the higher melting isomer (XI), the signals for the C-22 and C-23 protons all occur at approximately the same chemical shift so that only a slightly broadened (*ca.* 6 Hz) peak is observed centered at 217 Hz. The lower melting isomer (XII) gives a slight separation for the signals of these

protons. The C-22 proton gives a signal at 210 Hz while the C-23 protons give a broader signal centered at 220 Hz.

Based on the above examples, this method of assignment of conformation at C-22 appears to be sufficiently general to be considered whenever the C-20, C-22 diol system is present.

The author wishes to thank Dr. Marcel Gut for supplying most of the samples. Compound II,[4] and the epimeric pairs III and IV,[5] have previously been reported in the literature. The chemistry of the remaining compounds (V–XII), which were obtained from Dr. Gut, has not yet been published. Their nmr spectra agreed fully with the assigned structures.

Registry No.—I, 57-88-5; II, 516-72-3; III, 17954-98-2; IV, 22348-64-7; V, 38379-54-3; VI, 38379-55-4; VII, 38379-56-5; VIII, 38379-57-6; IX, 38379-58-7; X, 38379-59-8; XI, 38379-60-1; XII, 38379-61-2.

(4) V. Petrow and I. A. Stewart-Webb, *J. Chem. Soc.*, **46**, 75 (1956).
(5) N. K. Chaudhuri, R. Nickolson, H. Kimball, and M. Gut, *Steroids*, **15**, 525 (1970).

Sulfonation of Terpene Derivatives. Aluminum Hydride Desulfurization of Sultones

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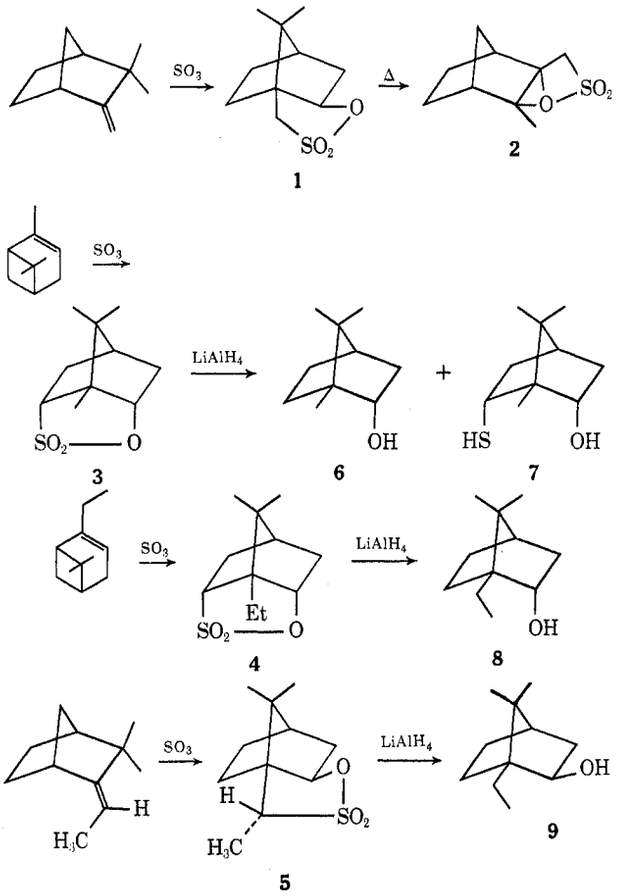
The reaction of camphene with sulfur trioxide–dioxane complex[1] in methylene chloride affords 10-isobornylsultone (**1**), which rearranges thermally at 150–170° to camphenesultone (**2**).[2] Herein we report that sulfonation of α-pinene, α-ethylapopinene, and 8-methylcamphene afford 6-bornylsultone (**3**), 10-methyl-6-bornylsultone (**4**), and 10-methyl-10-isobornylsultone (**5**), respectively, in poor to good yield.

6-Bornylsultone (**3**) exhibits normal sulfonate ester infrared absorption at 7.6 and 8.7 μ. The nmr spectrum, in addition to showing three methyl singlets, displays a broadened one-proton doublet centered at 4.60 ppm assigned to the C-2 proton and a broadened doublet of doublets centered at 3.15 ppm attributed to the C-6 proton.

The structure of **3** was confirmed by aluminum hydride[3] or lithium aluminum hydride reduction[2] to borneol (**6**). 6-*endo*-Mercaptoborneol (**7**) was also isolated from the lithium aluminum hydride reduction[4] and exhibited two eight-line nmr signals, after trifluoroacetic acid was added to remove the spin coupling of the –SH proton, consistent with the di-endo-configurational assignment.[5]

Sulfonation of 8-methylcamphene[6] yields a single isomer of 10-methyl-10-isobornylsultone (**5**), which is assigned an *endo*-10-methyl configuration on the assumption that sulfonation of the camphene double bond occurs from the more accessible exo face of the molecule.

10-Methyl-10-isobornylsultone (**5**) is transformed into 10-methyl-isoborneol (**9**) on reduction with aluminum hydride, while 10-methyl-6-bornylsultone affords 10-methylborneol (**8**) under the same conditions.



The sulfonation–desulfurization sequence described above provides a convenient method for the preparation of 10-substituted borneol and isoborneol derivatives. Although the sulfonation of pinene and camphene derivatives involve Wagner–Meerwein shifts, the reaction is free of Nametkin methyl migration, which plays an important role in the addition of acetic acid derivatives to 8-substituted camphene derivatives.[7] Desulfurization of sultones with lithium aluminum hydride proceeds slowly, and, at best, gives poor to fair yields of sulfur-free alcohol. Reduction with aluminum hydride, on the other hand, is relatively rapid and affords good yields of alcohols.

(1) For the sulfonation of olefins see F. Bordwell, R. D. Chapman, and C. E. Osbourne, *J. Amer. Chem. Soc.*, **81**, 2002 (1959); F. Pueshal and C. Kaiser, *Chem. Ber.*, **98**, 735 (1965), and references cited therein.
(2) J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).
(3) J. Wolinsky and R. Lau, *Syn. Commun.*, **2**, 327 (1972).
(4) The lithium aluminum hydride reduction of terpene sultones will be described in a forthcoming publication.
(5) We attribute the absence of eight-line signals in sultone **3** to the presence of the sultone ring which distorts the bond angles of the bornane ring.
(6) 8-Methylcamphene consists of a mixture of *anti*-8-methyl and *syn*-8-methyl isomers in a ratio of 13:1, respectively.[7]
(7) J. Wolinsky and E. J. Eustace, to be published.