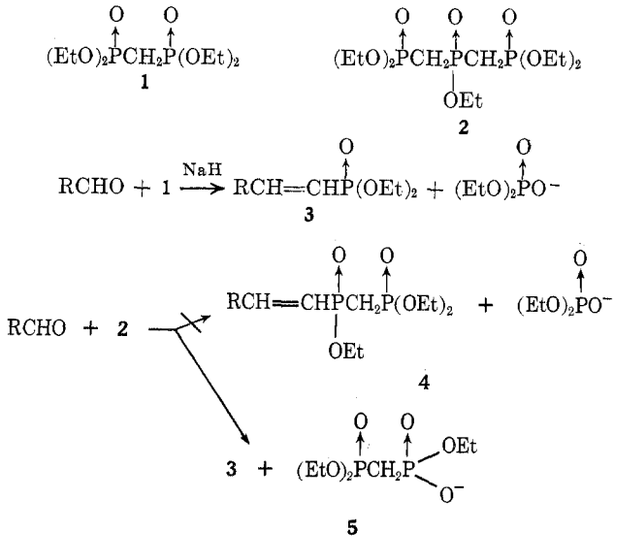
not easily prepared without the use of some unsymmetrical intermediate.



Experimental Section[4]

Diethyl β-Styrylphosphonate (3, R = Phenyl).—A solution of 15.8 g (0.04 mol) of **2**[5] in 25 ml of C_6H_6 was added dropwise to a stirred suspension of 1.7 g (0.04 mol) of sodium hydride (57% dispersion in mineral oil) in 50 ml of C_6H_6. When the solution had become clear, 4 g (0.038 mol) of benzaldehyde in 25 ml of C_6H_6 was added dropwise. Stirring was continued overnight. The C_6H_6 was washed with 100 ml of H_2O in five portions and was concentrated to an oil, which after distillation afforded 3.7 g (41%) of the phosphonate: bp 122–126° (0.025–0.05 mm) [lit. bp 137–138° (0.03 mm),[5a] 125–126° (0.3 mm),[6b] 134° (1.5 mm),[6c] 116–118° (0.35 mm),[2a] 138° (2 mm)[6d]]; $n^{20}D$ 1.5250 [lit. $n^{20}D$ 1.5665,[6a] 1.5298,[6c] 1.5325[6d]]; nmr[6b] (CCl_4) δ 7.35–8.06 (m, 6, C_6H_5CH=), 6.3 (t, 1, J = 18 Hz, C=CHP),[5b,7] 4.15 (m, 4, J = 9 Hz, $POCH_2$), and 1.35 (t, 6, J = 8 Hz, $POCH_2CH_3$); ir[6b] (neat) 690, 740 (phenyl), 1620 (CH=CH), 1160 (POC), and 1250 cm^{-1} (P=O).

The aqueous extract was evaporated to obtain a glassy solid, which was dried under reduced pressure. The resulting solid was pulverized to obtain 8.07 g (76%) of the sodium salt **5**, mp 104–109°. A 1-g sample of the salt was dissolved in 100 ml of water and passed through an Amberlite IR-120 H. C. P. column (2 × 32 cm). Evaporation of the eluate gave 0.93 g of triethyl hydrogen methylenediphosphonate (**5**) as a gum: nmr (CCl_4) δ 12.05 (s, 1, POH), 4.22 (m, 6, J = 8 Hz, $POCH_2$), 2.58 (t, 2, J = 22 Hz, PCH_2P) and 1.39 (t, 9, J = 8 Hz, $POCH_2CH_3$); ir (neat) 1240 (P=O) and 1170 cm^{-1} (POC).

Anal. Calcd for $C_7H_{18}O_6P_2$: C, 32.31; H, 6.97; P, 23.81. Found: C, 32.19; H, 6.77; P, 23.98.

Diethyl 3-Methyl-1-butenylphosphonate [3, R = $(CH_3)_2CH$].—The procedure was the same as that described above. Evaporation of the C_6H_6 layer gave a yellow liquid, which was distilled under reduced pressure to obtain 4.7 g (57%) of diethyl 3-methyl-1-butenylphosphonate: bp 45° (0.025 mm); $n^{25}D$ 1.4372; ir (neat) 1640 (CH=CH), 1375, 1395 (Me_2CH), 1250 (P=O), and 1165, 1025 cm^{-1} (POC); nmr[3c] (CCl_4) δ 6.84 (m, 1, J_{HH} = 7, J_{HH} = 18, J_{HP} = 23 Hz, CH=CP), 5.65 (t, 1, J_{HH} = J_{HP} = 18 Hz, C=CHP), 4.13 (m, 4, J = 7 Hz, $POCH_2$), 2.5 (m, 1, Me_2CH), 1.3 (t, 6, J = 7 Hz, $POCH_2CH_3$), and 1.1 (d, 6, J = 7 Hz, CH_3CHCH_3).

The nmr spectrum is consistent with that reported[3c] for the trans isomer.

Gc analysis indicates less than 1% of a compound with smaller retention volume than the major component. This minor component is believed to be the cis isomer.

Registry No.—**2**, 18033-91-5; *trans*-**3** (R = *i*-Pr), 33536-50-4; *cis*-**3** (R = *i*-Pr), 18689-34-4; **5**, 38379-50-9; **5** sodium salt, 38379-51-0.

Acknowledgment.—We wish to thank Dr. John K. Baker for helpful discussions of the nmr spectra.

(4) Melting points were taken on a Mel-Temp melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were taken on a Jeolco Model C-60-HL spectrometer using tetramethylsilane as an internal standard. Gas chromatograms were obtained with a 5 ft × 0.25 in. column packed with 10% 20M Carbowax on 80–100 mesh Chromosorb W. The column was maintained at 200° in a Perkin-Elmer Model 900 chromatograph equipped with a flame ionization detector. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(5) (a) L. Maier, *Angew. Chem., Int. Ed. Engl.*, **7**, 385 (1968); (b) K. O. Knollmeuler, U. S. Patent 3,534,125 (1970); *Chem. Abstr.*, **74**, 53989ρ (1971).

(6) (a) Ya. A. Levin and V. S. Galeev, *Zh. Obshch. Khim.*, **37**, 2736 (1967); (b) C. E. Griffin and T. D. Mitchell, *J. Org. Chem.*, **30**, 1935 (1965); (c) B. I. Ionin, K. S. Mingaleva, and A. A. Petrov, *Zh. Obshch. Khim.*, **34**, 2630 (1964); (d) K. K. Papok, K. N. Anisimov, B. S. Zuseva, and N. E. Kolobova, *Zh. Prikl. Khim.*, **32**, 656 (1959).

(7) A referee pointed out that the chemical shift we found is not consistent with that reported by Griffin.[3b] We have subsequently found that the chemical shift is concentration dependent and ranges from δ 6.28 (10%) to 6.75 (neat).

Claisen Condensation. A Method for the Synthesis of Long Chain Dicarboxylic Acids

HARRY COHEN* AND RICHARD SHUBART[1]

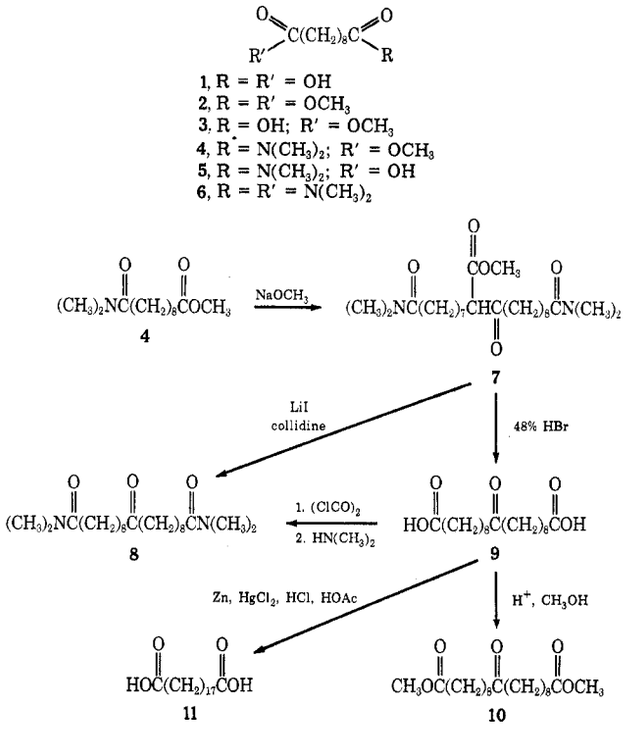
Department of Chemistry, Roosevelt University, Chicago, Illinois 60605

Received January 26, 1972

Earlier syntheses of α,ω-dicarboxylic acids utilized the oxidation of α,ω-glycols, the hydrolysis of dinitriles, the malonic ester synthesis with α,ω-dibromides, and the Crum-Brown–Walker[2] application of the Kolbe[3] synthesis. Combinations of these procedures have provided pathways for the syntheses of α,ω-dioic acids in the range of 11 to 34 carbon atoms.[4-8] Newer methods have been developed by Lettré,[9] Hünig,[10-13] Buchta,[14,15] and others.[16-23] It was our purpose to utilize a compound which could give even- and odd-numbered dicarboxylic acids. Methyl *N*,*N*-dimethylsebacamate (**4**) might be condensed by Claisen and acyloin procedures to yield dicarboxylic acids of 19 and 20 carbon atoms, respectively. Only the former was successful.

(1) Abstracted from the M.S. thesis of R. W. Shubart, Roosevelt University, June, 1970.

(2) A. Crum-Brown and J. Walker, *Justus Liebigs Ann. Chem.*, **261**, 107 (1891).
(3) H. Kolbe, *ibid.*, **69**, 257 (1849).
(4) P. Chuit, *Helv. Chim. Acta*, **9**, 264 (1925).
(5) P. Chuit, *ibid.*, **12**, 850 (1929).
(6) K. Ziegler and W. Hechelhammer, *Justus Liebigs Ann. Chem.*, **528**, 114 (1937).
(7) L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, **11**, 1174 (1928).
(8) D. A. Fairweather, *Proc. Roy. Soc. Edinburgh*, **45**, 283 (1925); *Chem. Abstr.*, **20**, 47 (1926).
(9) H. Lettré and A. Jahn, *Chem. Ber.*, **85**, 346 (1952).
(10) S. Hünig and E. Lücke, *ibid.*, **92**, 652 (1959).
(11) S. Hünig and W. Lendle, *ibid.*, **93**, 913 (1960).
(12) S. Hünig and H.-J. Buysch, *ibid.*, **100**, 4010 (1967).
(13) S. Hünig and H.-J. Buysch, *ibid.*, **100**, 4017 (1967).
(14) E. Buchta and W. Bayer *Naturwissenschaften*, **46**, 14 (1959).
(15) E. Buchta and C. Huhn, *Justus Liebigs Ann. Chem.*, **695**, 42 (1966).
(16) C. Wakselman, *C. R. Acad. Sci.*, **260**, 5056 (1965).
(17) Ng. Ph. Buu-Hoï, M. Sy, and N. Dat Xuong, *ibid.*, **240**, 442 (1955).
(18) A. Kreuchunas, *J. Amer. Chem. Soc.*, **75**, 3339 (1953).
(19) H. Stetter and W. Dierichs, *Chem. Ber.*, **85**, 290 (1952).
(20) H. Stetter and W. Dierichs, *ibid.*, **85**, 61 (1952).
(21) Hs. H. Günthard, S. D. Hinemann, and V. Prelog, *Helv. Chim. Acta*, **36**, 1147 (1953).
(22) V. Hnévosvá, V. Smělý, and I. Ernest, *Chem. Listy*, **50**, 573 (1956); *Chem. Abstr.*, **50**, 13749b (1956).
(23) J. C. Sauer, *J. Amer. Chem. Soc.*, **69**, 2444 (1947).



Sebacic acid (**1**) was readily converted into its dimethyl ester **2** by the method of Clinton and Laskowski.[24] Methyl hydrogen sebacate (**3**) was prepared through the formation of its barium salt[22] and subsequent acid treatment. The procedure of Dietzel[25] was also tried but gave no disproportionation. Thionyl chloride was used to convert **3** into its acid chloride, which was treated immediately with aqueous dimethylamine to give methyl *N*,*N*-dimethylsebacamate (**4**). The assigned structure was consistent with the observed spectral data and elemental analysis. In addition, compounds **5** (mp 54–56°) and **6** (mp 87–88°), prepared by the usual methods, completed the series.

The Claisen condensation of **4** was accomplished under anhydrous conditions without a solvent.[26] In order to confirm the structure of **7**, it was transformed into the diamide **8** by the procedure of Eschenmoser.[27] Hydrolysis of **7** with 48% hydrobromic acid yielded 10-oxononadecanedioic acid (**9**), which was readily converted into **8**. The dimethyl ester **10** had a melting range of 57–58° (lit. mp 50–52°[28] and 63.4°,[29,30] but spectral data was in agreement with the compound noted. The reduction of the 10-oxo group of **9** using the Huang-Minlon modification of the classical Wolff–Kishner procedure[11,31] was unsuccessful. A Clemmensen reduction following the procedure of Günthard[21] did give nonadecanedioic acid (**11**).

The acyloin condensation was run according to a known successful method[32] but it ran into difficulty from the start. The reaction evolved copious amounts of dimethylamine, indicating probable reaction with both functional groups of **4**. Several materials were isolated by chromatography but none was identified.

(24) R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, **70**, 3135 (1948).
(25) E. Dietzel, German Patent 800,403 (November 6, 1950); *Chem. Abstr.*, **45**, P1623*h* (1951).
(26) R. Briese and S. McElvain, *J. Amer. Chem. Soc.*, **55**, 1697 (1933).
(27) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).
(28) L. Ruzicka, M. Stoll, W. Scherrer, H. Schinz, and C. Seidel, *ibid.*, **15**, 1459 (1932).
(29) T. Bacchetti and L. Caprio, *Gazz. Chim. Ital.*, **83**, 832 (1953); *Chem. Abstr.*, **49**, 4680*d* (1955).
(30) H. Hatt and J. Lamberton, *Aust. J. Chem.*, **8**, 506 (1955); *Chem. Abstr.*, **50**, 8461*b* (1956).
(31) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).
(32) V. Hansley, *ibid.*, **57**, 2303 (1935).

Experimental Section

All chemicals were reagent grade unless otherwise indicated. Melting points were taken on a Fisher-Johns apparatus and are uncorrected. The elemental analyses were performed by Dr. F. B. Strauss of Oxford, England.

Methyl *N*,*N*-dimethylsebacamate (4).—A solution of **3** (75.7 g, 0.351 mol) in thionyl chloride (52.1 g, 0.438 mol) was heated on a hot-water bath for 1.5 hr. After removal of excess thionyl chloride under vacuum and flushing with benzene, the red acid chloride was added dropwise over 15 min to a precooled solution of 25% aqueous dimethylamine (648 ml) maintained at 5–10°. The solid was extracted immediately with benzene, the extracts were washed with water and dried with sodium sulfate, and the benzene was evaporated to give 71.4 g (0.295 mol, 83.7%) of a very low melting white crystalline solid. It was recrystallized by dissolution in hexane (500 ml) at room temperature and filtered from a small amount of insoluble white solid which was identified as **6**, and the clear solution was cooled. After several days in the refrigerator, the solid was collected and quickly washed with cold hexane. It was placed back in the refrigerator as 36.7 g (0.1516 mol, 43.2%) of white solid, mp 24°. Continued concentrations of the mother liquor gave more crops with successively lower melting points. Repeated recrystallizations from hexane gave clear colorless needles, mp 27–28°.[33]

Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 63.83; H, 10.07; N, 5.69.

***N*,*N*,*N*′,*N*′-Tetramethyl-9-carbomethoxy-10-oxononadecane Diamide (7).**—Fresh sodium methoxide was prepared by dissolving sodium metal (1.15 g, 0.05 mol) in methanol (30 ml). Careful evaporation of the excess methanol *in vacuo* left the sodium methoxide as a white powder in the bottom of the flask. Compound **4** (24.3 g, 0.10 mol) was added, and the mixture was placed in a hot-water bath. Vacuum from a water aspirator was applied as the mixture bubbled quite vigorously for 1 hr and then subsided. Total heating under vacuum was continued for 24 hr. After cooling, the "glassy" solid was treated while cooling with a mixture of 25% aqueous acetic acid (30 ml) and benzene (25 ml). After separation of the benzene layer, the aqueous layer was diluted with saline solution (30 ml) and extracted twice more with benzene. The combined benzene extracts were washed with a 50% saturated sodium chloride solution, dried over sodium sulfate, and evaporated to give 24.1 g (0.053 mol, 106%, crude) of a clear orange oil. Tlc showed the presence of a small amount of starting material (possibly 5%). The product could be purified by continuous extraction of the orange oil with hot hexane for 4 days (73% recovery) or for 7 days (90% recovery) to give a clear yellow oil which was then chromatographed on silica gel (80–200 mesh, 1.0 g of oil/14 g of silica). After removal of the starting material by elution with ethyl acetate, a mixture of ethyl acetate–acetone (1:1) eluted the product as an almost colorless clear oil. Yields ranged from 70 to 75%.

Anal. Calcd for $C_{25}H_{46}N_2O_5$: C, 66.05; H, 10.20. Found: C, 65.82; H, 10.30.

10-Oxononadecanedioic Acid (9).—A mixture of **7** (5.0 g, 0.011 mol) and 48% HBr (21 ml) was refluxed for 24 hr, cooled, and then diluted with an equal volume of water. The precipitated solid was collected and washed with water. Two recrystallizations from acetonitrile (75 ml) gave 2.94 g (0.0086 mol, 78%) of a white powder, mp 122–124° (lit. mp 123.5[34] and 124°[35]).

***N*,*N*,*N*′,*N*′-Tetramethyl-10-oxononadecanediamide (8).**—A. —A mixture of **7** (4.75 g, 0.0105 mol), anhydrous lithium iodide (10.6 g, 0.079 mol), prepared by heating the trihydrate under vacuum, and freshly distilled collidine (100 ml, bp 170°) was refluxed for 14 hr under nitrogen. After cooling to room temperature, the reaction mixture was acidified by the addition of concentrated HCl (87 ml) in water (250 ml). The acidified solution was extracted with benzene. The benzene layer was washed with water, dried over sodium sulfate, and evaporated to give 2.63 g

(33) It is also possible to distil **4** at 151–153° (0.03–0.04 mm), but it is very tedious and there is decomposition.
(34) R. Clement, *Bull. Soc. Chim. Fr.*, 150 (1963).
(35) J. Kenner and F. Morton, *Chem. Ber.*, **72B**, 452 (1939).

(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.

(36) A. Blomquist, *J. Amer. Chem. Soc.*, **74**, 4203 (1952).

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

THOMAS A. WITTSTRUCK

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

Received November 7, 1972

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).