

Replacement of Hydroxyl *via* the Chloroformate. A Convenient Synthesis of Cholesteryl Iodide

DENNIS N. KEVILL AND FREDERICK L. WEITL¹

Department of Chemistry,
Northern Illinois University, DeKalb, Illinois 60115

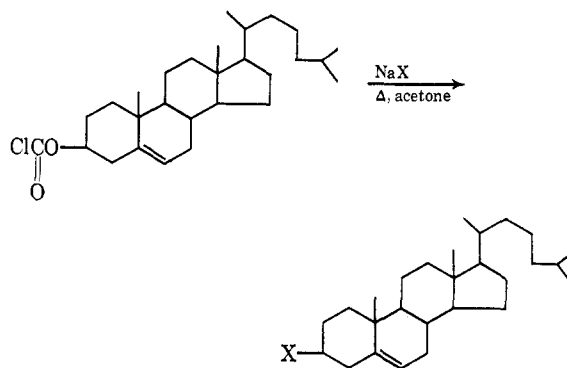
Received February 14, 1967

Cholesteryl iodide (3 β -iodocholest-5-ene) was first synthesized from cholesteryl *p*-toluenesulfonate by a two-step synthesis; methanolysis in the presence of potassium acetate gave 6 β -methoxy-3,5-cyclocholestane, which was subsequently treated with hydriodic acid.² It was later found that a direct conversion from the *p*-toluenesulfonate, or a similar sulfonic acid ester, could be carried out by warming at 60° with excess sodium iodide in acetone.³ More recent preparations have involved refluxing of diethyl ether containing cholesterol and aluminum iodide (prepared *in situ*)⁴ or reaction at 50–60° of cholesterol with methyl iodide and triphenyl phosphite methiodide.⁵ It is of interest that in a recent study,⁶ requiring very pure cholesteryl iodide, the original mode of synthesis was chosen.

We have found that the readily available cholesteryl chloroformate affords an excellent starting material for the synthesis of cholesteryl iodide. At slightly elevated temperatures, treatment of cholesteryl chloroformate with an excess of a concentrated solution of sodium iodide in acetone, followed by recrystallization, leads to reasonable yields of analytically pure cholesteryl iodide. Prolonged reaction times must be avoided since the cholesteryl iodide slowly undergoes further reaction, probably dehydrohalogenation,⁷ under the experimental conditions. The extent of conversion from the chloroformate can be conveniently monitored by evaporating small samples to dryness and following the disappearance of the carbonyl peak in the infrared spectrum.

Reaction is almost certainly initiated by a halide exchange to give the iodoformate, followed by a facile loss of carbon dioxide to give the corresponding iodide.⁸ Although this decomposition is probably unimolecular, halogenoformates can undergo bimolecular displacement in the presence of halide ion⁹ and the conversion of refluxing acetone solutions of cholesteryl chloroformate, in the presence of sodium chloride, could possibly have a bimolecular component; however, 3 β - and not 3 α -chlorocholest-5-ene was the isolated product. Owing to its greater resistance to dehydrohalogenation, the yield of cholesteryl chloride is rather better than that obtained for the corresponding iodide. Re-

action of a refluxing acetone solution of cholesteryl chloroformate with sodium bromide led to a mixture of cholesteryl bromide and cholesteryl chloride.



X = Cl, Br (bromide-chloride mixture resulted), I

Generalizations of this synthetic procedure could have application to other chloroformate esters and to other anionic reagents. One limitation, regarding the anionic reagent, is that the initial product formed from the replacement of chloride by the anion must in turn be capable of undergoing loss of carbon dioxide by either unimolecular decomposition or bimolecular anionic attack. For example, it was shown (by following the carbonyl shift in the infrared spectrum) that treatment of a refluxing acetone solution of cholesteryl chloroformate with an excess of sodium azide led fairly rapidly to cholesteryl azidoformate. However, even after maintaining the reaction mixture at refluxing acetone temperature for several days, the azidoformate remained as the only major product. The cholesteryl azidoformate was isolated and characterized.

Experimental Section¹⁰

Cholesteryl Iodide.—To 20.0 g (0.13 mole) of sodium iodide in 200 ml of acetone at 35.0° (constant-temperature bath) were added 5.0 g (0.0110 mole) of cholesteryl chloroformate and then sufficient diethyl ether (~20 ml) to make the solution homogeneous. Precipitation of sodium chloride was observed and, after 70 hr, the solution was evaporated to dryness under reduced pressure. The residue was dissolved using 100 ml of diethyl ether and 100 ml of water. The ether layer was washed with 50 ml of dilute sodium hydrogen sulfite solution and then with 25 ml of water, followed by evaporation to dryness. The residue was recrystallized from acetone to give 2.9 g of a white crystalline solid. A second recrystallization from acetone gave 2.7 g of cholesteryl iodide (49% yield), mp 107–108°, $[\alpha]_D^{25}$ -12.0° ; infrared spectrum includes λ_{\max} 14.88 μ (lit. mp 107–108°, $[\alpha]_D^{17}$ -12° , $[\alpha]_D$ -14° , λ_{\max} (in CS₂) 14.88 μ^{11}).

Anal. Calcd for C₂₇H₄₅I: C, 65.31; H, 9.14; I, 25.56. Found: C, 65.15; H, 9.27; I, 25.44.

Cholesteryl Chloride.—To 50 ml of acetone were added 5.0 g (0.0110 mole) of cholesteryl chloroformate and 10.0 g (0.17 mole) of sodium chloride and the mixture was refluxed for 250 hr. After cooling, the mixture was filtered and the precipitate was washed with 25 ml of diethyl ether. The ether was added to the mother liquor, which was then evaporated to dryness under reduced pressure, and the residue was recrystallized twice from acetone to give 3.0 g of white crystalline cholesteryl chloride (67% yield), mp 93–94°, $[\alpha]_D^{25}$ -27.5° ; infrared spectrum

(10) Melting points were determined with a Fisher-Johns block using a calibrated thermometer. Infrared spectra were obtained on a Beckman IR-8 using styrofoam disks. Optical rotations were obtained on an ETL-NPL automatic polarimeter using chloroform solutions. Microanalyses were by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

(11) D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J. Chem. Soc.*, 331 (1956).

(1) Support in the form of a graduate school fellowship is gratefully acknowledged.

(2) J. H. Benyon, I. M. Heilbron, and F. S. Spring, *J. Chem. Soc.*, 907 (1936).

(3) B. Helferich and E. Gunther, *Ber.*, **72B**, 338 (1939).

(4) J. Broome, B. R. Brown, and G. H. R. Summers, *J. Chem. Soc.*, 2071 (1957).

(5) S. R. Landauer and H. N. Rydon, *ibid.*, 2224 (1953).

(6) C. W. Shoppee, W. Connick, and R. H. Davies, *ibid.*, 4857 (1960).

(7) S. Winstein, D. Darwish, and H. J. Holness, *J. Am. Chem. Soc.*, **78**, 2915 (1956).

(8) Alkyl iodoformates are extremely unstable and no reference to the isolation of a compound of this type could be found within the literature.

(9) D. N. Kevill, G. H. Johnson, and W. W. Neubert, *Tetrahedron Letters*, 3727 (1966).

includes λ_{\max} 13.22 μ (lit. mp 97°, $[\alpha]^{20}_{\text{D}}$ -26°, λ_{\max} (in CS_2) 13.16 μ^{11}).

Anal. Calcd for $\text{C}_{27}\text{H}_{45}\text{Cl}$: C, 80.05; H, 11.20; Cl, 8.75. Found: C, 80.24; H, 11.19; Cl, 8.45.

Reaction with Sodium Bromide.—To 50 ml of acetone were added 5.0 g (0.0110 mole) of cholesteryl chloroformate and 10.0 g (0.097 mole) of sodium bromide and the mixture was refluxed for 150 hr. Work-up as for cholesteryl chloride, but with only one recrystallization from acetone, gave 4.0 g of white crystals, mp 96–99°; infrared spectrum includes λ_{\max} 13.23 and 14.22 μ (lit.¹¹ λ_{\max} (in CS_2) at 14.21 μ for cholesteryl bromide).

Anal. Calcd for 59% $\text{C}_{27}\text{H}_{45}\text{Br}$ and 41% $\text{C}_{27}\text{H}_{45}\text{Cl}$: C, 75.52; H, 10.56; Br + Cl, 13.93. Found: C, 75.35; H, 10.60; Br + Cl, 13.96.

Cholesteryl Azidoformate.—To 50 ml of acetone were added 5.0 g (0.0110 mole) of cholesteryl chloroformate and 5.0 g (0.077 mole) of sodium azide and the mixture was refluxed for 24 hr. During reaction the λ_{\max} for the carbonyl peak changed from 5.63 to 5.82 μ ; longer reflux times, prior to evaporation to dryness of small samples for infrared spectrum determination, led to no significant decrease in the intensity of the 5.82 μ peak. Work-up as for cholesteryl chloride gave 4.7 g of crude cholesteryl azidoformate (93% yield), mp 92–95°.

A 3.00-g portion of the crude product was chromatographed on a column consisting of (by weight) four parts of Florisil¹² and one part of Celite.¹³ The column was prepared using hexane and the azidoformate was eluted using a mixture of (by volume) three parts of benzene and seven parts of hexane. A 1.88-g fraction was found to be analytically pure cholesteryl azidoformate, mp 94.5–95.5°, $[\alpha]^{20}_{\text{D}}$ -34.0°; infrared spectrum includes λ_{\max} 4.59 (s), 4.63 (w), 4.70 (s),¹⁴ 5.82 (s, C=O), and 8.15 (s and broad, CO)¹⁵ μ .

Anal. Calcd for $\text{C}_{27}\text{H}_{43}\text{N}_3\text{O}_2$: C, 73.68; H, 9.96; N, 9.22. Found: C, 73.56; H, 9.84; N, 9.06.

Registry No.—Cholesteryl iodide, 2930-80-5; cholesteryl chloride, 910-31-6; cholesteryl bromide, 516-91-6; cholesteryl azidoformate, 13084-66-7.

(12) Florisil is a 60–100 mesh magnesium silicate supplied by the Floridin Co., Clarendon, Pa.

(13) Celite is a kieselguhr supplied by the Johns Manville International Corp., New York, N. Y.

(14) For a recent discussion of the adsorption bands due to the asymmetric stretching vibrations of the azide group in the infrared spectra of organic azides, including azidoformates, see Yu. N. Sheinker, L. B. Senyavina, and V. N. Zheltova, *Dokl. Akad. Nauk SSSR*, **160**, 1339 (1965).

(15) For cholesteryl chloroformate, the corresponding λ_{\max} is at 8.65 μ .

The Formation of 1,6-Bis(trichlorosilyl)hexane by the Chloroplatinic Acid Catalyzed Hydrosilylation of 1-Hexyne

ROBERT A. BENKESER, ROBERT F. CUNICO, STANLEY DUNNY, PAUL RONALD JONES, AND PRABHAKAR G. NERLEKAR

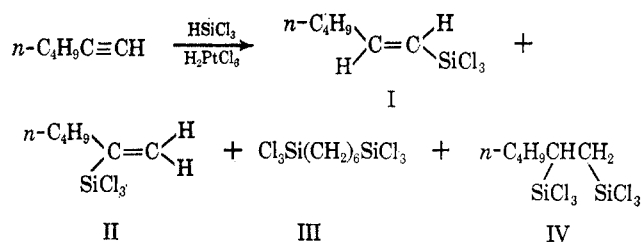
Department of Chemistry, Purdue University,
West Lafayette, Indiana 47907

Received December 8, 1966

A previous investigation from this laboratory¹ showed that the terminal adduct formed when trichlorosilane is added to monosubstituted acetylenes in the presence of chloroplatinic acid is almost exclusively the *trans* isomer arising from a *cis* addition.

Recently we had occasion to make a detailed study of the addition of trichlorosilane to 1-hexyne catalyzed by chloroplatinic acid. While we have substan-

tiated our earlier findings¹ regarding the stereochemistry of this reaction, we found that, by increasing the severity of the reaction conditions, the usual monoadduct products can be virtually eliminated in favor of diadducts.



Thus, a 1:1 mole ratio of trichlorosilane to 1-hexyne (experiment 2, Table I) and 1 ml of catalyst produced the monoadducts I and II in good yield as the sole products of the reaction. When a 2:1 mole ratio of trichlorosilane to 1-hexyne and a smaller amount of catalyst was used (experiment 1, Table I), monoadducts were still formed exclusively even though the reflux time was increased. Experiments 4–6 (Table I) show that an increase in catalyst concentration² seems to favor the formation of the diadducts III and IV. Experiment 3 (Table I) graphically illustrates the effect of reaction time. After 42 hr of reaction, only monoadducts had formed, but after 111 hr, considerable quantities of III and IV had been produced.

The structure of compound I was established by isolating it from the reaction mixture (vpc) and comparing its infrared spectrum with that of an authentic sample. We had synthesized authentic samples of both *cis*- and *trans*-1-trichlorosilyl-1-hexene for this purpose by adding trichlorosilane to 1-hexyne in the presence of benzoyl peroxide.³ The *trans* isomer could be easily distinguished from the *cis* by virtue of its strong infrared absorption at 10.1 μ .

The structure proof for II rests on its distinctive nmr spectrum. The vinylic protons of this compound possess a small coupling constant (total peak width only 6 cps at half-peak height). Any other arrangement of groups would give a larger coupling constant and a more complicated splitting pattern for the vinylic protons.

In order to establish the structure of compound III, a mixture of the diadducts was isolated from the reaction by distillation and then methylated with methylmagnesium iodide. The product, when analyzed by vpc, showed two peaks in the ratio of 5:95. The material responsible for the major peak was isolated and shown to be 1,6-bis(trimethylsilyl)hexane by its infrared spectrum which corresponded to that of an authentic sample prepared by coupling the di-Grignard reagent derived from 1,6-dibromohexane with trimethylchlorosilane.

(2) There are unassessed variables operative in such "platinum-catalyzed" reactions which markedly influence their rate. For instance, in some cases we found freshly prepared catalyst solutions ineffective in causing diadduct formation (monoadduct formation occurred readily), but, after standing 2 days, the same catalyst solution became quite effective in this regard. Hence, it is possible that the catalyst concentration effects noted here are in reality artifacts, being caused by certain other unknown and hence uncontrolled variables. For example, possibly trace amounts of catalyst inhibitors are present whose effects are being swamped out by the increased catalyst concentration.

(3) A reaction known to give a mixture of *cis* and *trans* isomers with a predominance of the former.¹

(1) R. A. Benkeser, M. L. Burrous, L. E. Nelson, and J. V. Swisher *J. Am. Chem. Soc.*, **83**, 4385 (1961).