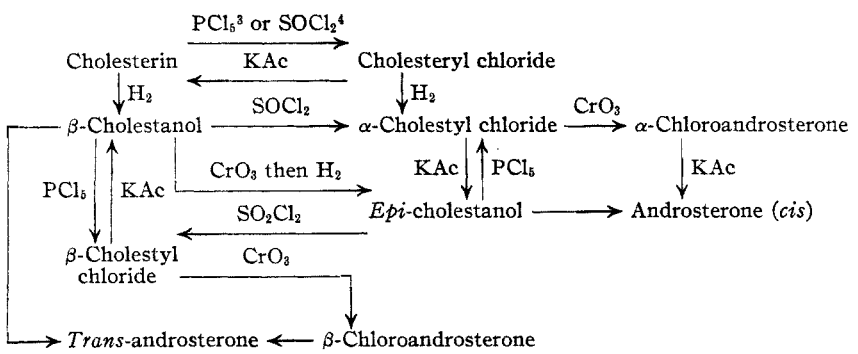
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE AND THE PARKE, DAVIS RESEARCH LABORATORIES OF DETROIT, MICHIGAN]

Androsterone and Related Sterols

BY RUSSELL E. MARKER, FRANK C. WHITMORE AND OLIVER KAMM

In the preparation of androsterone and other physiologically active compounds it is often necessary to change the —OH in the sterols from the *trans*- into the *cis*-form. This was shown by Ruzicka[1] and co-workers in the preparation of *trans* and *cis* androsterone in which they showed that the *cis*-form which is the natural androsterone (*epi*-OH) had about seven times the activity of the *trans* derivative. This conversion into the *epi*-form was brought about by first reducing cholesterin to beta-cholestanol. This was oxidized to beta-cholestanone which was then reduced by hydrogen in butyl ether at 70° according to the method of Vavon and Jakubowicz.[2] This reaction requires two catalytic reductions and an oxidation, which due to the small solubility of the compounds and the large amount of platinum oxide catalyst necessary, is very expensive and time-consuming. To overcome this, advantage is taken of the following scheme to produce the *epi*-form of the sterols in quantity. Also conversion of the *cis*-form back into the *trans*-form can be brought about by these reactions.



When cholesterol is treated with either phosphorus pentachloride or thionyl chloride cholesteryl chloride is formed. This on hydrolysis gives cholesterol with the —OH unchanged. However, if cholesteryl chloride is reduced with platinum oxide and hydrogen, α-cholestyl chloride is formed which on hydrolysis then gives the —OH in the *cis*-form. In the first case there was no Walden inversion in the final product, whereas in the reduced product a Walden inversion occurred in one of the steps.

Whereas when cholesterol is treated with either phosphorus pentachloride or thionyl chloride the same chloride is formed, if beta-cholestanol is treated with thionyl chloride it gives beta-cholestyl chloride and when treated with thionyl chloride alpha-cholestyl chloride. A Walden inversion occurs in one of the halogenations and not in the other. The same is true for *epi*-cholestanol. When this is treated with phosphorus pentachloride it gives alpha-cholestyl chloride but when treated with thionyl chloride it gives beta-cholestyl chloride.

In the hydrolysis of the various chlorides, alpha-cholestyl chloride gives *epi*-cholestanol while beta-cholestyl chloride gives beta-cholestanol.

When alpha-cholestyl chloride is oxidized it gives alpha-chloroandrosterone which apparently is identical to the chloride produced by Butenandt and Dannenbaum[5] by the reduction of an unsaturated chloro ketone isolated from urine. This chloro ketone on hydrolysis gives androsterone. α-Chlorocholanic acid is isolated as a by-product of this oxidation. Since this work was completed Ruzicka and co-workers[6] have prepared α-chloroandrosterone from *epi*-cholestanol.

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Experimental

Cholesteryl Chloride.—This was prepared both by the method of Mauthner[3] by the use of phosphorus pentachloride on cholesterol and by the method of Diels and Blumberg[4] by the action of thionyl chloride on cholesterol. Mixed melting points showed the two products to be identical, m. p. 95° (uncorr.).

(1) Ruzicka, *Helv. Chim. Acta*, **17**, 1395 (1934).
(2) Vavon and Jakubowicz, *Bull. soc. chim.*, [4] **53**, 584 (1933).
(3) Mauthner, *Monatsh.*, **15**, 87 (1894).
(4) Diels and Blumberg, *Ber.*, **44**, 2848 (1911).
(5) Butenandt and Dannenbaum, *Z. physiol. Chem.*, **229**, 192 (1934).
(6) Ruzicka and co-workers, *Helv. Chim. Acta*, **18**, 998 (1935).

α-Cholestyl Chloride.—(1) By reduction of cholesteryl chloride. Fifty grams of cholesteryl chloride was dissolved in 500 cc. of ether and 2 g. of platinum oxide and 10 cc. of glacial acetic acid added. The product was shaken for one hour with hydrogen at 45 pounds pressure. Although reduction was complete in fifteen minutes it was shaken for one hour. The product was crystallized from acetone; m. p. 112° (uncorr.).

(2) By the action of phosphorus pentachloride on *epi*-cholestanol. Five grams of *epi*-cholestanol, m. p. 185°, was added to 2.5 g. of phosphorus pentachloride and ground in a mortar until a paste was obtained. This was added to water and boiled for thirty minutes. The product was extracted with ether and crystallized twice from alcohol–ether, then three times from acetone; m. p. 112° (uncorr.). Mixing with α-cholestyl chloride prepared by the first method gave no depression in the melting point.

(3) By the action of thionyl chloride on beta-cholestanol. Five grams of beta-cholestanol was added to 5 g. of thionyl chloride. The product was let stand overnight, then poured into a 2% sodium hydroxide solution. It was extracted with ether, then crystallized twice from alcohol–ether and three times from acetone; m. p. 112° (uncorr.). Mixed with α-cholestyl chloride prepared by the two previous methods it showed no depression in the melting point, whereas when mixed with pure beta-cholestyl chloride it gave a depressed melting point of 75–80°; yield, 4 g.

Anal. Calcd. for $C_{27}H_{47}Cl$: C, 79.7; H, 11.7. Found: C, 79.9; H, 11.8.

Beta-Cholestyl Chloride.—(1) By the action of phosphorus pentachloride on beta-cholestanol. This was prepared according to the method described by Ruzicka and co-workers[1] giving a product melting at 102–103° (uncorr.) after crystallizing from acetone. Mixture with α-cholestyl chloride gave a depression to 78–83°.

2. By the action of thionyl chloride on *epi*-cholestanol. Three grams of *epi*-cholestanol was treated with 5 cc. of thionyl chloride and let stand at 40° overnight. This was shaken with 2% sodium hydroxide, extracted with ether, crystallized first from alcohol–ether, then from acetone; m. p. 102–103° (uncorr.). Mixture with beta-cholestyl chloride showed no depression, whereas mixture with α-cholestyl chloride gave a depression to 78–80°.

Anal. Calcd. for $C_{27}H_{47}Cl$: C, 79.7; H, 11.7. Found: C, 79.5; H, 11.9.

Hydrolysis of α-Cholestyl Chloride.—One gram of α-cholestyl chloride was added to 10 g. of potassium acetate in 20 cc. of valeric acid. The product was refluxed for thirty hours, then alkali added. The neutral product was extracted with ether, then boiled with alcoholic potassium hydroxide for two hours. The alcohol was distilled off and the product extracted with ether. This was treated with norit and the product crystallized from alcohol; m. p. 185–186°. Mixed with *epi*-cholestanol prepared by the method of Vavon and Jakubowicz,[2] it showed no depression in melting point. Mixture with beta-cholestanol gave a depression of the melting point to 131°.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.4; H, 12.5. Found: C, 83.6; H, 12.5.

Hydrolysis of Beta-Cholestyl Chloride.—Three grams of beta-cholestyl chloride was hydrolyzed as described for α-cholestyl chloride. The product was crystallized from alcohol four times; m. p. 139°. Mixture with beta-cholestanol showed no depression in melting point, whereas mixture with *epi*-cholestanol gave a melting point of 116°.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.4; H, 12.5. Found: C, 83.3; H, 12.7.

α-Chloroandrosterone.—A total of 700 g. of α-cholestyl chloride was oxidized in 100-g. quantities; one hundred grams of the chloride was added to 3.5 liters of glacial acetic acid and heated to 95°. A solution of 250 g. of chromic oxide in 175 cc. of water and 400 cc. of glacial acetic acid was slowly run in over a period of four hours. It was then heated an additional ten hours on a steam-bath with stirring. The acetic acid from the seven oxidations was evaporated *in vacuo* and the residue dissolved in water and ether. The ether extract was washed with water and then treated with a 10% sodium hydroxide solution by shaking. An insoluble sodium salt of α-chlorocholanic acid precipitated. This was extracted with ether and the ether distilled to one liter. Two liters of alcohol was added and the remainder of the ether distilled off. On cooling the unoxidized chloride precipitated out. This was filtered off, washed with cold alcohol and dried at 100°; 310 g. of unchanged chloride was obtained. This was again oxidized in 100-g. quantities, and the total alcoholic filtrates evaporated to dryness on a steam-bath. The residue was then steam distilled to remove volatile ketones. The neutral oil was dissolved in 400 cc. of alcohol, filtered and 44 g. of semicarbazide hydrochloride and 53 g. of sodium acetate added. The product was heated for thirty minutes then put in a refrigerator for two days. The crystalline material was filtered, washed with ether and boiled with water. It was filtered again and washed with cold alcohol then ether; m. p. of crude material 272–273° (dec.). This was crystallized several times from alcohol–chloroform; m. p. 279–281° (dec.); yield, 9.2 g. and 4 g. additional with a slightly lower decomposition point recovered from the alcohol.

Four grams of the semicarbazone was added to 200 cc. of 75% alcoholic solution of hydrochloric acid. This was refluxed for three hours, neutralized and evaporated to one-third. The product was extracted with ether, treated with norit and recrystallized from methyl alcohol and finally from hexane, m. p. 170–171° (uncorr.).

Anal. Calcd. for $C_{19}H_{29}OCl$: C, 73.9; H, 9.5. Found: C, 74.0; H, 9.7.

α-Chlorocholanic Acid.—The insoluble sodium salt from the oxidation of α-cholestyl chloride was filtered, washed with dilute alkali, extracted with ether, then treated with hydrochloric acid. The oily material was extracted with ether and crystallized from acetone; m. p. 174–175°.

Anal. Calcd. for $C_{24}H_{39}O_2Cl$: C, 73.0; H, 10.0. Found: C, 73.2; H, 10.1.

We wish to thank Dr. F. W. Breuer for the micro-analyses on the compounds reported in this paper.

Summary

A method of converting *cis*-OH sterols into the *trans*-OH form, and the *trans* back into the *cis*

has been established. α-Chlorocholestane has been oxidized to produce α-chloroandrosterone and α-chlorocholanic acid.

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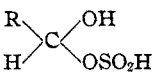
The Constitution of the Bisulfite Addition Compounds of Aldehydes and Ketones

BY WALTER M. LAUER AND CARL M. LANGKAMMERER

Since the discovery of the first aldehyde and ketone bisulfite addition compounds[1] many difficulties have been encountered in attempting to decide between the α-hydroxysulfite ester formula (I) and the α-hydroxysulfonic acid formula (II) for these compounds.



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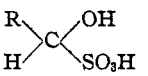
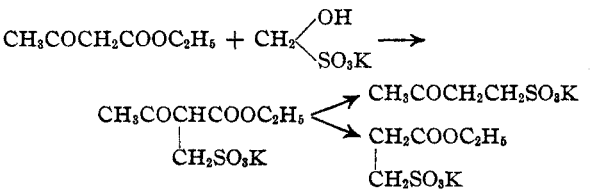


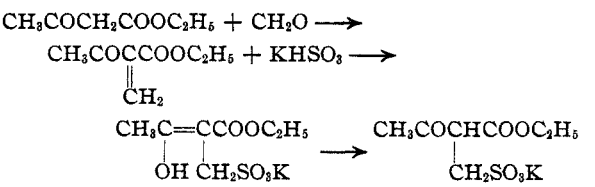
II

Each structure had its proponents[2] and the problem apparently was solved many years ago with the preparation of a "hydroxymethane sulfonic acid" which was not identical with formaldehyde bisulfite.[3] Since then additional "α-hydroxysulfonic acids" have been prepared;[4] they too differed from the corresponding bisulfite addition products. It is natural, therefore, that formation of the α-hydroxynitriles upon treatment of the bisulfite addition compounds with potassium cyanide came to be regarded as characteristic of the $-O-SO_2H$ group.[5] These views were current until the time of the exemplary investigations of Raschig and Prahl.[6] These investigators were able to show that the "hydroxymethane sulfonic acid" obtained by Müller on sulfonating methyl alcohol was actually symmetrical acetone disulfonic acid, formed by the sulfonation of acetone present in the methyl alcohol of that early date. The "hydroxymethane sulfonic acid" described by Glimm and by Reinking, Dehnel and Labhardt as the product of the action of sulfuric acid on methyl alcohol was demonstrated to be an isomer, methyl hydrogen sulfate. Likewise, the "α-hydroxyisopropyl sulfonic acid," $(CH_3)_2C(OH)SO_3H$, which Schroeter prepared by the hydrolysis of the diphenyl ester of dimethylmethionic acid, $(CH_3)_2C(SO_2OC_6H_5)_2$, and which was not identical with the acetone bisulfite addition compound, was shown to be the methyl ether of this sulfonic acid.

After thus removing much of the evidence which was damaging to the α-hydroxysulfonic acid structure (II), Raschig and Prahl submitted the reaction



as indicative of structure II, since the cleavage products were definitely sulfonic acids. However, these investigators[7] were not unmindful of the possibility of intermediate formation of methylene-acetoacetic ester with subsequent 1,4-addition of potassium bisulfite but their evidence led them to regard this as unlikely.



Backer and Mulder[8] a short time ago have introduced independent evidence for the hydroxysulfonic acid structure, for the compound $NH_2CH_2SO_3H$ (or $NH_3^+CH_2SO_3^-$) obtained by treating formaldehyde bisulfite with ammonia contains a carbon–sulfur linkage since treatment with nitrosyl chloride yields chloromethane sulfonic

(1) Redtenbacker, *Ann.*, **65**, 37–43 (1848); Tilley, *ibid.*, **67**, 105–15 (1848); Bertagnini, *ibid.*, **85**, 179–196, 268–288 (1853); Limpricht, *ibid.*, **93**, 238–242 (1855).

(2) Mendeleff, *ibid.*, **110**, 241 (1859); Schiff, *ibid.*, **210**, 123 (1881); Eibner, *ibid.*, **316**, 89 (1901).

(3) Müller, *Ber.*, **6**, 1031 (1873); Glimm, "Inaug.-Diss.," Freiburg, 1902; Reinking, Dehnel and Labhardt, *Ber.*, **38**, 1069 (1905).

(4) Schroeter, *Ann.*, **418**, 161–257 (1919); *Ber.*, **59**, 2341–2343 (1926); *ibid.*, **61**, 1616–1627 (1928).

(5) Knoevenagel, *ibid.*, **37**, 4059–4065 (1904).

(6) Raschig and Prahl, *Ber.*, **59**, 859–865 (1926); *Ann.*, **448**, 265–312 (1926); *Ber.*, **59**, 2025–2028 (1926); *ibid.*, **61**, 179–189 (1928).

(7) See also Schroeter, *Ber.*, **61**, 1621 (1928).

(8) Backer and Mulder, *Rec. trav. chim.*, **52**, 454–468 (1933); *ibid.*, **53**, 1120–1127 (1934).