[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

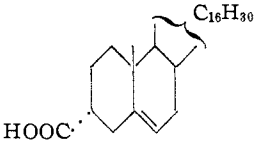
The Stereochemistry of the 3-Carboxy-, 3-Carboxymethyl- and 3-Acetylcholestanes and Δ^5-Cholestenes

BY ELIAS J. COREY AND RICHARD A. SNEEN

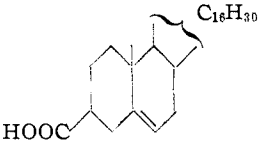
RECEIVED MAY 25, 1953

The carbonation product of cholesterylmagnesium chloride (I) has been shown to be 3β-carboxy-Δ^5-cholestene. I does not form a lactone in the presence of hydrogen chloride or *p*-toluenesulfonic acid in chloroform, indicating that the 3-carboxyl group is β-oriented. I has been converted to 3-acetylcholestane (VII), without epimerization at $C_{(3)}$ and thence to cholestane-3β-ol with perbenzoic acid, which also indicates β-orientation at $C_{(3)}$. Contrary to previous reports the carbonation product of *cholestanyl*magnesium chloride has the same configuration at $C_{(3)}$ as does the carbonation product of the *cholesteryl* Grignard reagent. Configurations at $C_{(3)}$ are also assigned to the epimeric 3-carboxymethyl-Δ^5-cholestenes and the first unambiguous evidence is presented for the occurrence of a nucleophilic displacement with inversion at $C_{(3)}$ in cholesteryl tosylate.

Because of its utility as a model compound for certain stereochemical studies in progress we were led to investigate the stereochemistry and reactions at $C_{(3)}$ of the cholesteryl carboxylic acid, m.p. 226–227°, (I) which is formed by carbonation of cholesterylmagnesium chloride. This substance, which was first prepared by Marker, *et al.*,[1] has recently been assigned the formula 3α-carboxy-Δ^5-cholestene (Iα) by Baker and Petersen[2] on the basis of the relationships indicated in Fig. 1 and the



Iα



Iβ

assumption that the reaction of cholesteryl tosylate with ethyl sodiomalonate proceeds *via* the cyclocholesteryl cation with over-all retention of configuration at $C_{(3)}$.

This paper reports the chemical evidence which leads us to formulate I as the alternative structure, 3β-carboxy-Δ^5-cholestene.

Another point of interest here is the stereochemistry of the carbonation product (II) of *cholestanyl*magnesium chloride. Squire[4] has recently reported the remarkable finding that the orientation of the carboxyl function in II *differs* from that in the *cholesteryl*magnesium chloride carbonation product (I) and, in line with the work of Baker, has assigned the β-orientation of carboxyl to the former.

It has been suggested[2] that this reported difference in the stereochemical course of the carbonation of *cholesteryl* and *cholestanyl* Grignard reagents might be due to participation of the 5,6-double bond in the cholesteryl system. The occurrence of such participation and the existence of an intermediate cyclocholesteryl anion, apart from being unexpected, would be of considerable theoretical interest and, consequently, we have made a careful examination of the stereochemistry of II. Here

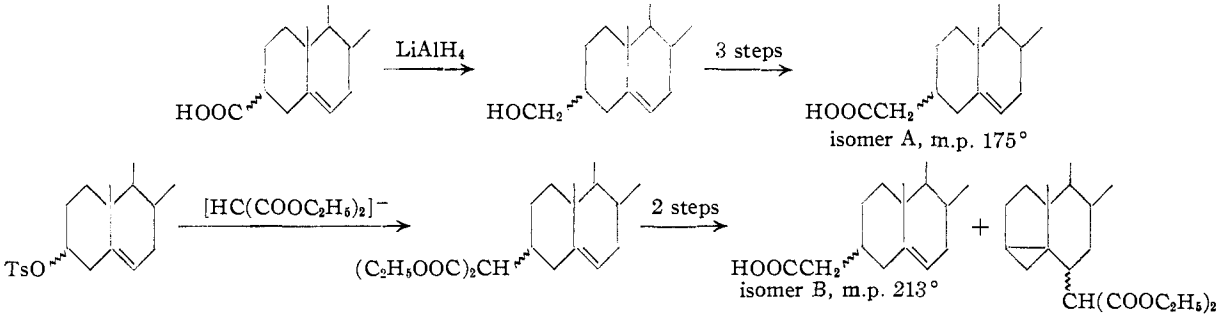


Fig. 1.

Since this assumption finds no real justification, the assignment of α-orientation to the carboxyl group in I cannot be regarded as necessarily valid.[3] again our findings have led to conclusions which are contrary to those previously reported.[4]

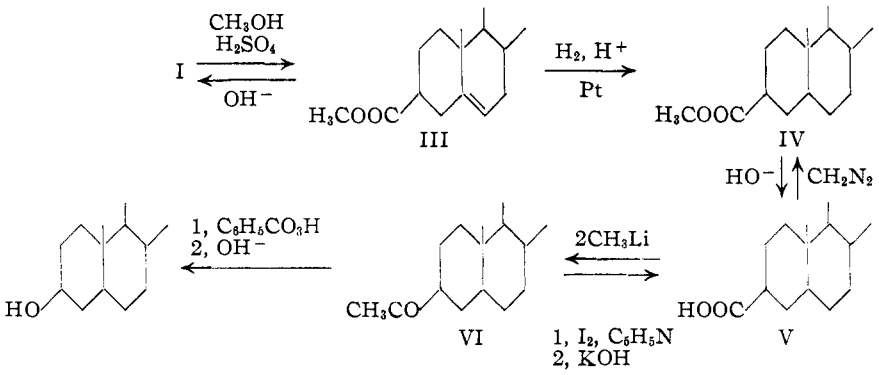
The Carbonation Product of the Cholesteryl Grignard Reagent.—We assign structure Iβ to the acid I derived from the cholesteryl Grignard reagent on the basis of two independent pieces of evidence. The more compelling evidence for the β-orientation of carboxyl in I has been obtained in the following way. Catalytic reduction of the pure methyl ester (III) of I in acidic medium afforded the corresponding 3-carbomethoxycholestane (IV) which was converted to the correspond-

(1) R. E. Marker, T. S. Oakwood and H. M. Crooks, THIS JOURNAL, **58**, 481 (1936).

(2) R. H. Baker and Q. R. Petersen, *ibid.*, **73**, 4080 (1951).

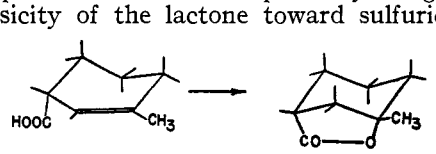
(3) The non-polar nature of the solvent (xylene) used for the cholesteryl tosylate–ethyl sodiomalonate reaction should be more favorable to direct displacement (SN2 or SN2') of tosylate by malonate ion than to prior ionization of the tosylate. Hence, direct displacement, which is usually not observed in reactions of cholesteryl tosylate, might be operative here. Furthermore, in reactions involving the cyclocholesteryl cation attack by the nucleophilic species is invariably much faster at $C_{(6)}$ than at $C_{(3)}$ [S. Winstein and Rowland Adams, *ibid.*, **70**, 838 (1948)], and under conditions such that the reaction at $C_{(6)}$ is irreversible, only the product of attack at $C_{(6)}$ is isolated [W. Stoll, *Z. physiol. Chem.*, **207**, 147 (1932); T. Wagner-Jauregg and L. Werner, *ibid.*, **213**, 119 (1932)]. The isolation of both the product of attack at $C_{(3)}$ and at $C_{(6)}$ (the former predominating) from the irreversible cholesteryl tosylate–ethyl sodiomalonate reaction [E. Kaiser and J. J. Svarz, THIS JOURNAL, **67**, 1309 (1945); **69**, 847 (1947)] is therefore an indication that the $C_{(3)}$ substituted product is not formed from the cyclocholesteryl cation.

(4) E. N. Squire, *ibid.*, **73**, 5768 (1951).



ing 3-acetylcholestane (VI) by hydrolysis and subsequent treatment of the acid (V) with methyllithium. That no epimerization at $C_{(3)}$ hadoccur red during reactions where epimerization might conceivably take place was demonstrated by carrying out the reverse transformations which are indicated. The possibility of epimerization at $C_{(3)}$ during the reduction of III to IV can be ruled out since both of the esters III and IV are stable to prolonged refluxing with sulfuric acid or sodium methoxide and since only a short time (*ca.* 30 minutes) is required for complete reduction. Reaction of the ketone VI with perbenzoic acid in ether followed by gentle hydrolysis yielded cholestane-3β-ol and no detectable amount of cholestane-3α-ol. In view of the fact that the peracid–ketone reaction has been shown to take place with retention of configuration of the migrating group,[5,6] the acids I and V, the esters III and IV and the ketone VI must all have a β-oriented 3-substituent. In addition the 3-acetyl-Δ^5-cholestene prepared by Baker and Squire[7] must be the 3β-epimer.

We have also determined that *I does not form a lactone* upon treatment with hydrogen chloride or *p*-toluenesulfonic acid in chloroform. Experimentally, this statement is based on the fact that no lactone carbonyl absorption could be detected by infrared analysis of the total reaction mixture and the fact that no lactone could be isolated upon basic extraction of the reaction mixture in the cold to remove unreacted acid. Boorman and Linstead[8] have reported that 3-methyl-Δ^2-cyclohexenecarboxylic acid (VII) can be converted readily to its lactone by boiling with water or by treatment with 60% sulfuric acid at room temperature. Under the first set of conditions the equilibrium mixture of lactone and acid consists of *ca.* 33% lactone and under the second set of conditions over 90% of lactone is present, the difference probably being due to the basicity of the lactone toward sulfuric acid.



VII

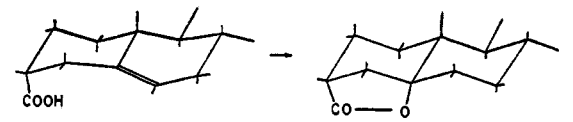
(5) R. B. Turner, THIS JOURNAL, **72**, 878 (1950).

(6) T. F. Gallagher and T. H. Kritchevsky, *ibid.*, **72**, 882 (1950).

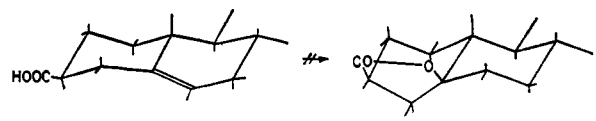
(7) R. H. Baker and E. N. Squire, *ibid.*, **70**, 1487 (1948). For other Δ^5-allosteroid derivatives containing 3β-substituents see *ibid.*, **70**, 4134 (1948); **71**, 1383 (1949). The stigmastane and Δ^5-sitostene carboxylic acids described by Squire [*ibid.*, **75**, 493 (1953)] must also possess 3β-oriented carboxyl groups.

(8) E. J. Boorman and R. P. Linstead, *J. Chem. Soc.*, 258 (1953).

The position of the lactone–acid equilibrium with 3α-carboxy-Δ^5-cholestene (Iα) under a given set of conditions should approximate closely that with the model compound VII. In chloroform containing hydrogen chloride Iα should be almost completely lactonized. In the case of Iβ lactonization should occur to a much smaller extent or not at all since ring A must assume the unfavorable boat conformation in the lactone as shown. Thus, the non-lactonization of I is a strong argument in favor of the Iβ structure for this substance.



Iα



Iβ

The Carbonation Product of the Cholestanyl Grignard Reagent.—The acid II obtained by the carbonation of the *cholestanyl* Grignard reagent has as reported by Squire,[4] m.p. 206–207°, but is not homogeneous. However, this acid and the methyl ester, m.p. 67–68°, which is made from the acid using diazomethane, are in reality only slightly impure samples of the acid V, m.p. 209–210°, and the methyl ester IV, m.p. 71.5–72.5°, which are derived from Iβ, the carbonation product of the *cholesteryl* Grignard reagent. This is indicated by mixture melting points, optical rotations and infrared spectra (see Experimental). Furthermore, chromatography of the methyl ester, m.p. 67–68°, affords in high yield material that is identical in all respects with pure samples of the ester V, m.p. 71–72°, obtained by hydrogenation of III.

Since we have obtained exactly the same results from three separate carbonation experiments with the cholestanyl Grignard reagent we are forced to conclude that the original observations of Squire are in error and that the predominating product from *both the cholesteryl and cholestanyl* Grignard reagents is that in which the carboxyl is *β-oriented.* From this finding it is apparent that the Δ^5-double bond does not significantly alter the stereochemical course of the carbonation reaction. We can provide no satisfactory explanation for the results reported by Squire.

The 3-Carboxymethyl-Δ^5-cholestenes.—It is now clear that the 3-carboxymethyl-Δ^5-cholestene prepared from the acid Iβ is the β-epimer and that the material prepared from cholesteryl tosylate (Fig. 1) is the α-epimer. The production of a 3α-substituted-Δ^5-cholestene in the cholesteryl tosylate–ethyl sodiomalonate reaction indicates that substitution at $C_{(3)}$ has taken place with inversion of

configuration and presumably by an S_N2 process. To our knowledge this is the first unambiguous example of an ionic replacement reaction at $C_{(3)}$ in cholesteryl tosylate which proceeds with Walden inversion and not over-all retention of configuration.[9]

At this point it is not possible to say whether the $C_{(6)}$ substituted cyclocholestane which is also formed in the cholesteryl tosylate–ethyl sodiomalonate reaction is formed *via* the cyclocholesteryl cation or by an S_N2'-type process. The latter possibility deserves serious consideration, however, in view of the demonstrated tendency of the ethyl malonate ion to take part in S_N2' displacements.[10] It is noteworthy that in the reaction of cholesteryl tosylate with thiourea there are indications that part of the reaction (which gives a single product, the 3β-isothiuronium salt) may proceed by a path involving initial S_N2'-type attack by thiourea.[11]

Experimental[12]

3β-Carbomethoxy-Δ⁵-cholestene (III).—3β-Carboxy-Δ⁵-cholestene (Iβ) was prepared from cholesterylmagnesium chloride[1,8] by carbonation with gaseous carbon dioxide at room temperature for 10 hours. The pure acid, m.p. 226–227° (melt opaque), $[\alpha]_D$ −10° (*c* 0.65, chloroform), was obtained by four recrystallizations of the crude acid from benzene. The acid (5.00 g.) was esterified by refluxing with methanol (160 ml.) containing concentrated sulfuric acid (2 ml.) for 44 hours. Dilution of the reaction mixture and recrystallization of the resulting solid from methanol afforded 4.70 g. of pure ester, m.p. 101.5–102.0°, $[\alpha]^{25}D$ −14.6° (*c* 1.43, chloroform) (lit.[8] m.p. 101.5°, $[\alpha]^{27}D$ −16°). The same high yield of pure ester was obtained when crude acid, m.p. 218–222°, was used in the esterification. The pure ester was unchanged after *ca.* 100 hours refluxing in 1 *N* methanolic sulfuric or in methanol containing sodium methoxide (12 equivalents) and a little methyl formate (to prevent hydrolysis of the steroid ester).

The ester (2.50 g.) was hydrolyzed by boiling for 4 hours with 100 ml. of methanol containing 3.5 g. of potassium hydroxide. Acidification of the hot solution and dilution with water afforded 2.38 g. of essentially pure acid, which after recrystallization from benzene–cyclohexane amounted to 2.17 g., m.p. and mixture m.p. with the parent acid, 226–227°.

3β-Carbomethoxycholestane (IV).—The unsaturated ester III (2.0 g.) dissolved in 200 ml. of ether and 10 ml. of glacial acetic acid was shaken with hydrogen (2.3 atmospheres) in the presence of 0.40 g. of Adams platinum catalyst for 30 minutes. Three recrystallizations of the product from ether–methanol–water furnished 1.81 g. of pure IV as colorless needles, m.p. 71.5–72.5°, $[\alpha]^{26}D$ +29.7° (*c* 2.53, chloroform) (lit.[4] m.p. 71.5–73°, $[\alpha]^{25}D$ +30.1°). Hydrolysis of the methyl ester with methanolic potassium hydroxide yielded 3β-carboxycholestane, m.p. 210–211°, $[\alpha]^{25}D$ +28.8 ± 1.7° (*c* 1.70, chloroform) (lit.[4] m.p. 209–211°, $[\alpha]^{26}D$ +40.5° (*c* 0.59, chloroform).[13]

The same ester was prepared using diazomethane from a sample of 3β-carboxycholestane which had been made by carbonation of cholestanylmagnesium chloride and which had m.p. 206–207° (mixture melting point with the acid described above, 207–209°). Two recrystallizations of the methyl ester so produced from ether–methanol afforded 82% of still impure 3β-carbomethoxycholestane as long colorless needles, m.p. 67–68°, undepressed upon admixture with the methyl ester, m.p. 71.5–72.5°, obtained by reduction of 3β-carbomethoxy-Δ⁵-cholestene and not changed by two more recrystallizations. The rotation of this material, $[\alpha]^{25}D$ +25.8° (*c* 2.36, chloroform), differed only slightly from that of the pure material of m.p. 71.5–72.5° described above. Furthermore, the infrared spectra of the two materials taken in carbon disulfide or carbon tetrachloride were identical. Chromatography of a 0.350-g. sample of material m.p. 67–68° on a 10 × 1 cm. column of alumina afforded 0.288 g. of crystalline solid in the main fraction (eluted with cyclohexane–benzene, 10:1). Recrystallization yielded 0.26 g. of colorless needles, m.p. 72–72.5°, $[\alpha]^{25}D$ +30.0° (*c* 1.46, chloroform), no depression upon admixture with a sample of the pure material described above. Hydrolysis of this ester produced 3β-carboxycholestane, m.p. 210–211° alone or admixed with the material m.p. 210–211° described above. The ester was not changed by long refluxing (*ca.* 100 hours) with either sodium methoxide or sulfuric acid in methanol.

3β-Acetylcholestane (VI).—To 1.0 g. of pure 3β-carboxycholestane, m.p. 210–211°, dissolved in 90 ml. of ether was added 10 ml. of 0.5 *M* methyllithium in ether. The ethereal solution was heated to reflux for 15 minutes, cooled, washed with two 100-ml. portions of ice-water, dried over calcium chloride and evaporated. Recrystallization of the residue afforded 947 mg. of crude ketone m.p. 103–108° which was contaminated with a small amount of dimethylcholestanylcarbinol. The mixture was easily separated by chromatography on a 16 × 1.5 cm. column of alumina. The ketone was eluted with cyclohexane–benzene (9:1), wt. 845 mg. and the carbinol was eluted with benzene, wt. 83 mg. Recrystallization of the combined ketone fractions twice from ethanol–water gave 742 mg. of pure VI, m.p. 110–111°, $[\alpha]^{25}D$ +29.5° (*c* 1.53, chloroform), carbonyl absorption at 5.85 μ (1712 cm.$^{-1}$).

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.16; H, 12.12.

Three recrystallizations of the carbinol fraction from ethanol–water gave pure carbinol, 44 mg., m.p. 145–146°, $[\alpha]^{25}D$ +22.5° (*c* 1.55, chloroform). The infrared spectrum of this material showed hydroxyl absorption and no trace of carbonyl absorption.

Anal. Calcd. for $C_{30}H_{54}O$: C, 83.65; H, 12.64. Found: C, 83.62; H, 12.41.

Reaction of 3β-Acetylcholestane with Perbenzoic Acid.—A solution of 75 mg. of the ketone VI and 2 ml. of 0.25 *M* perbenzoic acid in ether was allowed to stand at 25–28° for 94 hours, treated with an additional 2 ml. of 0.25 *M* ethereal perbenzoic acid and allowed to stand for another 40 hours. The ether was evaporated and the residue refluxed for 1 hour with 10 ml. of 2 *N* potassium hydroxide in 95% ethanol. Dilution of the hot solution with water furnished 64 mg. of colorless solid which was chromatographed on a 0.7 × 10 cm. column of alumina. Fractions 2 and 3, which were eluted with cyclohexane–benzene (10:1), yielded after recrystallization 25.6 mg. of starting material (VII), m.p. and mixed m.p. 110–111°. Fraction 6 which was eluted with ether furnished after recrystallization 23 mg. of cholestane-3β-ol, m.p. 141–142°, undepressed upon admixture with an authentic sample. Admixture with dimethylcholesterylcarbinol gave material m.p. 119–126°. The infrared spectrum of this material was also identical with that of authentic cholestane-3β-ol. No cholestane-3α-ol could be detected in fractions 4 and 5 which consisted of only a few mg. of oil.

Conversion of 3β-Acetylcholestane to 3β-Carboxycholestane.—The procedure described previously[7] was followed using 200 mg. of 3β-acetylcholestane and 100 mg. of iodine in 4 ml. of dry pyridine to form the pyridinium salt and cleaving the salt with dilute ethanolic potassium hydroxide. The reaction mixture furnished after recrystallization from cyclohexane 79 mg. of 3β-carboxycholestane, m.p. 207–209°, undepressed upon admixture with an authentic sample. This acid was converted to the methyl ester with

(9) For an example of inversion during ionic displacement at $C_{(3)}$ in 7-ketocholesteryl tosylate see R. E. Marker, O. Kamm, G. H. Fleming, A. H. Popkin and E. L. Wittle, THIS JOURNAL, **59**, 619 (1937). We are at present investigating other possible cases of inversion at $C_{(3)}$ with cholesteryl tosylate.

The product of the addition of ethyl sodiomalonate to 3,5-cholestadiene-7-one which has been reported recently [J. W. Ralls, *ibid.*, **75**, 2123 (1953)] to be ethyl 7-keto-3β-cholesterylmalonate on the basis of its transformation to Kaiser and Svarz's (ref. 3) 3-cholesterylmalonic acid, m.p. 203°, must now be formulated as the 3α-substituted compound.

(10) R. E. Kepner, S. Winstein and W. G. Young, *ibid.*, **71**, 115 (1949).

(11) R. G. Pearson, L. C. King and S. H. Langer, *ibid.*, **73**, 4149 (1951).

(12) We are indebted to Mr. Joseph Nemeth for the microanalyses and to Miss Helen Miklas and Mrs. Rosemary Hill for the infrared spectra reported herein.

(13) The rotation which we report is the average value obtained on three different samples of pure 3β-carboxycholestane. The higher rotation reported previously[4] seems to be in error.

diazomethane, 54 mg. (after chromatography) m.p. 71–72° undepressed upon admixture with an authentic sample of 3β-carbomethoxycholestane.

Attempted Lactonization of 3β-Carboxy-Δ⁵-cholestene.—A solution of 750 mg. of pure 3β-carboxy-Δ⁵-cholestene (Iβ) in 250 ml. of alcohol-free chloroform was saturated with hydrogen chloride at 20° and allowed to stand at *ca.* 25°. Three runs were made using reaction times of 30 minutes, 5 and 70 hours. The total mixture was isolated by removal of the solvent and hydrogen chloride under reduced pressure. The infrared spectra of these materials (in chloroform or nujol mull) showed no trace of carbonyl absorption at 5.0–5.8 μ indicating the complete absence of lactone. When a solution of the total reaction product in 200 ml. of ether was washed quickly with two 1-l. portions of 0.5 *N* sodium hydroxide solution (10°) and then evaporated only a few mg. of yellow oil could be obtained. Upon acidification and extraction with ether the basic wash solution afforded the starting acid Iβ in almost pure condition. After one recrystallization from benzene pure acid 610–630 mg. (two runs), m.p. 224–225.5, was obtained.

The same results were obtained in a run using *p*-toluenesulfonic acid in chloroform.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF KITASATO INSTITUTE]

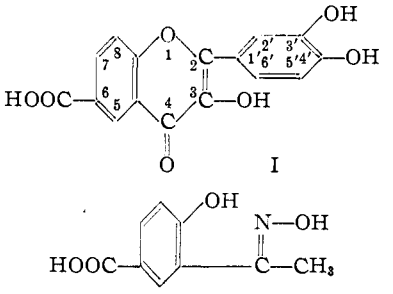
Preparation of 3′,4′-Dihydroxy-6-carboxyflavonol

BY TOYOYUKI NAGANO AND KONOMU MATSUMURA

RECEIVED JUNE 1, 1953

Using *p*-acetoxybenzoic acid as starting material, 3′,4′-dihydroxy-6-carboxy-flavonol was prepared, *via* 2-hydroxy-5-carboxyacetophenone, 3,4-methylenedioxy-2′-hydroxy-5′-carboxychalcone and 3′,4′-methylenedioxy-6-carboxyflavonol.

The preparation of certain derivatives of flavone and flavanone, which would contain a carboxy group in addition to the phenol groups present and which have not been found as yet in natural products, was undertaken with the thought that such compounds might possess "vitamin P"-like activity, as has been shown by rutin and hesperidin. Also of interest would be the expected increase in the solubility of these compounds in weak alkali. Details of the preparation of 3′,4′-dihydroxy-6-carboxyflavanol (I) are reported in this paper.



I

II

The Fries reaction with 4-acetoxybenzoic acid gave 2-hydroxy-5-carboxyacetophenone in 50% yield. The substituted chalcone was obtained on condensation of the latter compound with piperonal. By the reaction of the chalcone with hydrodrogen peroxide in methanolic sodium hydroxide, 3′,4′-methylenedioxy-6-carboxyflavonol was prepared. The removal of the methylene at the 3′,4′-position was effected by aluminum chloride in nitrobenzene.

The oxime II of 2-hydroxy-5-carboxyacetophenone, on Beckmann rearrangement with sulfuric acid, produced a mixture of 3-acetamino-4-hydroxybenzoic acid and 2-methyl-5-carboxybenzoxazole. Thus the configuration of the oxime is *cis* with respect to the methyl, assuming that spacial isomerization did not take place during the treatment.

Experimental

2-Hydroxy-5-carboxyacetophenone.—A solution of *p*-acetoxybenzoic acid (10 g., 0.056 mole) and aluminum chloride (15 g., 0.112 mole) in nitrobenzene (100 ml.) was heated gradually in an oil-bath.

After about one hour heating at 150°, the mixture turned to a gel and heating was continued for another three hours at that temperature. After the solution was cooled, ice-water was added, the nitrobenzene removed by steam distillation and the solution was filtered hot to remove a small amount of a resinous solid and acidified strongly with concentrated hydrochloric acid. The precipitated crystals were collected after standing overnight, yield 5.2 g., m.p. 233–234°. On crystallization from ethanol, colorless plates melting at 241–242° were formed; on further purification, the m.p. remained unchanged.

Chattaway and Calvet[1] reported the m.p. of this compound as 246–247° and that of its phenylhydrazone as 286°. It was almost insoluble in hot water, and an alcoholic solution gave a deep red color with ferric chloride.

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.44. Found: C, 60.01; H, 4.36.

The resinous solid (5 g.) which was deposited at the end of steam distillation yielded 1.2 g. of 2-hydroxy-5-carboxyacetophenone of inferior quality (m.p. 210–234°). The oxime, m.p. 273° dec., formed colorless prisms on crystallization from ethanol and gave a purple color with ferric chloride in ethanol.

Anal. Calcd. for $C_9H_9NO_4$: N, 7.18. Found: N, 7.22.

The phenylhydrazone, m.p. 282° dec., was obtained as colorless prisms.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: N, 10.37. Found: N, 10.50.

3,4-Methylenedioxy-2′-hydroxy-5′-carboxychalcone.—A mixture of 2-hydroxy-5-carboxyacetophenone (1.8 g., 0.01 mole), piperonal (1.5 g., 0.01 mole), methanol (15 ml.) and aqueous sodium hydroxide (2 g., 0.05 mole, in 5 ml. of water) was refluxed gently for six hours. The cooled reaction fluid was acidified with dilute hydrochloric acid, and the precipitated yellow solid was filtered and washed with water and ethanol, yield 2.7 g. (86.5%), m.p. 250–253°.

Upon two recrystallizations from ethanol, it formed yellow needles, m.p. 261–263°, which were shown to be chromatographically pure and gave a reddish-brown color with ferric chloride in ethanol and were almost insoluble in ether or benzene; they were only very slightly soluble in hot water, but soluble in aqueous sodium carbonate which was neutral to phenolphthalein.

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.38; H, 3.85. Found: C, 65.37; H, 4.01.

3′,4′-Methylenedioxy-6-carboxyflavonol.—Oyamada's[2] method was used for this preparation. The chalcone (1 g.,

(1) F. D. Chattaway and F. Calvet, *J. Chem. Soc.*, 692 (1927).

(2) T. Oyamada, *J. Chem. Soc. Japan*, **55**, 1256 (1934).