bright yellow needles melting largely at 230–232° but giving a clear melt at 233.3°.

Anal.[25] Calcd. for $C_{20}H_{12}O$: C, 89.53; H, 4.51. Found: C, 89.65; H, 4.75.

Summary

Δ^4-Tetrahydrophthalic anhydride reacts with arylmagnesium or arylzinc halides to give unsaturated keto acids in reasonably good yield, and the hexahydride when condensed with benzene in the presence of aluminum chloride affords 2-benzoylcyclohexane-1-carboxylic acid in excellent yield. The use of hydro derivatives of phthalic anhydride in syntheses in the anthracene and 1,2-benzanthracene series expands the possibilities for synthetic operations, particularly since the hydro derivatives of the intermediate anthrones are stable in the ketonic form and hence amenable to additions, or to reduction to the carbinols. Thus a new synthesis of 4,10-ace-1,2-benzanthracene has been worked out starting with the condensation of α-naphthylzinc chloride and Δ^4-tetrahydrophthalic anhydride. The hydrocarbon obtained has a higher melting point than products prepared by two earlier syntheses and shown to possess considerable carcinogenic potency.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. CXXXVI. Sapogenins. LVII. The Structure of the Side-Chain of Chlorogenin

BY RUSSELL E. MARKER, D. L. TURNER AND EMERSON L. WITTBECKER

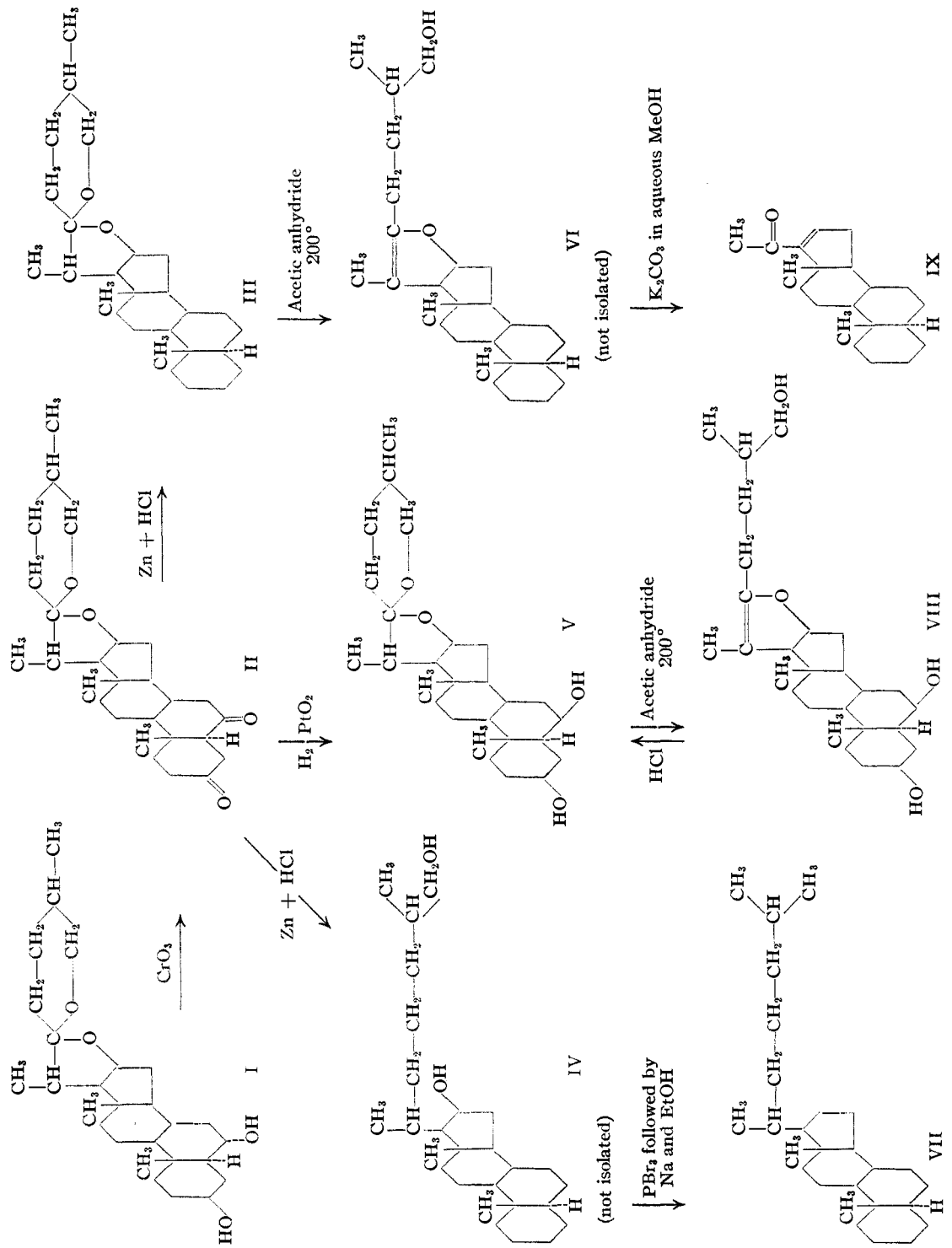
Diosgenin was shown recently to have the carbon skeleton of cholesterol by converting it to a mixture of cholesterol and 5-cholestene.[1] The method employed to effect this conversion has now been extended to chlorogenone (II). The reduction of chlorogenone by the Clemmensen method followed by halogenation and reduction gave cholestane (VII). This provides additional proof that chlorogenin is similar to the other sapogenins in its carbon skeleton and that it has the same steric configuration as cholestane. Conditions have been found by Marker and Rohrmann[2] which enable the nuclear carbonyl groups of chlorogenone to be removed by reduction with zinc and hydrochloric acid without alteration of the side-chain. The resulting desoxychlorogenin (III) was identical with desoxytigogenin. That the side-chain in this substance is intact has been shown by the conversion of desoxychlorogenin (III) to 16-*allo*-pregnen-20-one (IX) using the method of Marker and Rohrmann.[3] This involves the oxidation of pseudo-desoxychlorogenin (VI) with chromic anhydride and hydrolysis of the oxidation product. The 16-*allo*-pregnen-20-one (IX) was reduced to *allo*-pregnan-20-one (XIII) which was identified by comparison with a sample obtained from *allo*-pregnan-3,20-dione.[4]

A substance obtained by the catalytic reduction of chlorogenone in neutral medium and designated β-chlorogenin (V) was assumed to differ from chlorogenin only in the configuration of the C-6 hydroxyl group.[5] That this is indeed the case has now been shown by the preparation of pseudo-β-chlorogenin (VIII) and by the oxidation of its acetate to a substance which on hydrolysis gives 16-*allo*-pregnen-3,6-diol-20-one (XI). When pseudo-β-chlorogenin was oxidized without prior acetylation and the product was hydrolyzed, 16-*allo*-pregnen-3,6,20-trione (X) was obtained. This is identical with the substance previously described.[6] The other hydrolysis product, α-methylglutaric acid (XII), was also isolated.[7] This indicates that the side-chain of pseudo-β-chlorogenin is identical with that assigned to the other pseudosapogenins.[7,8]

The catalytic reduction of 16-*allo*-pregnen-3,6-diol-20-one (XI) and of 16-*allo*-pregnen-3,6,20-trione (X) led to the same product in each case, *allo*-pregnan-3(β),6(β),20(β)-triol (XIV). The behavior of 16-*allo*-pregnen-3,6,20-trione on reduction is thus similar to that of chlorogenone.[5]

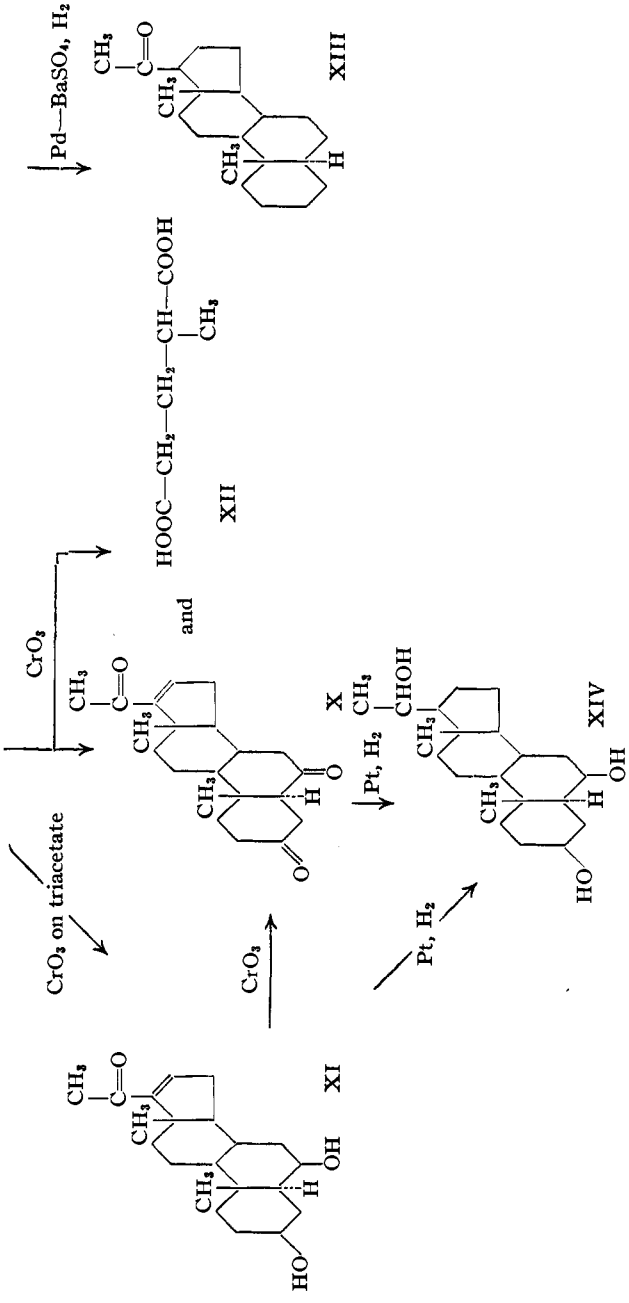
We wish to thank Parke, Davis and Company for their generous help.

(1) Marker and Turner, THIS JOURNAL, **63**, 767 (1941).
(2) Marker and Rohrmann, *ibid.*, **61**, 946 (1939).
(3) Marker and Rohrmann, *ibid.*, **62**, 518 (1940).
(4) Marker and Lawson, *ibid.*, **61**, 852 (1939).
(5) Marker, Jones and Turner, *ibid.*, **62**, 2537 (1940).
(6) Marker, Jones, Turner and Rohrmann, *ibid.*, **62**, 3006 (1940).
(7) *Cf.* Marker, *et al.*, *ibid.*, **63**, 779 (1941).
(8) Marker, *et al.*, *ibid.*, **63**, 774 (1941).



Experimental

Cholestane from Chlorogenin.—To a boiling solution of 5 g. of chlorogenone in 500 cc. of ethanol containing 150 g. of amalgamated zinc was added 150 cc. of concentrated hydrochloric acid over a period of three hours. Water was added and the product was extracted with ether. The combined ethereal solution from three runs was evaporated, the residue was dissolved in 20 cc. of pyridine and 20 g. of succinic anhydride was added. This mixture was heated for one hour on a steam-bath. Water and ether were added and the pyridine was removed by washing the ethereal solution with dilute hydrochloric acid. The solution was then shaken with potassium carbonate solution to



remove the succinic esters. The aqueous solution was acidified and extracted with ether; the solvent was removed and the residue was hydrolyzed with alcoholic potassium hydroxide. The neutral carbinol fraction thus obtained could not be crystallized. The solvent was removed and the residue was heated on a steam-bath for one hour with 15 cc. of phosphorus tribromide. The mixture was poured into water and extracted with ether. The ethereal extract was washed with water and sodium bicarbonate solution and then with water. The solvent was removed and the residue was dissolved in 300 cc. of absolute ethanol. To this was added 23 g. of sodium in small portions. After the sodium had dissolved, water was added and the product was extracted with ether. The solvent was removed and the residue which did not crystallize was dissolved in ether and acetic acid, and shaken with 1 g. of platinum oxide catalyst under a pressure of 45 pounds of hydrogen for one hour. The catalyst was filtered and the solvent was removed. The residue was crystallized from acetone. A first fraction which was not cholestane was discarded. The mother liquor from this was crystallized from acetone and from acetone-ether, m. p. 78°. Mixed with cholestane, it melted at 78°.

Anal. Calcd. for $C_{27}H_{48}$: C, 87.0; H, 13.0. Found: C, 87.2; H, 13.1.

The non-carbinol fraction from the succinate treatment gave desoxychlorogenin.

16-*allo*-Pregnen-20-one from Desoxychlorogenin.—A mixture of 5 g. of desoxychlorogenin and 10 cc. of acetic anhydride was heated at 200° for ten hours in a bomb tube. The acetic anhydride was distilled *in vacuo* and the residue was refluxed for thirty minutes with 5 g. of potassium hydroxide in 100 cc. of methanol. Water was added and the product was extracted with ether. The solvent was removed and the residue was dissolved in 200 cc. of acetic acid. A solution of 5 g. of chromic anhydride in 50 cc. of 90% acetic acid was added and the product was kept at 30° for two hours. Water was added and the mixture was extracted with ether; the ethereal solution was washed well with water and the ether was removed. The residue was hydrolyzed by refluxing with 5 g. of potassium carbonate in 100 cc. of methanol and 20 cc. of water. The neutral fraction was extracted with ether; the ether was washed with water and the solvent was removed. The residue was crystallized from methanol and from acetone, m. p. 155–157°. When mixed with an authentic sample of 16-*allo*-pregnen-20-one, there was no depression in melting point.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.9; H, 10.7. Found: C, 84.0; H, 10.8.

A solution of 100 mg. of the above product in methanol–ether was shaken with 1 g. of palladium-barium sulfate catalyst and hydrogen for one hour. The catalyst was filtered and the solvent was removed. The residue was crystallized from ether–methanol, m. p. 130–132°. When mixed with *allo*-pregnan-20-one prepared from *allo*-pregnanediol (urine) m. p. 130–132° there was no depression in melting point.

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.4; H, 11.3. Found: C, 83.2; H, 11.1.

Pseudo-β-chlorogenin.—A mixture of 13 g. of β-chlorogenin and 20 cc. of acetic anhydride was heated in a bomb tube at 200° for ten hours. The excess solvent was removed *in vacuo* and the residue was hydrolyzed by refluxing with alcoholic potassium hydroxide for fifteen minutes.

Water was added and the product was extracted with a large volume of ether. The ethereal solution was concentrated to a small volume; the product separated in crystalline form. It was recrystallized from ether, m. p. 180–182°.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 75.0; H, 10.3. Found: C, 74.8; H, 10.3.

Conversion of Pseudo-β-chlorogenin into β-Chlorogenin.—To a solution of 100 mg. of pseudo-β-chlorogenin in 20 cc. of methyl alcohol was added 2 cc. of concentrated hydrochloric acid. The product was refluxed for one hour, then poured into water and extracted with ether. The solvent was removed and the residue was crystallized from acetone, m. p. 240–251°. When mixed with an authentic sample of β-chlorogenin, m. p. 249–251°, there was no depression in melting point.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 75.0; H, 10.3. Found: C, 74.9; H, 10.2.

Oxidation of Pseudo-β-chlorogenin.—To a solution of 5 g. of pseudo-β-chlorogenin in 100 cc. of acetic acid at 25° was added a solution of 4 g. of chromic anhydride in 25 cc. of 90% acetic acid. It was allowed to stand at room temperature for ninety minutes. Water was added and the product was extracted with ether. The solvent was removed and the residue was refluxed with alcoholic potassium carbonate solution for one hour on a steam-bath. The product was diluted with water and extracted with ether. The solvent was removed and the residue was crystallized from aqueous acetone, m. p. 223–226°. When mixed with an authentic sample of 16-*allo*-pregnen-3,6,20-trione, m. p. 224–227°, there was no depression in melting point.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.8; H, 8.6. Found: C, 76.7; H, 8.6.

The carbonate solution from the above hydrolysis of the oxidation product was acidified and thoroughly extracted with ether. The ether was removed and the residue was sublimed in a high vacuum at 80–100°. The sublimate was crystallized from ether–pentane, m. p. and mixed m. p. with α-methylglutaric acid 76–78°.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.2; H, 6.9. Found: C, 49.6; H, 7.0.

Catalytic Reduction of 16-*allo*-Pregnen-3,6,20-trione.—A mixture of 100 mg. of 16-pregnen-3,6,20-trione, 1 g. of Adams catalyst and 50 cc. of acetic acid was shaken for two hours with hydrogen at 45 pounds pressure. The solution was filtered and the solvent was removed *in vacuo*. The residue was crystallized from acetone, m. p. 224–225°. Mixed with *allo*-pregnan-3,6,20-triol, m. p. 224–226°, obtained by the reduction of 5-*allo*-pregnen-3,6,20-trione, gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 75.0; H, 10.8. Found: C, 75.1; H, 10.7.

Oxidation of Pseudo-β-chlorogenin Triacetate.—A mixture of 4 g. of pseudo-β-chlorogenin and 15 cc. of acetic anhydride was refluxed for thirty minutes. The excess solvent was removed and the residue was dissolved in 150 cc. of glacial acetic acid and cooled to 20°. To this was added a solution of 3 g. of chromic anhydride in 30 cc. of 90% acetic acid. It was kept at 30° for ninety minutes, water added and the product extracted well with ether. The excess acid was removed by washing with sodium bicarbonate solution. The solvent was removed and the residue was hydrolyzed by refluxing for fifteen minutes with 200 cc. of a 2% alcoholic potassium hydroxide solution. The product was extracted with ether, the solvent removed and the residue crystallized from methanol and from acetone, m. p. 214–216°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.7. Found: C, 75.7; H, 9.6.

When refluxed with acetic anhydride it gave a diacetate which was crystallized from methanol, m. p. 233–235°.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.1; H, 8.7. Found: C, 72.3; H, 8.5.

Oxidation of 16-*allo*-Pregnen-3(β),6(β)-diol-20-one.—To a solution of 100 mg. of 16-*allo*-pregnen-3(β),6(β)-diol-20-one in 20 cc. of acetic acid was added a solution of 100 mg. of chromic anhydride in 10 cc. of 90% acetic acid. It was allowed to stand for one hour at room temperature, water was added and the product was extracted with ether. The solvent was removed and the residue was crystallized from aqueous acetone, m. p. 223–226°. It gave no depression in melting point when mixed with an authentic sample of 16-*allo*-pregnen-3,6,20-trione.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.8; H, 8.6. Found: C, 76.7; H, 8.4.

Reduction of 16-*allo*-Pregnen-3(β),6(β)-diol-20-one.—A mixture of 100 mg. of 16-*allo*-pregnen-3(β),6(β)-diol-20-one, 0.1 g. of platinum oxide catalyst and 50 cc. of glacial acetic acid was shaken under hydrogen at 45 pounds pressure for two hours. The solution was filtered and the solvent was removed *in vacuo*. The residue was crystallized from acetone, m. p. 224–226°. When mixed with an authentic sample of *allo*-pregnan-3(β),6(β),20(β)-triol it gave no depression in melting point.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 75.0; H, 10.8. Found: C, 75.0; H, 10.7.

Summary

1. The reduction of chlorogenone by the Clemmensen method followed by halogenation and reduction gave cholestane.

2. Transformations have been carried out which indicate conclusively that β-chlorogenin differs from chlorogenin only in the configuration of the C-6 hydroxyl group.

3. Desoxychlorogenin has been converted to *allo*-pregnan-20-one.

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