

not investigated since a careful study of this fraction has already been made by other workers. The non-digitonin precipitable fraction was treated with succinic anhydride in pyridine to separate the carbinols from the non-carbinol fraction. This yielded 0.8 g. of carbinols upon hydrolysis. These were sublimed at about 10^{-3} mm.; a fraction distilling at $110\text{--}140^\circ$ was collected. This gave no depression in melting point when mixed with an authentic sample of *epi*-coprosterol prepared by the reduction of coprostanone; yield 0.1 g. It gave no precipitation with digitonin in alcohol.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.4; H, 12.5. Found: C, 83.4; H, 12.4.

Summary

1. *epi*-Smilagenin has been prepared from smilagenone.
2. The administration of 4-dehydrostigogenone to a dog led to an excretion of diosgenin, smilagenin and *epi*-smilagenin in the feces.
3. *epi*-Coprosterol is excreted normally in the feces of the dog.
4. The significance of these facts has been discussed.

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

Sterols. CXL. 17-Bromo-*allo*-pregnanone-20 and 17,21-Dibromo-*allo*-pregnanone-20*

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For a study of the reactions of the 20-ketopregnanone series, *allo*-pregnanone-20 is a model compound since it is easily obtained from *allo*-pregnanedione-3,20¹ and there are no other complicating reactive groups in the molecule. We have, therefore, used it as a test compound for many of the reactions of the 17-bromo- and 17,21-dibromo-20-ketopregnanone series.² Some of these reactions are now presented for the *allo*-pregnanone-20 series.

allo-Pregnanone-20 was prepared by partial Clemmensen reduction of *allo*-pregnanedione-3,20 as previously reported.¹ Treatment of *allo*-pregnanone-20 with 1 mol of bromine in acetic solution in the presence of hydrogen bromide led to formation in good yield of a crystalline 17-monobromide. Reduction of the monobromide with zinc or iron and acetic acid or with hydrogen-palladium in the presence of pyridine gave *allo*-pregnanone-20. Refluxing of a pyridine solution of the monobromide for four hours gave a good yield of Δ^{16} -*allo*-pregnanone-20. The latter compound was reconvertible to *allo*-pregnanone-20 by hydrogen-palladium reduction.

The direct treatment of *allo*-pregnanone-20 with 2 mols of bromine in acetic acid solution or treatment of the monobromide with 1 mol of bromide gave good yields of 17,21-dibromo-*allo*-pregnanone-20. The dibromide was reconvertible to the

parent ketone by reduction with zinc or iron in acetic acid or by potassium formate-formic acid (bomb reaction, ten hours at 130°).

Refluxing of the 17,21-dibromide with alcoholic potassium hydroxide yielded Δ^{17-20} -*allo*-pregnenoic acid-21 which on ozonolysis gave androstanone-17 isolated as the semicarbazone and characterized as the free ketone.

The reactions are summarized in the accompanying chart.

We thank Parke, Davis and Company for their assistance.

Experimental

17-Bromo-*allo*-pregnanone-20.—To a solution of 10 g. of *allo*-pregnanone-20 in 200 cc. of glacial acetic acid were added 10 drops of concentrated hydrobromic acid and 33.2 cc. of 1 *M* bromine solution in acetic acid. After standing for fifteen minutes, the solution was poured into water, extracted with ether and the extract washed free of acetic acid with water and dilute sodium carbonate solution. Evaporation of the ether gave a residue which was crystallized from ether-methanol to give 8 g., m. p. $113\text{--}121^\circ$. Recrystallization from acetone gave crystals, m. p. $127\text{--}9^\circ$ containing halogen (Beilstein test) which depressed the melting point of *allo*-pregnanone-20, m. p. 132° , twenty degrees.

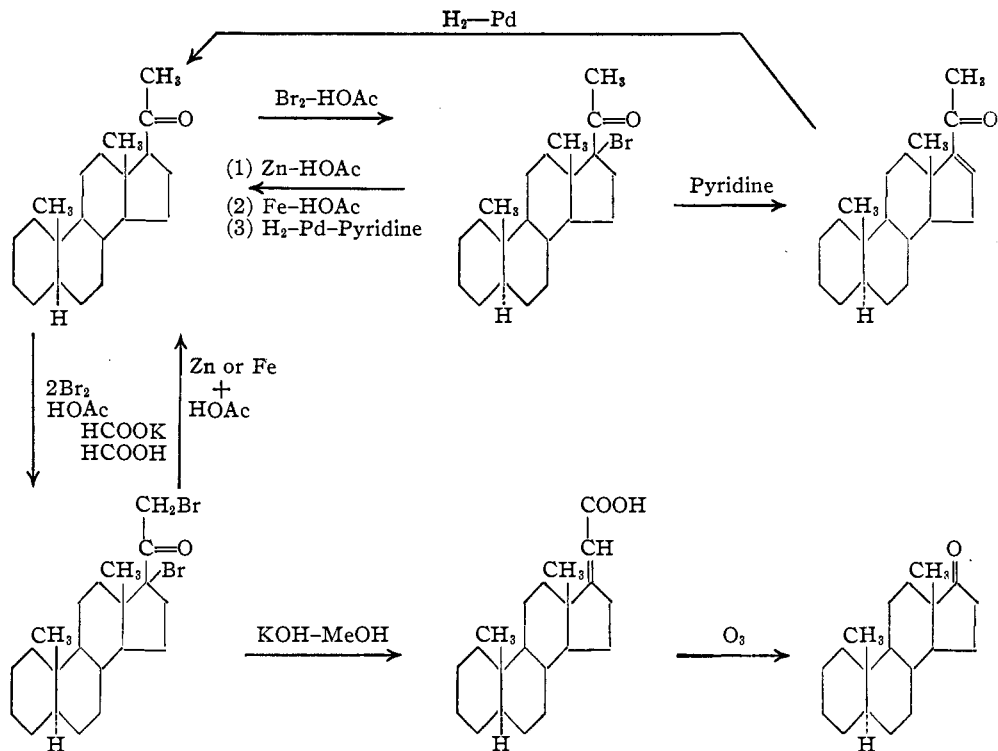
Anal. Calcd. for $C_{21}H_{38}OBr$: C, 66.2; H, 8.7. Found: C, 65.6; H, 8.8.

Reduction of 17-Bromo-*allo*-pregnanone-20. (a) **Zinc and Acetic Acid.**—A solution of 500 mg. of the 17-monobromide in 20 cc. of glacial acetic acid was warmed on the steam-bath one hour with 500 mg. of powdered zinc. The solution was decanted into water from the excess zinc, extracted with ether and the ether washed well with water.

* Original manuscript received July 5, 1941.

(1) Marker and Lawson, *THIS JOURNAL*, **61**, 852 (1939).

(2) Marker and co-workers, *ibid.*, **64**, 210, 213, 817 (1942).



Crystallization of the ether residue from ether-methanol gave crystals, m. p. 128–130°, 220 mg., mixed m. p. with *allo*-pregnanone-20 (132°) was 129–32°, with 17-bromo-*allo*-pregnanone-20 (127–29°) was 105–111°. The compound was halogen free.

(b) **With Iron and Acetic Acid.**—A solution of 500 mg. of 17-bromo-*allo*-pregnanone-20 in 20 cc. of glacial acetic acid was heated one hour on the steam-bath with 500 mg. of iron filings (100 mesh). The product was worked up as in (a); yield 240 mg., m. p. 129–30°. Mixed with *allo*-pregnanone-20 (132°) it melted at 130–132°. The product was halogen-free.

(c) **With Palladium-Barium Sulfate Catalyst and Pyridine.**—A mixture of 2.0 g. of 17-bromo-*allo*-pregnanone-20, 1.0 g. of palladium-barium sulfate catalyst, 3 cc. of pyridine and 300 cc. of methanol was shaken for two hours with hydrogen (2 atm.) at room temperature. The reaction mixture was diluted with water and the solid extracted with ether. The ethereal extract was washed successively with dilute hydrochloric acid and water and evaporated on the steam-bath. The product was crystallized from methanol-ether, m. p. 132–133.5°. A mixed m. p. with an authentic sample of *allo*-pregnanone-20, m. p. 132°, gave no depression. A yield of 1.3 g. of pure product was obtained.

Anal. Calcd. for $C_{21}H_{34}O$; C, 83.4; H, 11.3. Found: C, 83.7; H, 11.1.

17-Bromo-*allo*-pregnanone-20 and Pyridine.—A solution of 1 g. of 17-bromo-*allo*-pregnanone-20 in 10 cc. of dry pyridine was refluxed four hours. The solution was poured into water, extracted with ether and the ether washed free of pyridine with dilute acid and water. Evaporation of the ether gave a solid, recrystallized from

methanol and from acetone to a m. p. of 156–158°; yield 735 mg. This was Δ^{16} -*allo*-pregnenone-20.

Anal. Calcd. for $C_{21}H_{32}O$; C, 83.9; H, 10.7. Found: C, 83.8; H, 10.7.

Reduction of Δ^{16} -*allo*-Pregnenone-20.—A solution of 200 mg. of Δ^{16} -*allo*-pregnenone-20 in 25 cc. of ethanol-dioxane was reduced with hydrogen in the presence of 250 mg. of palladium-barium sulfate catalyst (3%) for thirty minutes. The catalyst was removed by filtration and the solvent distilled *in vacuo*. The residue was crystallized from ether-methanol, 180 mg., m. p. 130–132°. Mixed with *allo*-pregnanone-20 (132°) the melting point was 131–132°. Mixed with *allo*-pregnanone-20 (132°) the melting point was 131–132°.

17,21-Dibromo-*allo*-pregnanone-20.—To a solution of 5 g. of *allo*-pregnanone-20 in 100 cc. of glacial acetic acid was added 10 drops of concentrated hydrogen bromide and 33.2 cc. (2 mols) of a 1 M solution of bromine in acetic acid, the rate of addition being governed by the speed of disappearance of the bromine color. To ensure complete reaction the solution was warmed to 40° for addition of the second mol of bromine. The solution was allowed to stand for thirty minutes, then poured into 500 cc. of ice-water and filtered. The rather gummy precipitate was taken up in ether, washed free of acid with water and saturated sodium bicarbonate solution and the ether evaporated. The residue was crystallized from acetone to give 4.8 g., m. p. 128–130°. This gave a depression when mixed with a sample of the monobromide (127–129°) or with the original *allo*-pregnanone-20 (132°).

Anal. Calcd. for $C_{21}H_{32}OBr_2$; C, 55.0; H, 6.6. Found: C, 54.8; H, 7.0.

To 500 mg. of 17-bromo-*allo*-pregnanone-20 in 35 cc. of

glacial acetic acid were added 2 drops of 45% hydrogen bromide solution and 1.3 cc. of 1.0 *M* bromine solution in acetic acid at 35°. After standing for one hour the solution was diluted with water, filtered, and the solid washed with water. Crystallization from acetone yielded a product melting at 128–130°. This gave no depression with the above product.

Reduction of 17,21-Dibromo-*allo*-pregnanone-20. (a)

Zinc-Acetic Acid.—To a solution of 300 mg. of the dibromide in 30 cc. of glacial acetic acid on the steam-bath was added 500 mg. of zinc dust, and heating was continued for one hour. The product was worked up as usual and crystallized from ether-methanol; yield 100 mg.; m. p. 128–130°; mixed m. p. with *allo*-pregnanone-20 (132°) was 129–132°.

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

(b) **Iron-Acetic Acid.**—To a solution of 300 mg. of dibromide in 30 cc. of glacial acetic acid was added 300 mg. of powdered iron (100 mesh) and the mixture was heated one hour on the steam-bath. Worked up as usual, it gave 80 mg., m. p. 127–130°. Mixed with *allo*-pregnanone-20 (132°) it melted at 128–131°.

(c) **Potassium Formate-Formic Acid.**—A solution of 2 g. of dibromide in 50 cc. of formic acid with 4 g. of potassium formate was heated in a bomb tube at 130° for ten hours. The reaction product was extracted with ether from a water suspension. The ether was washed free of salt and acid and was treated with Norite. Evaporation of the ether and crystallization of the residue from ether-methanol gave 1.1 g. of crystals, m. p. 129–131°, which gave no depression when mixed with *allo*-pregnanone-20 (132°).

Δ^{17-20} -*allo*-Pregnenic Acid-21.—To a solution of 1.85 g. of 17,21-dibromo-*allo* pregnanone-20 in 100 cc. of methanol was added a solution of 9.25 g. of potassium hydroxide in 85 cc. of hot methanol. The mixture was evaporated on the steam-bath to a volume of approximately 50 cc. and an additional 100 cc. of methanol added. The solution was again evaporated to a volume of approximately 50 cc., cooled and shaken with 100 cc. of ether. The potassium salt of the acid was filtered and washed with ether. The ether insoluble salt was slurried with water, acidified with hydrochloric acid and the solid extracted with ether. The ethereal extract was washed with water and the ether was

evaporated. The residue was crystallized from ethyl acetate; m. p. 242–244°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.1. Found: C, 79.5; H, 10.1.

Conversion of $\Delta^{17,20}$ -*allo*-Pregnenic Acid-21 to Androstanone-17.—A solution of 1.0 g. of $\Delta^{17,20}$ -*allo*-pregnenic acid-21 and 200 cc. of chloroform, cooled by ice and hydrochloric acid was ozonized for sixteen minutes with oxygen containing 7% ozone at a rate of 30 liters of oxygen per hour. The chloroform solution was stirred for one hour with 200 cc. of water and then heated on the steam-bath for an additional hour. The solid product was extracted with ether. The ethereal extract was washed successively with a dilute sodium carbonate solution and water and evaporated on the steam-bath. The residue was dissolved in 50 cc. of methanol and to this was added a methanolic solution of semicarbazide acetate. The mixture was heated on the steam-bath for one hour and filtered. The white solid was washed with water, dried and crystallized from chloroform; m. p. 284–285° dec.

Anal. Calcd. for $C_{20}H_{28}ON_2$: C, 72.4; H, 10.0. Found: C, 72.1; H, 10.1.

To 350 mg. of the semicarbazone in 100 cc. of ethanol was added 3 cc. of concentrated sulfuric acid in 7 cc. of water. The mixture was refluxed for one hour and diluted with water. The solid was extracted with ether, washed, and the ether was evaporated. The residue was crystallized from aqueous methanol; m. p. 117–119°. A yield of 150 mg. of pure product was obtained.

Anal. Calcd. for $C_{19}H_{26}O$: C, 83.1; H, 11.0. Found: C, 82.9; H, 11.0.

Summary

The 17-mono- and 17,21-dibromides of *allo*-pregnanone-20 have been prepared. Both compounds were reduced to the parent ketone. The 17-monobromide was converted to Δ^{16} -*allo*-pregnenone-20, which in turn was reduced to *allo*-pregnanone-20.

17,21-Dibromo-*allo*-pregnanone-20 was converted to Δ^{17-20} -*allo*-pregnenic acid-21 and the latter oxidized to androstanone-17.

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