Assuming the ester has a maximum rotation of +90.8°, this product corresponds to 93% purity.

The *l*-product was collected at 126–130° (17 mm.); $n^{20}D$ 1.4730; d^{20}_4 1.043.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.41; H, 8.69.

Rotation. $\alpha^{20}D$ −88.26° (pure liquid); *l*, 1; $[\alpha]^{20}D$ −84.6°.

***d*- and *l*-1-Hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone.**—These were prepared from the previously described *d*- and *l*-ethyl 5-methylcyclohexanone-2-carboxylates in a synthesis identical with that for the *dl*-modification.[8]

The *d*- and *l*-products were purified from methanol, m. p. 177° (cor.) in each case.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.03. Found: (dextro form) C, 75.97; H, 7.98; (levo form) C, 76.17; H, 8.13.

Rotation. (*d*-form) 0.3936 g. made up to 25 cc. with ethanol at 28° gave αD +4.20°; *l*, 2; $[\alpha]^{27}D$ +133°. 0.0205 g. made up to 5 cc. with chloroform at 25° gave αD +0.56°; *l*, 1; $[\alpha]^{25}D$ +137°. Leaf, Todd and Wilkinson[8] gave $[\alpha]^{24}D$ +130.3° in chloroform. (*l*-form) 0.1214 g. made up to 25 cc. with ethanol at 27° gave αD −1.23°; *l*, 2; $[\alpha]^{27}D$ −127°.

***d*- and *l*-1-Hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran.**—These were prepared from the optically active pyrones with rotations given above by use of excess methylmagnesium iodide as previously described for the *dl*-modification.

The *d*-form had a b. p. of 175–185° (0.1 mm.), bath temp. 205–210°; $n^{20}D$ 1.4550; the *l*-form had identical b. p. and index of refraction.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: (*d*-form) C, 80.01; H, 9.63. (*l*-form) C, 80.07; H, 9.67.

Rotation. (*d*-form) 0.1742 g. made up to 5 cc. with ethanol at 20° gave αD +5.41°; *l*, 1; $[\alpha]^{20}D$ +155°. 0.1456 g. of a sample which had $[\alpha]^{25}D$ +147° in ethanol, made up to 5 cc. with chloroform at 25° gave αD +4.32°; *l*, 1; $[\alpha]^{25}D$ +147.5°. Leaf, Todd and Wilkinson[8] report $[\alpha]^{20}D$ +134.8°. (*l*-form) 0.0873 made up to 5 cc. with ethanol at 26° gave αD −1.99°; *l*, 1; $[\alpha]^{26}D$ −114°.

Pharmacological Tests.—These were performed by the dog-ataxia method as described in previous papers.[7,11,12]

Summary

1. The *d*- and *l*-forms of 3-methylcyclohexanone have been synthesized; the former was prepared by hydrolysis of pulegone; the latter by resolution of the *dl*-methylcyclohexanone through the *l*-menthydrazone.

2. These were converted to the active ethyl 5-methyl-cyclohexanone-2-carboxylates, which were condensed with olivetol to form the *d*- and *l*-pyrones. By the action of excess methylmagnesium iodide, the *d*- and *l*-1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyrans resulted.

3. The *l*-modification had four to five times the marihuana activity of the *d*-form.

(11) Loewe, *J. Pharm. Exper. Therap.*, **66**, 23 (1939); *J. Am. Pharm. Soc.*, **28**, 427 (1939).

(12) Matchett and Loewe, *ibid.*, **30**, 130 (1941).

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

Sterols. CLI. Rearrangement of 17,21-Dibromo-*allo*-pregnan-3(β)-ol-20-one Acetate[1]

BY RUSSELL E. MARKER, HARRY M. CROOKS, JR., R. B. WAGNER AND EMERSON L. WITTBECKER

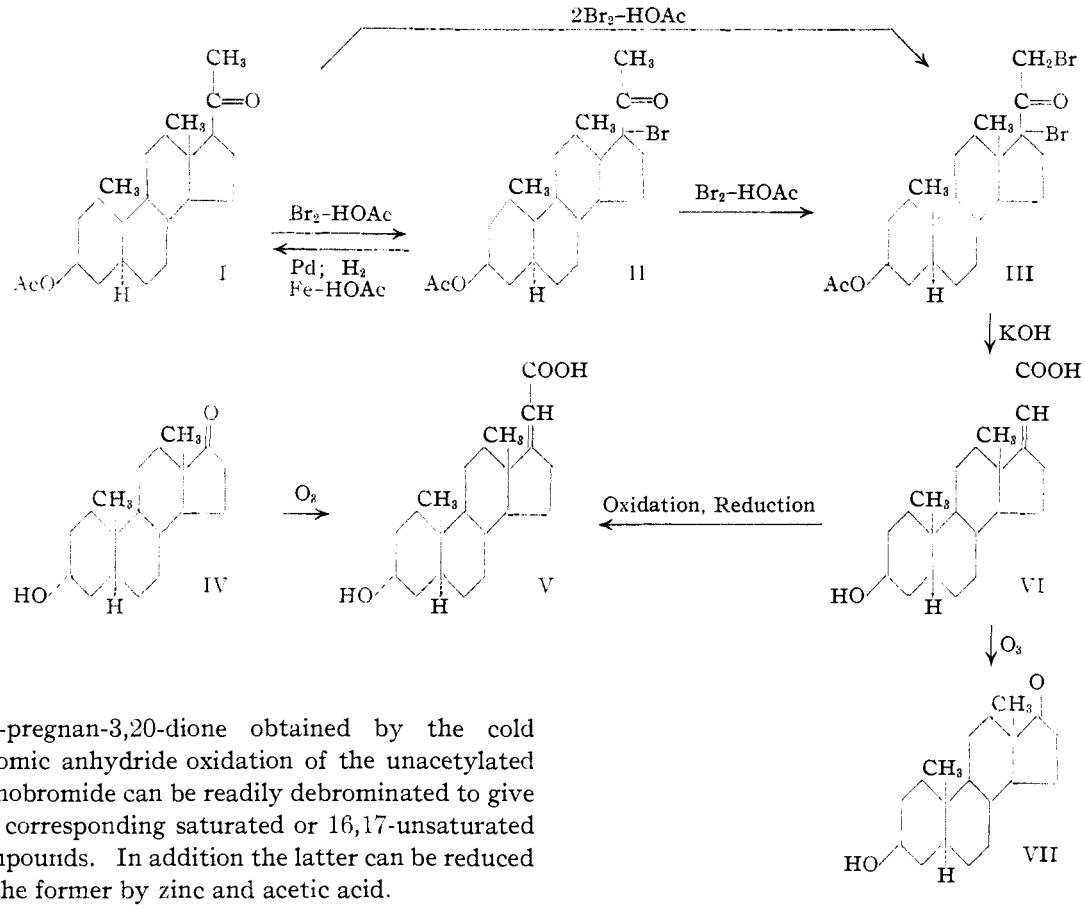
Recently,[2] we have shown that an equimolecular quantity of bromine with 20-keto-pregnane compounds introduces a bromine atom at C-17. Further bromination of these compounds substitutes a second bromine atom at C-21. Studies with these compounds have shown them to be particularly susceptible to rearrangement. The monobromo derivative[3] treated with methanolic potassium bicarbonate rearranges to place methyl and carbomethyoxyl groups at C-17. The 17,21-dibromo derivatives[2] under more vigorous alkali treatment yield Δ^{17-20}-pregnen-21-oic acids. The latter rearrangement products are particularly interesting since they can be degraded easily to the etio-cholane series. This fact has given support for their structure. We have now extended some of these reactions to *allo*-pregnan-3(β)-ol-20-one as a further study of the 17,21-dibromo-20-keto-pregnane rearrangement in the *allo* series.

allo-Pregnan-3(β)-ol-20-one or its acetate (I) with an equimolecular quantity of bromine readily forms a 17-monobromide (II) which can be reconverted to the parent compound or converted to 16-*allo*-pregnen-3(β)-ol-20-one by reactions described before.[2] In the same manner 17-bromo-

(1) Original manuscript received July 16, 1941.

(2) Marker and co-workers, THIS JOURNAL, **64**, 210, 213, 817, 822 (1942).

(3) Marker and Wagner, *ibid.*, **64**, 216, 1273 (1942).



allo-pregnan-3,20-dione obtained by the cold chromic anhydride oxidation of the unacetylated monobromide can be readily debrominated to give the corresponding saturated or 16,17-unsaturated compounds. In addition the latter can be reduced to the former by zinc and acetic acid.

allo-Pregnan-3(β)-ol-20-one acetate (I) with twice the molecular quantity of bromine forms 17,21-dibromo-pregnan-3(β)-ol-20-one acetate (III). The latter can be formed equally well by the treatment of the monobromide (II) with an equimolecular quantity of bromine.

By the same alkali treatment used for the rearrangement of its C-5 isomer,[2] the dibromide (III) rearranges to give 3(β)-hydroxy-Δ^{17-20}-*allo*-pregnen-21-oic acid (VI). Oppenauer oxidation of the latter followed by a Meerwein reduction of the resulting keto-acid gives the epimeric pregnenoic acid (V). The structures of these acids are now established by ozonolysis. The 3(β)-hydroxy acid (VI) yields isoandrosterone (VII) and the 3(α)-hydroxy acid (V) yields androsterone (IV). As early as 1913 Faworskii[3] showed that 3-methyl-1,3-dibromobutan-2-one reacting with alcoholic potassium hydroxide readily undergoes a rearrangement to give β,β'-dimethylacrylic acid. As a model experiment we have shown that the corresponding dibromide of methyl cyclohexyl ketone in a like manner is converted to cyclohexylidene acetic acid. The pregnenoic acids are analogous to this acid and to that obtained by Faworskii.[4]

The reactions are summarized in the accompanying chart.

We thank Parke, Davis and Company for their generous assistance.

Experimental Part

17-Bromo-*allo*-pregnan-3(β)-ol-20-one Acetate (II).—To a solution of 11 g. of *allo*-pregnan-3(β)-ol-20-one acetate (I) in 500 cc. of acetic acid was added 31 cc. of molar bromine in acetic acid solution, dropwise at room temperature. The solution was allowed to stand for one hour. Ice and cold water were added, and the monobromide was extracted with ether. The ethereal layer was washed successively with water, dilute sodium carbonate solution and water. The solvent was removed and the monobromide acetate was crystallized three times from methanol, m. p. 155°; yield 6.0 g.

Anal. Calcd. for $C_{23}H_{35}O_3Br$: C, 62.9; H, 8.0. Found: C, 62.6; H, 8.0.

17-Bromo-*allo*-pregnan-3(β)-ol-20-one.—To a solution of 17 g. of *allo*-pregnan-3(β)-ol-20-one in 1 l. of acetic acid was added dropwise 54 cc. of molar bromine in acetic acid solu-

(4) Faworskii, *J. Russ. Phys.-Chem. Soc.*, **44**, 1358 (1913); *J. prakt. Chem.*, [2] **88**, 658 (1913).

tion at room temperature. The solution was allowed to stand ten minutes, and then 1 l. of water was added. The monobromide was extracted with ether. The ether layer was washed well with water and evaporated. The monobromide was crystallized once from dilute methanol and then from ether–pentane, m. p. 93–96°; yield 9 g.

Anal. Calcd. for $C_{21}H_{33}O_2Br$: C, 63.5; H, 8.4. Found: C, 63.6; H, 8.1.

***allo*-Pregnan-3(β)-ol-20-one Acetate** from **17-Bromo-*allo*-pregnan-3(β)-ol-20-one.**—A mixture of 2 g. of the bromo compound (II) in 500 cc. of methanol–dioxane mixture and 3 cc. of pyridine was hydrogenated at 40 pounds pressure for two hours using 2 g. of palladium catalyst. The catalyst was filtered off and the filtrate concentrated. An ethereal solution of the residue was washed successively with water, dilute hydrochloric acid solution and water, and then evaporated. The residue was crystallized from methanol, m. p. and mixed m. p. with *allo*-pregnan-3(β)-ol-20-one acetate (I), 142–144°; yield 1 g.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.4; H, 10.0.

Reduction of 17-Bromo-*allo*-pregnan-3(β)-ol-20-one with Iron.—A mixture of 0.20 g. of the bromo compound (II), 1 g. of powdered iron and 10 cc. of glacial acetic acid was heated on a steam-bath for two hours. After filtering, water was added and the product extracted with ether. After evaporation of the solvent, the residue was crystallized from methanol, m. p. and mixed m. p. with *allo*-pregnan-3(β)-ol-20-one, 193–194°; yield 0.12 g.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 78.9; H, 10.8.

Catalytic Reduction of 17-Bromo-*allo*-pregnan-3(β)-ol-20-one.—A mixture of 0.50 g. of the bromo compound (II), 5 cc. of pyridine, 50 cc. of dioxane and 1 g. of palladium–barium sulfate catalyst was shaken with hydrogen for three hours at 40 pounds pressure. The catalyst was filtered and the filtrate was vacuum distilled. An ethereal solution of the residue was washed well with water and evaporated. The product was crystallized from methanol, m. p. and mixed m. p. with *allo*-pregnan-3(β)-ol-20-one, 193–194°; yield 0.26 g.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.0; H, 10.7.

16-*allo*-Pregnen-3(β)-ol-20-one Acetate from 17-Bromo-*allo*-pregnan-3(β)-ol-20-one Acetate.—A mixture of 1 g. of the bromo compound (II) and 5 cc. of pyridine was refluxed for five hours. Water was added and the mixture was extracted with ether. The ether layer was washed with water, dilute hydrochloric acid and water. The solvent was removed and the residue was treated with Norite in methanol. It was crystallized, m. p. and mixed m. p. with 16-*allo*-pregnen-3(β)-ol-20-one acetate, 163–165°; yield 0.6 g.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.0; H, 9.2.

Treatment of 17-Bromo-*allo*-pregnan-3(β)-ol-20-one with Pyridine.—A mixture of 0.50 g. of 17-bromo-*allo*-pregnan-3(β)-ol-20-one and 5 cc. of pyridine was refluxed for six hours. The product was extracted with ether, washed with dilute hydrochloric acid and crystallized from methanol, m. p. and mixed m. p. with 16-*allo*-pregnen-3(β)-ol-20-one, 202–204°; yield 0.25 g.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.1.

***allo*-Pregnan-3(β)-ol-20-one Acetate from 16-*allo*-Pregnen-3(β)-ol-20-one Acetate.**—A mixture of 3 g. of the unsaturated acetate and 6 g. of zinc dust in 150 cc. of acetic acid was heated on the steam-bath for two hours. The zinc was filtered and water was added to the filtrate. This was then extracted with ether. The ethereal solution was washed with water, dilute sodium carbonate solution and again with water. The solvent was removed and the residue was crystallized from methanol and from acetone, m. p. and mixed m. p. with *allo*-pregnan-3(β)-ol-20-one acetate, 143°; yield 2.6 g.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 77.0; H, 9.9.

Oxidation of 17-Bromo-*allo*-pregnan-3(β)-ol-20-one.—To a solution of 3 g. of the bromo compound in 50 cc. of acetic acid was added a solution of 1.5 g. of chromic anhydride in 15 cc. of 80% acetic acid at room temperature. After standing for thirty minutes, water was added and the product was extracted with ether. The acetic acid was washed out. Attempts to crystallize the product gave material with a melting point range.

(a) To a solution of 0.5 g. of the above product was added 10 cc. of dry pyridine and the mixture was refluxed for six hours. Water was added and the product was extracted with ether. The pyridine was removed and the residue was crystallized from ether, m. p. and mixed m. p. with 16-*allo*-pregnen-3,20-dione, 210–212°; yield 0.3 g.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.1; H, 9.6. Found: C, 80.1; H, 9.7.

(b) A solution of 0.50 g. of the crude bromo product in 25 cc. of acetic acid was refluxed for two hours with 1 g. of anhydrous potassium acetate. The solvent was removed and the residue was extracted with ether. Upon concentration, it crystallized, m. p. and mixed m. p. with 16-*allo*-pregnen-3,20-dione, 211–212°; yield 0.30 g.

(c) A solution of 0.50 g. of the crude bromo product was heated on a steam-bath for two hours with 1 g. of iron dust and 20 cc. of acetic acid. It was filtered and the filtrate was extracted with ether. The ethereal solution was washed with water and evaporated. The residue was crystallized from acetone, m. p. and mixed m. p. with *allo*-pregnan-3,20-dione, 200°; yield 0.27 g.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.0.

***allo*-Pregnan-3,20-dione from 16-*allo*-Pregnen-3,20-dione.**—A solution of 0.50 g. of 16-*allo*-pregnen-3,20-dione in 20 cc. of acetic acid was heated with 1 g. of zinc dust on a steam-bath for one hour. The zinc was filtered and water was added to the filtrate. The solid was filtered and crystallized from acetone, m. p. and mixed m. p. with *allo*-pregnan-3,20-dione, 200°; yield 0.35 g.

17,21-Dibromo-*allo*-pregnan-3(β)-ol-20-one Acetate (III).—To a solution of 18 g. of 17-bromo-*allo*-pregnan-3(β)-ol-20-one acetate (II) in 1 l. of acetic acid was added 41.0 cc. of molar bromine in acetic acid at 40°. Water was added and the dibromide was extracted with ether. The ether layer was washed with water, dilute sodium

carbonate solution and water. The solvent was removed and the dibromide acetate was crystallized from methanol, m. p. 174°; yield 12 g.

Anal. Calcd. for $C_{23}H_{34}O_3Br_2$: C, 53.4; H, 6.6. Found: C, 53.0; H, 6.7.

3(β)-Hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic Acid (VI).—A solution of 1.5 g. of 17,21-dibromo-*allo*-pregnan-3(β)-ol-20-one acetate (III) in 200 cc. of methanol was heated with 5 g. of potassium hydroxide on the steam-bath for two hours. After adding water, the mixture was extracted with ether. The aqueous layer was acidified and the organic acid (VI) was extracted with ether and crystallized from methanol, m. p. 249°; yield 0.8 g.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 75.7; H, 9.5.

Isoandrosterone (VII) from 3(β)-Hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic Acid (VI).—A chloroform solution of 6.7 g. of the acetate of 3(β)-hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic acid (VI) was treated with oxygen containing about 6% ozone at the rate of 30 liters of oxygen per hour for three hours. The chloroform solution was poured into 300 cc. of water and stirred for forty-five minutes. The chloroform was distilled on a steam-bath and the water layer extracted with ether. The ether was evaporated and the residue hydrolyzed with 6 g. of potassium hydroxide in 200 cc. of methanol for twenty minutes. Water was added and the mixture extracted with ether. The ether layer was washed with water and then evaporated. The residue was dissolved in 200 cc. of ethanol and refluxed with 4 g. of semicarbazide hydrochloride and 5 g. of sodium acetate in 10 cc. of water for one hour. Water was added and the precipitate was filtered and washed with water and ether. The semicarbazone was crystallized twice from ethyl alcohol–chloroform mixture, m. p. 260–262° dec.; yield 2.1 g.

Anal. Calcd. for $C_{20}H_{33}O_2N_3$: C, 69.1; H, 9.6. Found: C, 69.2; H, 9.6.

A mixture of 0.2 g. of the above semicarbazone in 50 cc. of alcohol was refluxed for an hour with 50 cc. of alcohol containing 5 cc. of concd. sulfuric acid and 10 cc. of water. Water was added and the product was extracted with ether. The ether was evaporated and the residue was crystallized from aqueous methanol, m. p. and mixed m. p. with isoandrosterone (VII), 173–174°; yield 0.1 g.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.2; H, 10.3.

3(α)-Hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic Acid (V).—A mixture of 3 g. of 3(β)-hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic acid (VI), 10 g. of aluminum tertiary-butoxide, 100 cc. of dry toluene and 25 cc. of dry acetone was refluxed for six hours. Ether and hydrochloric acid were added. The ether layer was washed with water and evaporated. The residue was refluxed with 200 cc. of dry isopropyl alcohol and 10 g. of aluminum isopropylate overnight. The solvent was then slowly distilled off over a period of five hours. Ether and hydrochloric acid were added. The ether layer was washed with water and evaporated. The 3(α)-hydroxy acid (V) was dissolved in ether and crystallized. It appears to be much more soluble than the β-form. It was also crystallized from ethyl acetate and finally again from ether, m. p. 232–235°. It gave a depression of 18° when mixed with a sample of 3(β)-hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic acid (VI). It did not precipitate with digitonin.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7. Found: C, 75.8; H, 9.7.

Androsterone (IV) from 3(α)-Hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic Acid (V).—A solution of 1 g. of the above acid in 200 cc. of chloroform was treated with ozone and the product worked up as described for the β-acid. It gave a semicarbazone, m. p. 260–264° dec.; yield 0.4 g.

Anal. Calcd. for $C_{20}H_{33}O_2N_3$: C, 69.1; H, 9.6. Found: C, 69.4; H, 9.5.

A solution of 0.4 g. of the above semicarbazone was refluxed for one hour with 50 cc. of ethanol containing 5 cc. of sulfuric acid and 10 cc. of water. Water was added and the product was extracted with ether. The ether was evaporated and the residue was crystallized from aqueous methanol, m. p. 182–183°. There was no depression in melting point when mixed with an authentic sample of androsterone (XI).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.4; H, 10.4.

Cyclohexylidene-acetic Acid from Methyl Cyclohexyl Ketone.—To 31.5 g. of methyl cyclohexyl ketone was added 8.0 g. of bromine at 0°. To this mixture was added a solution of 80 g. of potassium hydroxide in 1 l. of absolute ethanol. This was allowed to stand at room temperature overnight. Water was added and the mixture was then extracted with ether. The water layer was acidified and the acid was extracted with ether. The ether was evaporated and the residue was distilled. The cyclohexylidene acetic acid was solid and was crystallized from dilute methanol, m. p. 89–91°.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.5; H, 8.6. Found: C, 68.8; H, 8.7.

Summary

The 17-monobromide (II) of *allo*-pregnan-3(β)-ol-20-one and its acetate (I) has been prepared and its dehalogenation reactions studied.

The 17,21-dibromide (III) of *allo*-pregnan-3-(β)-ol-20-one acetate (I) has been shown to undergo a Faworskii rearrangement to give 3(β)-hydroxy-Δ$^{17-20}$-*allo*-pregnen-21-oic acid (VI). The structure has been established by conversions to isoandrosterone (VI) and androsterone (V).

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