

ment with Norit, was crystallized from methanol to give thick white needles, m. p. 141–142°, yield 0.6 g. This gave no depression with the acetate of 16-pregnen-3(β)-ol-20-one, m. p. 142–144°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.2; H, 9.7.

Pyridine on 17-Bromopregnan-3(β)-ol-20-one.—A solution of 1 g. of 17-bromopregnan-3(β)-ol-20-one in 50 cc. of dry distilled pyridine was refluxed for four hours. A white solid had separated at the end of this time. The reaction mixture was worked up in the usual manner to give compact white crystals from acetone, m. p. 169–172°, yield 0.6 g. This gave no depression when mixed with 16-pregnen-3(β)-ol-20-one, m. p. 170–171°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 10.4.

Treatment with boiling acetic anhydride gave the acetate, m. p. 143–145°, which gave no depression with the acetate of 16-pregnen-3(β)-ol-20-one.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 77.4; H, 9.3.

16-Pregnene-3,20-dione from 17-Bromopregnan-3(β)-ol-20-one.—To a solution of 2 g. of 17-bromopregnan-3(β)-ol-20-one in 80 cc. of acetic acid at room temperature was added a solution of 1 g. of chromic anhydride in 20 cc. of 90% acetic acid. After standing for forty-five minutes at room temperature, water was added and the product was extracted with ether, and washed free from acid with 5% sodium bicarbonate solution and water. No definite crystalline product was isolated. The entire product was dissolved in 15 cc. of dry distilled pyridine and refluxed for six hours. At the end of this time a solid had precipitated. The reaction mixture was poured into water and extracted with ether. The ethereal extract was washed free of pyridine with 10% hydrochloric acid and then washed with 5% sodium bicarbonate and water. After treatment with Norit, the ether was evaporated. The residue was crystal-

lized from acetone to give white plates, m. p. 198–200°, yield 0.3 g. This did not depress the melting point of an authentic sample of 16-pregnene-3,20-dione.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.1; H, 9.6. Found: C, 80.0; H, 9.3.

Pregnane-3,20-dione from 17-Bromopregnan-3(β)-ol-20-one.—The non-crystalline product from the oxidation of 1 g. of 17-bromopregnan-3(β)-ol-20-one as described above was dissolved in 75 cc. of methanol. The solution was shaken with 2 g. of palladium-barium sulfate catalyst, 3 cc. of pyridine and hydrogen at 3 atm. and room temperature for three hours. The reaction mixture was filtered and the filtrate was poured into water. The precipitated solid was extracted with ether and the ether extract was washed with 10 per cent. hydrochloric acid and water. The ether was evaporated and the residue was crystallized from ethanol to give white crystals, m. p. 117–119°, yield 0.5 g. This gave no depression with an authentic sample of pregnane-3,20-dione, m. p. 118–120°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.6; H, 9.9.

Zinc-Acetic Acid Reduction of 16-Pregnene-3,20-dione.—A mixture of 500 mg. of 16-pregnene-3,20-dione, 20 cc. of acetic acid and 1 g. of zinc dust was heated on a steam-bath for one hour. The reaction mixture was worked up in the usual manner and the product was crystallized from aqueous methanol, m. p. 118–120°. This did not depress the melting point of an authentic sample of pregnane-3,20-dione.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 80.0; H, 10.3.

Summary

17-Bromopregnan-3(β)-ol-20-one and its acetate have been prepared and some of their debromination reactions studied.

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

Sterols. CXXVIII. 17,21-Dibromopregnan-2(β)-ol-20-one and its Conversion to Pregnanol-3(β),21-diol-20-one*

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

The ease of mono-bromination¹ of pregnan-3(β)-ol-20-one opened up the possibility that if a dibromide could be as easily obtained it would offer a likely method of obtaining 21-hydroxy-20-ketosterols closely related to desoxycorticosterone. We have now prepared 17,21-dibromopregnan-3(β)-ol-20-one and studied some of its conversion products.

Pregnan-3(β)-ol-20-one or the acetate on direct dibromination in acetic acid solution gave a yield

of 60% or more of 17,21-dibromide with or without the intermediate separation of the monobromide. That the formation of the dibromide was not attended by any rearrangement was shown by its ready reduction to the starting material by zinc or iron and acetic acid.

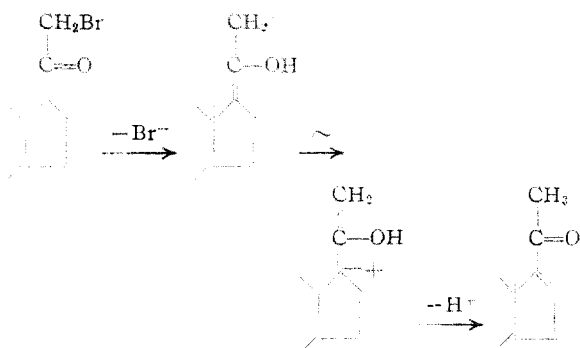
The position of the second bromine atom was proved as follows. Treatment of the dibromide with potassium acetate in acetic acid under mild conditions removed the less stable 17-bromine as hydrogen bromide to form 21-bromo-16-pregnen-3(β)-ol-20-one. The conjugation of the carbonyl

* Original manuscript received April 29, 1941.

(1) Marker, Crooks and Wagner, *THIS JOURNAL*, **64**, 210 (1942).

group with the double bond appeared greatly to increase the resistance of the primary halogen to replacement. Pregnan-3(β)-ol-20-one could be obtained from 21-bromo-16-pregnen-3(β)-ol-20-one either by reduction with zinc or iron and acetic acid or by hydrogen-palladium reduction in pyridine. If the compound was reduced with hydrogen-palladium in the absence of pyridine the product was 21-bromopregnan-3(β)-ol-20-one. Treatment of this latter compound with potassium acetate in acetic acid² gave 21-acetoxy-pregnan-3(β)-ol-20-one of the same melting point as that obtained by Reichstein by treatment of 21-diazo-pregnan-3(β)-ol-20-one with acetic acid.

The conversion of 21-bromopregnan-3(β)-ol-20-one to the 21-acetoxy-compound was complicated, and the yield correspondingly lowered, by the simultaneous formation of 16-pregnen-3(β)-ol-20-one. This by-product was very likely the result of a relatively simple rearrangement³—removal of the bromine followed by an allylic shift of the enol form of the ketone to give a fragment convertible to 16-pregnen-3(β)-ol-20-one by expulsion of a proton from C-16.



It is entirely possible that this same type of rearrangement complicates the 21-diazo conversion of Reichstein,² necessitating chromatographing to obtain the pure 21-acetoxy or 21-halo compound. This is apparently a type of rearrangement not previously recognized.

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

Experimental Part

Bromination of Pregnan-3(β)-ol-20-one and of its Acetate.—A solution of 5 g. of pregnan-3(β)-ol-20-one acetate from sarsasapogenin in 150 cc. of glacial acetic acid was warmed to 40°. Two drops of 48% hydrobromic acid was added and then 29 cc. of 1 M bromine in acetic

acid was added dropwise. After standing for fifteen minutes the mixture was poured into water. The precipitated solid was filtered and washed free of acid. The material crystallized from acetone; m. p. 190–191°; yield 5.0 g.

Anal. Calcd. for $C_{23}H_{34}O_3Br_2$: C, 53.3; H, 6.6. Found: C, 52.9; H, 6.7.

Bromination of pregnan-3(β)-ol-20-one by the same procedure gave a product which crystallized from ether as thick white needles, m. p. 190–192°, and depressed the melting point when mixed with dibromopregnan-3(β)-ol-20-one acetate; yield 10.0 g. from 10 g. of pregnan-3(β)-ol-20-one.

Anal. Calcd. for $C_{21}H_{32}O_2Br_2$: C, 52.9; H, 6.8. Found: C, 52.5; H, 6.7.

Reduction of 17,21-Dibromopregnan-3(β)-ol-20-one Acetate. (a) **With Zinc and Acetic Acid.**—To a solution of 2 g. of 17,21-dibromopregnan-3(β)-ol-20-one acetate in 50 cc. of glacial acetic acid was added 4 g. of zinc dust. The mixture was heated on a steam-bath for thirty minutes. The reaction mixture was filtered and the filtrate poured into water. The precipitated solid was extracted with ether and the ether extract was washed with water, 5% sodium bicarbonate solution, and water. The ether was removed and the residue crystallized from methanol to give 1.2 g. of white plates, m. p. 117–119°; no depression in melting point with pregnan-3(β)-ol-20-one acetate, m. p. 117–119°.

(b) **With Iron and Acetic Acid.**—Substitution of powdered iron for the zinc dust of reduction (a) with heating continued for a total of two hours gave a yield of 1.1 g., m. p. 123°, white plates, from 2 g. of dibromide; no depression with pregnan-3(β)-ol-20-one acetate.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.7; H, 10.0.

(c) Similar treatment of 17,21-dibromopregnan-3(β)-ol-20-one with iron and acetic acid gave white crystals from methanol, m. p. 144–146°; no depression with pregnan-3(β)-ol-20-one.

21-Bromo-16-pregnen-3(β)-ol-20-one Acetate from 17,21-Dibromo-16-pregnen-3(β)-ol-20-one Acetate.—A solution of 5 g. of 17,21-dibromo-16-pregnen-3(β)-ol-20-one acetate and 5 g. of fused potassium acetate in 800 cc. of glacial acetic acid was refluxed for ninety minutes. The reaction mixture was concentrated to 100 cc. *in vacuo*, and poured into water. The precipitated solid was extracted with ether. The ether extract was washed with 5% sodium bicarbonate solution and with water. The ether was removed and the residue crystallized from methanol to give 1.5 g. of white crystals, m. p. 190–191°; this gave no depression with the starting material. The mother liquors were concentrated to give white plates which were recrystallized from methanol; 2 g.; m. p. 151–154°; depressed 30° with 17-bromo-pregnan-3(β)-ol-20-one acetate.

Anal. Calcd. for $C_{23}H_{36}O_3Br$: C, 63.1; H, 7.6. Found: C, 63.3; H, 7.8.

Similar treatment of 2 g. of 17,21-dibromo-16-pregnen-3(β)-ol-20-one yielded 0.8 g. of white crystals, m. p. 155–157°; depressed 20° with 21-bromo-16-pregnen-3(β)-ol-20-one acetate, m. p. 151–4°; gave a positive Beilstein test for halogen.

Anal. Calcd. for $C_{21}H_{32}O_2Br$: C, 63.8; H, 7.9. Found: C, 63.6; H, 7.4.

(2) Reichstein, *Helv. Chim. Acta*, **23**, 658 (1940).

(3) Cf. F. C. Whitmore and co-workers and W. G. Young and co-workers, *This Journal*, 1932 to date.

In similar runs with the free hydroxy compound some unreacted material was first isolated. The desired product could then be isolated from the mother liquors.

Reduction of 21-Bromo-16-pregnen-3(β)-ol-20-one Acetate.—(a) A mixture of 1.7 g. of 21-bromo-16-pregnen-3(β)-ol-20-one acetate, 3.4 g. of zinc dust and 50 cc. of acetic acid was heated on the steam-bath for thirty minutes. The reaction mixture was filtered and the filtrate poured into water. The precipitated solid was extracted with ether and the extract washed free of acid. The ether was evaporated and the residue was dissolved in 100 cc. of methanol containing 2 g. of potassium bicarbonate and refluxed on the steam-bath for two hours. The mixture was poured into water and the precipitated solid was extracted with ether. The ether was removed and the residue was crystallized from ether-pentane to give 0.5 g. of fine white crystals, m. p. 139°; no depression with pregnan-3(β)-ol-20-one.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 78.6; H, 10.8.

(b) 2.3 g. of 21-bromo-16-pregnen-3(β)-ol-20-one acetate was reduced with palladium and hydrogen in methanol containing pyridine and the product hydrolyzed with potassium bicarbonate to give 1.2 g. of white crystals, m. p. 144°; no depression with pregnan-3(β)-ol-20-one, m. p. 144°.

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

21-Bromopregnan-3(β)-ol-20-one Acetate from 21-Bromo-16-pregnen-3(β)-ol-20-one Acetate.—A solution of 1.0 g. of 21-bromo-16-pregnen-3(β)-ol-20-one acetate in 100 cc. of dioxane was shaken with 3 g. of palladium-barium sulfate catalyst and hydrogen at 3 atm. and room temperature for two hours. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was crystallized from methanol to give 0.9 g. of fine white needles, m. p. 145–147°. This material gave a positive Beilstein test for halogen and depressed the melting point of the starting material 20° and that of 17-bromopregnan-3(β)-ol-20-one acetate 25°.

Anal. Calcd. for $C_{23}H_{36}O_3Br$: C, 62.8; H, 8.0. Found: C, 62.5; H, 8.1.

Similar reduction of 2 g. of 21-bromo-16-pregnen-3(β)-ol-20-one gave 1.6 g. of white crystals of m. p. 127–128° which gave a positive Beilstein test for halogen.

Anal. Calcd. for $C_{21}H_{32}O_2Br$: C, 63.4; H, 8.4. Found: C, 63.1; H, 8.3.

Pregnan-3(β),21-diol-20-one Diacetate from 21-Bromopregnan-3(β)-ol-20-one Acetate.—A solution of 0.8 g. of 21-bromopregnan-3(β)-ol-20-one acetate and 1 g. of fused potassium acetate in 100 cc. of glacial acetic acid was refluxed for three hours. The solution was concentrated *in vacuo* and poured into water. The precipitated solid was extracted with ether. The ether extract was washed with water and the ether then evaporated. The residue was crystallized from methanol to give 200 mg. which melted at 145–146°; negative Beilstein test; depressed the melting point of the starting material 20° and that of 16-pregnen-3(β)-ol-20-one acetate, m. p. 145°, by 30°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.7; H, 9.2. Found: C, 71.8; H, 9.3.

From the mother liquors of similar runs was isolated material which melted at 139–141°. This contained no bromine. It gave a depression of 30° with the above compound. With 16-pregnen-3(β)-ol-20-one acetate, m. p. 144°, there was no depression.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 77.0; H, 9.6. Found: C, 76.6; H, 9.6.

Similar treatment of 0.9 g. of 21-bromopregnan-3(β)-ol-20-one with potassium acetate in acetic acid gave 0.3 g. of 21-acetoxy-pregnan-3(β)-ol-20-one, m. p. 121–3°, no halogen present.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.3; H, 9.6. Found: C, 72.9; H, 9.6.

Acetylation of the mother liquors and crystallization from methanol gave a small amount of material, m. p. 141°; no depression with 16-pregnen-3(β)-ol-20-one acetate.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.0; H, 9.6. Found: C, 76.8; H, 9.5.

Summary

1. The 17,21-dibromide of pregnan-3(β)-ol-20-one and of its acetate have been prepared.
2. These dibromides were converted to 21-bromo-16-pregnen-3(β)-ol-20-one and 21-bromopregnan-3(β)-ol-20-one.
3. 21-Bromopregnan-3(β)-ol-20-one and its acetate were converted to pregnan-3(β)-21-diol-20-one, mono and di-acetates, respectively.
4. A new rearrangement of α -halo-ketones has been described.

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