[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Reaction of Peracids with $\Delta^{20(21)}$-Steroid Enol Acetates

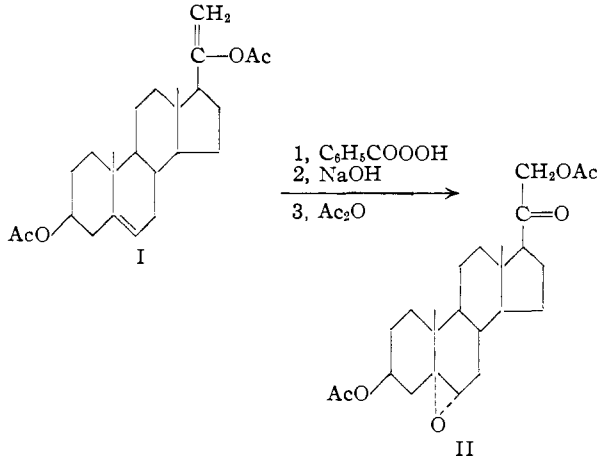
BY ROBERT BRUCE MOFFETT AND GEORGE SLOMP, JR.

RECEIVED JANUARY 28, 1954

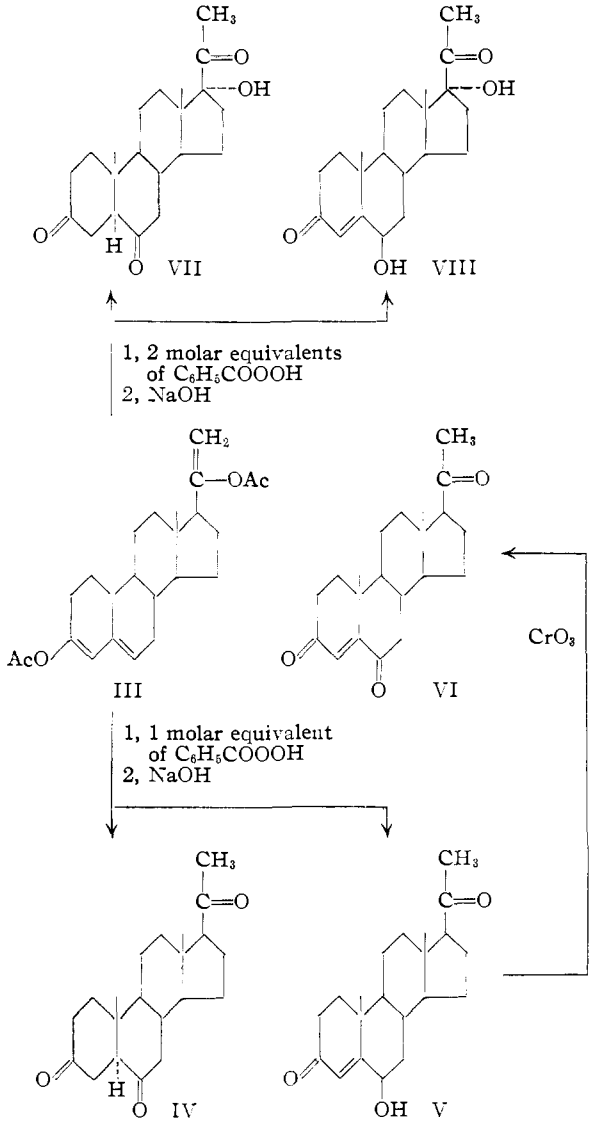
A study has been made of the action of perbenzoic (or peracetic) acid on $\Delta^{20(21)}$-steroid enol acetates. The $\Delta^{20(21)}$-enol acetate from pregnenolone (I) by treatment with perbenzoic acid followed by hydrolysis and reacetylation gave the (5,6)α-oxido-21-acetoxy derivative (II). The $\Delta^{3,5,20(21)}$-dienol acetate (III) from progesterone gave preferentially oxygenation in the 6-β position. Addition of peracid to 20-acetoxy-$\Delta^{16(17),20(21)}$-diene steroids gives preferentially 16,17-oxides with the $\Delta^{20(21)}$-enol acetate groupings still intact. These were converted to the corresponding (16,17)-oxido-20-keto-21-acetoxy steroids by addition of bromine followed by treatment with potassium acetate. Under more strenuous conditions both the 16(17) and 20(21) double bonds could be epoxidized with perbenzoic acid.

The preparation of $\Delta^{20(21)}$ steroid enol acetates by the acid-catalyzed reaction of isopropenyl acetate with 20-keto steroids has been described in a previous article[1] from these laboratories.

Vanderhaeghe, Katzenellenbogen, Dobriner and Gallagher[2] have prepared the enol acetate 3β,20-diacetoxy-20-allopregnene by a similar procedure and converted it to the 21-acetoxy compound, 3β,-21-diacetoxyallopregnan-20-one, by means of perbenzoic acid followed by hydrolysis and reacetylation. We independently carried out this series of reactions in connection with a study of steroid $\Delta^{20(21)}$-enol acetates. In a similar way the $\Delta^{20(21)}$-enol acetate from pregnenolone[1,2] (I) was converted by way of the diepoxide to the known 3β-21-diacetoxy-(5,6)α-oxidopregnan-20-one (II).[3]



A study was then made of the reaction of perbenzoic acid with 3,20-diacetoxy-3,5,20-pregnatriene (III, the dienol acetate of progesterone). An excess of perbenzoic acid was added at 0° to a solution of this enol acetate and aliquots were titrated at intervals with sodium thiosulfate. The results are expressed in Fig. 1 and indicate that one molar equivalent of perbenzoic acid reacted in about seven minutes while two molar equivalents had not been completely absorbed after four hours.[4] In order to determine which double bond reacted first, epoxidations were carried out using one molar equivalent of perbenzoic acid at 0°. After one hour the mixtures were treated with dilute sodium hydroxide and worked up giving two products. One was the known[5] allopregnane-3,6,20-trione (IV), and the other was shown to be 6-hydroxyprogesterone (V). 6-Hydroxy-Δ^4-3-ketones of this type are known to rearrange very easily to the saturated 3,6-dike-



(1) R. B. Moffett and D. I. Weisblat, THIS JOURNAL, **74**, 2183 (1952).

(2) H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, *ibid.*, **74**, 2810 (1952).

(3) L. Ruzicka, Pl. A. Plattner, H. Henner and O. Ernst, *Helv. Chim. Acta*, **29**, 248 (1946).

(4) A kinetic study was made from these data by Dr. Edward Garrett of our Department of Physics and will be published separately.

(5) (a) M. Ehrenstein and T. O. Stevens, *J. Org. Chem.*, **5**, 318 (1940); (b) S. Lieberman, K. Dobriner, B. R. Hill, L. F. Fieser and C. P. Rhoads, *J. Biol. Chem.*, **172**, 263 (1948).

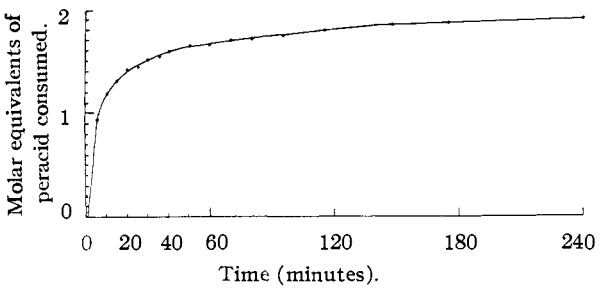
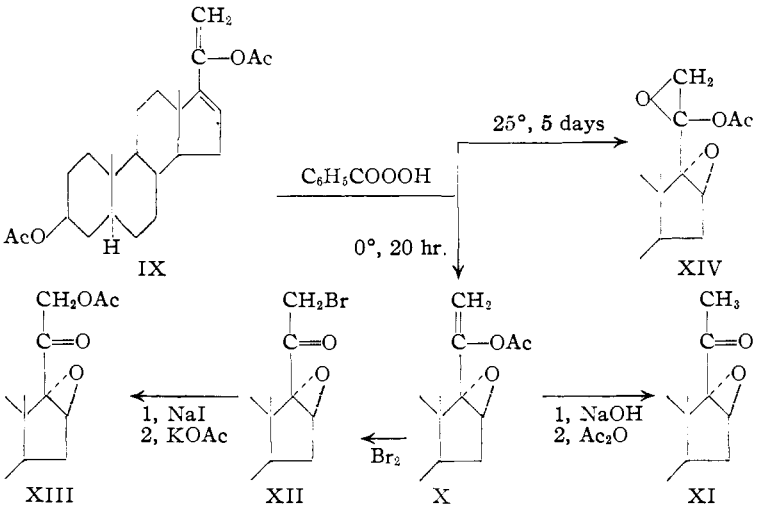


Fig. 1.—Reaction of perbenzoic acid with 3,20-diacetoxy-3,5,20-pregnatriene (III).

tones.[6] The structure of V was established by analysis, spectra and oxidation to the known 6-ketoprogesterone (VI).[7] The preparation of both the 6α- and 6β-hydroxyprogesterone by Balant and Ehrenstein[8] confirmed the 6-hydroxy structure of our compound and moreover showed it to be the 6β-isomer. When slightly over two molar equivalents of perbenzoic acid was allowed to stand for 5 days at room temperature with the enol acetate III and the product was hydrolyzed, two other products were isolated. Analyses and spectra showed them to be a saturated monohydroxy triketone and a dihydroxy diketone with α,β-unsaturation. This indicated that they might be the 21-hydroxy analogs of IV and V. However, the reporting of these structures by Herzig and Ehrenstein[9] showed this was not the case. It was possible that these might be the 17α-hydroxy analogs, VII and VIII, formed by the rearrangement of the 20-21 double bond to the 17(20)-position prior to the addition of perbenzoic acid. This rearrangement has previously been demonstrated.[2] The 17α-hydroxy structures were indeed found to be correct by comparison of one of them, the α,β-unsaturated ketone (VIII), with 6β,17α-dihydroxyprogesterone which Meister, *et al.*,[10] obtained by biological oxygenation of 17α-hydroxyprogesterone. Since the products (VII and VIII) were isolated in only small yields it is highly probable that the expected 21-hydroxy analogs were also present in the reaction mixture.

A study was made of the action of perbenzoic acid on 3β,20-diacetoxy-16,20-allopregnadiene[1] (IX) in the hope that oxygen could be introduced in both the 17- and 21-positions. Even though an excess of perbenzoic acid was allowed to stand with this diene at 0° for 23 hours, titration of an aliquot indicated that only one molar equivalent had reacted. The remainder of the reaction mixture afforded a good yield of 3β,20-diacetoxy-(16,17)α-oxido-20-allopregnene (X). The structure of this compound was established by analysis and infrared absorption spectrum which showed the band at 1660 cm.$^{-1}$ characteristic of $\Delta^{20(21)}$-enol acetate.[1,2] This was confirmed by hydrolysis and reacetylation to the known 3β-acetoxy-(16,17)-α-oxidoallopregnan-20-one[11] (XI). By the addition of bromine to the enol acetate X, the 21-bromo compound XII was obtained. This was converted to 3β,21-diacetoxy-(16,17)α-oxidoallopregnan-20-one (XIII) by the action of sodium iodide followed by potassium acetate. This appeared to be identical with that prepared previously by Plattner, *et al.*,[12] by another method. When the enol acetate IX was allowed to stand with perbenzoic acid at room temperature for five days, two molar equivalents added and the diepoxide XIV was isolated.



In a similar way, the action of perbenzoic acid on 3β,20-diacetoxy-5,16,20-pregnatriene XV was studied. Titration of aliquots of the reaction mixture gave the curve shown in Fig. 2 which indicates that at 25° two molar equivalents reacted within one hour while the third required about 30 hours to

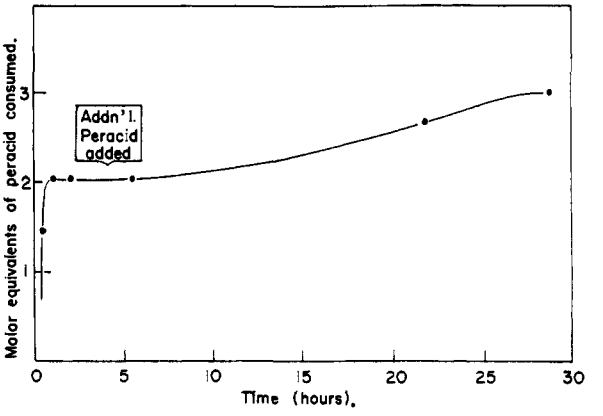


Fig. 2.—Reaction of 3β,20-diacetoxy-5,16,20-pregnatriene (XV) with first 3.26 molar equivalents, then 6.53 molar equivalents of perbenzoic acid.

(6) M. Ehrenstein, *J. Org. Chem.*, **13**, 214 (1948).

(7) (a) M. Ehrenstein, *ibid.*, **4**, 506 (1939); (b) R. B. Moffett, J. E. Stafford, J. Linsk and W. M. Hoehn, THIS JOURNAL, **68**, 1857 (1946).

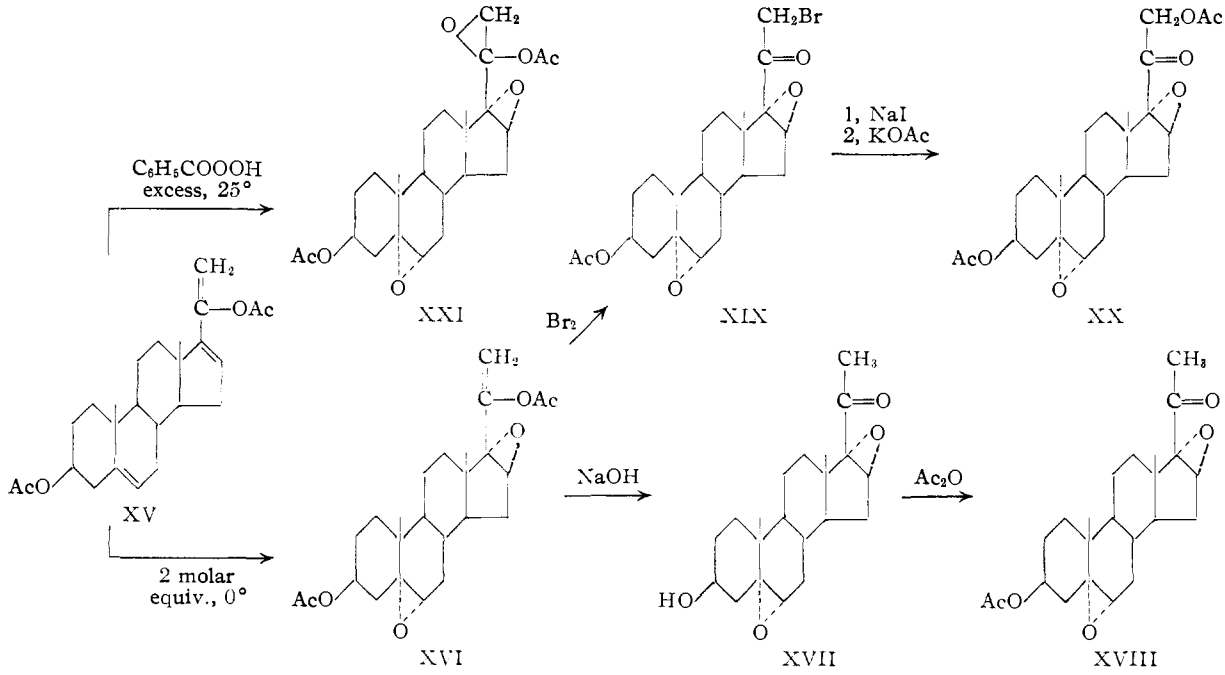
(8) C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1587 (1952).

(9) P. T. Herzig and M. Ehrenstein, *ibid.*, **16**, 1050 (1951).

(10) P. D. Meister, D. H. Peterson, H. C. Murray, G. B. Spero, S. H. Eppstein, A. Weintraub, L. M. Reineke and H. M. Leigh, THIS JOURNAL, **75**, 416 (1953).

(11) P. A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 385 (1947); Pl. A. Plattner, H. Heusser and M. Fluser, *ibid.*, **31**, 2210 (1948).

(12) Pl. A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *ibid.*, **30**, 395 (1947).



react completely. In a run in which two molar equivalents of perbenzoic or peracetic acid was allowed to react at 0° for 15 hours, 3β,20-diacetoxy-(5,6)α,(16,17)α-dioxido-20-pregnene (XVI) was isolated. The structure of this compound was established not only by analogy with the above reactions in the allo series, but also by hydrolysis to the diepoxide XVII of which an authentic sample was available[13] for comparison. The diepoxide was converted to its acetate XVIII.

The addition of bromine to the enol acetate XVI gave the 21-bromo compound XIX which was converted by sodium iodide followed by potassium acetate to 3β,21-diacetoxy-(5,6)α,(16,17)α-dioxido-pregnan-20-one (XX). When the enol acetate XV was allowed to react with three molar equivalents of perbenzoic acid for two days at room temperature a non-crystalline compound was obtained which appears to be the triepoxide XXI.

Experimental[14,15]

3β,21-Diacetoxy-(5,6)α-oxidopregnan-20-one (II).—To a solution of 1.0 g. (0.0025 mole) of 3β,20-diacetoxy-5,20-pregnadiene (I) in 3 ml. of benzene was added 7.28 ml. of a benzene solution containing 0.006 mole of perbenzoic acid. After standing at 25° for 24 hours the solution was mixed with 250 ml. of 0.096 *N* sodium hydroxide in 97% methanol, and allowed to stand an additional four hours at 25°. One ml. of acetic acid was added and the solution was distilled to dryness, under reduced pressure, the temperature being held below 30°. The residue was mixed with ether and washed with water, sodium bicarbonate solution, and again with water and dried over sodium sulfate. Removal of the ether gave an oily residue which was acetylated with acetic anhydride and pyridine at 25°. The product was crystallized from ether giving 0.15 g. of white crystals, m.p. 173–177°. Recrystallization from ethyl acetate yielded the diacetate as colorless needles, m.p. 181.5–182.5°, $[\alpha]^{25}D$ +20° (2% in chloroform). This compares well with the values reported by Ruzicka, *et al.*,[2] who give m.p. 180–182°, $[\alpha]D$ +22.8° (chloroform).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.50; H, 8.30.

6β-Hydroxyprogesterone (V).—To a solution of 1 g. (0.0025 mole) of 3,20-diacetoxy-3,5,20-pregnatriene (III) in 50 ml. of chloroform, cooled to below 0° was added 50 ml. of a benzene solution containing 0.0025 mole of perbenzoic acid. After one hour at 25° the solvent was removed under reduced pressure, below 30° temperature. The residue was dissolved in 50 ml. of methanol, and 52.6 ml. (0.01 mole) of 0.19 *N* sodium hydroxide solution in 80% ethanol was added slowly with stirring and cooling below 0°. After standing at 25° for 2.25 hours, the solution was neutralized with acetic acid and the solvent was removed under reduced pressure (temperature below 30°). The crystalline residue was shaken with a mixture of ether and cold dilute aqueous sodium bicarbonate solution, collected on a filter, washed with water and ether and dried yielding 0.57 g. (65%) of white crystals, m.p. 140–155°. After recrystallization first from acetone–ether and then from methylene chloride–ether 0.175 g. of 6β-hydroxyprogesterone was obtained, m.p. 174–177°, $[\alpha]^{24}D$ +103° (0.33% in chloroform); ultraviolet spectrum λ_{max}^{alc} 238 mμ, ε 13,680. These properties are in agreement with those reported by Balant and Ehrenstein[8] who report, m.p. 178–179°, $[\alpha]^{28}D$ +106.8° (1% in chloroform), λ_{max}^{alc} 235.5 mμ, ε 12,390.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.03; H, 9.16.

Allopregnane-3,5,20-trione (IV).—In another run under essentially the same conditions as the above, a small amount of the rearranged triketone was isolated. Recrystallization from acetone–ether yielded purified triketone, m.p. 232–234°, $[\alpha]^{24}D$ +44° (0.51% in chloroform), $[\alpha]^{24}D$ +48° (0.45% in ethanol) which is in good agreement with the values reported in the literature.[5]

6-Ketoprogesterone (VI).—To a solution of 0.2 g. (0.0006 mole) of 6β-hydroxyprogesterone in 5 ml. of acetic acid was added with cooling 5 ml. of a solution containing 0.0013 equivalent of chromic acid in 95% acetic acid. After 5 minutes in the ice-bath and one hour at room temperature the solution was poured into 100 ml. of water. The precipitate was collected, washed with water and dried giving 0.145 g. of crystalline 6-ketoprogesterone, m.p. 160–180°.

(13) This was prepared by Dr. W. P. Schneider in these laboratories by the reaction of perbenzoic acid with 3β-acetoxy-5,16-pregnadien-20-one followed by saponification and reaction with hydrogen peroxide under alkaline conditions. This work is to be published separately.

(14) All melting points were taken on a Fisher–Johns block and are uncorrected. Analysis and rotations were by Mr. William A. Struck and associates of our Analytical Chemistry Laboratory. Spectra were by Dr. James L. Johnson and associates of our Department of Physics.

(15) Infrared absorption spectra[14] were secured on all pure products and showed nothing inconsistent with the assigned structures.

After two recrystallizations from acetone–ether the melting point was raised to 197–199°. The ultraviolet absorption curve was essentially the same as that given by Ehrenstein[7] who reports a m.p. 185–188° for this compound.

6β,17α-Dihydroxyprogesterone (VIII).—To a solution of 1 g. (0.0025 mole) of 3,20-diacetoxy-3,5,20-pregnatriene (III) in 50 ml. of chloroform was added with cooling 50 ml. of a benzene solution containing 0.005 mole of perbenzoic acid. The solution was allowed to stand at room temperature, washed with dilute sodium bicarbonate solution, then with water and dried over sodium sulfate. Removal of the solvent gave a colorless gum which was dissolved in 50 ml. of methanol and then 52.6 ml. of 0.19 *N* sodium hydroxide solution in 80% ethanol was added slowly with cooling. After standing at room temperature for 2.5 hours the solution was neutralized with acetic acid and the solvent was removed keeping the temperature below 30°. The residue was mixed with methylene chloride and ether and the organic phase washed with dilute sodium bicarbonate, water and dried over sodium sulfate. Removal of the solvent gave a residue which crystallized on boiling with ether, yield 0.18 g., m.p. 208–213°. Recrystallization from methanol–ether yielded material, m.p. 233–235°. A mixed melting point with a known sample of 6β,17α-dihydroxyprogesterone[10] (m.p. 237.5–240°) gave no depression. Although the melting point of this substance seems to vary considerably depending on the rate of heating, etc., comparison of the infrared spectra of the two samples showed conclusively that they were the same. The ultraviolet spectrum was also in agreement with the proposed structure.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.75; H, 8.50.

17α-Hydroxyallopregnane-3,6,20-trione (VII).—Another run under essentially the same conditions as the above resulted in a mixture of gum and crystalline material. The gum was dissolved in boiling acetone leaving a small yield of crystals, m.p. 205–232°, which were recrystallized from methanol–methylene chloride, m.p. 248–251° dec. A mixed m.p. with the above 6β,17α-dihydroxyprogesterone gave a good depression (mixed m.p. 212–218°). Infrared spectra showed they were not the same, and indicated this compound contained several unconjugated ketone groups and a hydroxyl group. The high melting point rules out 21-hydroxyallopregnan-3,6,20-trione.[9] In view of the corresponding products IV and V obtained with one molar equivalent of peracid this material VII was accordingly presumed to be 17α-hydroxyallopregnane-3,6,20-trione.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.46; H, 8.85.

3β,20-Diacetoxy-(16,17)α-oxido-20-allopregnene (X).—To a solution of 1.2 g. (0.003 mole) of 3β,20-diacetoxy-16,20-allopregnadiene[1] (IX) in 10 ml. of chloroform and 10 ml. of benzene was added with cooling 4.15 ml. of a benzene solution containing 0.004 mole of perbenzoic acid. After standing at 0° for 16 hours it was diluted with ether, extracted with cold dilute sodium bicarbonate solution, then with water and dried over sodium sulfate. The solvent was removed and the residue was crystallized from petroleum hexane giving 0.95 g. (76.2%) of white crystals, m.p. 127–129°. A sample recrystallized from the same solvent gave the oxido enol acetate X, m.p. 128–131°, $[\alpha]^{24}D$ +30° (0.59% in chloroform). The infrared spectrum was consistent with the proposed structure, including a band at 1666 cm.$^{-1}$ characteristic of $\Delta^{20(21)}$-enol acetate.[1,2]

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71; CH_3CO, 20.66. Found: C, 71.75; H, 8.74; CH_3CO, 20.10.

Hydrolysis and Reacetylation of X to 3β-Acetoxy-(16,17)α-oxidoallopregnan-20-one (XI).—To a solution of 0.093 g. (0.000224 mole) of the above compound X in 5 ml. of alcohol was added 1.34 ml. (0.000246 mole) of 0.184 *N* sodium hydroxide in 80% ethanol. After allowing this solution to stand at 25° for 4 days a few drops of acetic acid was added, the solvent was removed under reduced pressure and the residue was mixed with ether, washed with water and the ether layer dried over sodium sulfate. The solvent was removed and the residue was acetylated with acetic anhydride and pyridine at room temperature. The product was crystallized from ether–pentane giving 0.035 g. of white crystalline acetate, m.p. 188–189°, $[\alpha]^{20}D$ +42° (1.4% in chloroform). Plattner, *et al.*,[11] give m.p. 186–187°, $[\alpha]^{20}D$ +51.6° (1.3% in chloroform) for this compound.

3β-Acetoxy-(16,17)α-oxido-21-bromoallopregnan-20-one (XII).—A solution of 0.416 g. (0.001 mole) of the oxido enol acetate X in 10 ml. of methylene chloride was cooled in an ice–salt-bath to about −10° and 9.25 ml. (0.001 mole) of 0.216 *N* bromine solution in methylene chloride was slowly added with stirring during a period of one hour. The solvent was removed under reduced pressure, below room temperature. The white crystalline residue was recrystallized from acetone–pentane giving 0.25 g. of the corresponding 21-bromo compound, m.p. 184–187°. Recrystallization from acetone raised the melting point to 188–190°, $[\alpha]^{24}D$ +45° (0.82% in chloroform).

Anal. Calcd. for $C_{23}H_{33}BrO_4$: C, 60.92; H, 7.34; Br, 17.63. Found: C, 60.91; H, 7.27; Br, 17.99.

3β,21-Diacetoxy-(16,17)α-oxidoallopregnan-20-one (XIII).—A mixture of 0.2 g. (0.00044 mole) of the bromo compound XII, 0.15 g. of powdered sodium iodide and 10 ml. of acetone was refluxed for 15 minutes and filtered. The filtrate was mixed with 1.5 g. of potassium bicarbonate and 0.9 ml. of acetic acid and shaken under reflux for 12 hours. This was diluted with ice-water and extracted with ether. The ether solution was washed with cold dilute sodium thiosulfate, then with water and dried over sodium sulfate. The solvent was removed and the product was crystallized from methanol giving 0.12 g. (63%) of the 21-acetate as white crystals, m.p. 145–148°. Recrystallization from ether–pentane raised the melting point to 151–152.5°, $[\alpha]^{24}D$ +57° (1.56% in chloroform). Plattner, *et al.*,[12] report, m.p. 153–154°; $[\alpha]^{23}D$ +64.2° (0.65% in chloroform) for this compound.

3β,20-Diacetoxy-(16,17)α,(20,21)-dioxidoallopregnane (XIV).—To a solution of 0.4 g. (0.001 mole) of 3β,20-diacetoxy-16,20-allopregnadiene (IX)[1] in 3 ml. of benzene was added 2.4 ml. of a benzene solution containing 0.00246 mole of perbenzoic acid. After standing for 5 days at room temperature it was worked up as described for the monooxido compound X above. The product crystallized from ether–pentane giving white crystals of the dioxide enol acetate, m.p. 125–134°. Recrystallization from ether raised the melting point to 136–138°. A mixture with the monooxido compound showed a definite melting point depression.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.42; H, 8.39; CH_3CO, 19.90. Found: C, 69.53; H, 8.51; CH_3CO, 18.16.

3β,20-Diacetoxy-(5,6)α,(16,17)α-dioxido-20-pregnene (XVI).—This compound was prepared from 2.0 g. (0.005 mole) of 3β,20-diacetoxy-5,16,20-pregnatriene (XV)[1] as described above for X in the allo series using 2.45 ml. of a benzene solution containing 0.01 mole of perbenzoic acid. The product was crystallized from ether giving 0.70 g. (32.6%) of the corresponding dioxido enol acetate as white crystals, m.p. 160–164°. A sample was recrystallized from methanol–ether, m.p. 163.5–165.5°, $[\alpha]^{24}D$ −25° (1.13% in chloroform). The infrared spectrum was consistent with structure XVI including the band at 1660 cm.$^{-1}$ characteristic of the $\Delta^{20(21)}$-enol acetate.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96; CH_3CO, 20.00. Found: C, 69.84; H, 7.94; CH_3CO, 20.15.

This same compound also was prepared on a larger scale by treating, at 0°, 34.22 g. (0.086 mole) of XV in 812 ml. of chloroform with 49 ml. of 40% peracetic acid to which had been added 1.06 g. of sodium acetate. The yield in this run after one crystallization from methanol was 17.20 g. (46.5%) of product melting at 161–162°. A second recrystallization from methanol yielded 14.6 g. (39.6%) of pure material, m.p. 166–167°.

(5,6)α,(16,17)α-Dioxidopregnan-3β-ol-20-one (XVII).—To a solution of 13.33 g. of the dioxido enol acetate XVI, m.p. 166–167°, in 200 ml. of methanol, was added 400 ml. of a 5% solution of sodium hydroxide in 90% methanol. After standing for 35 minutes it was diluted with 1.8 l. of water and extracted with chloroform. The combined extract was washed to neutrality with water and dried over sodium sulfate. The solvent was removed by distillation and the product was crystallized from methanol to yield a first crop of 9.80 g. (91.3%), m.p. 187–188°, $[\alpha]D$ −22° (1.15% in chloroform).

Recrystallization from methanol yielded white opaque plates, m.p. 193–196°. Mixed melting point with material prepared by a different method[13] showed no depression.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 72.80; H, 8.73. Found: C, 73.00; H, 8.60.

The 3β-Acetoxy-(5,6)α,(16,17)α-dioxidopregnan-20-one (XVIII).—A 0.17-g. portion of diepoxide (XVII) (m.p. 193–196°) in 3 ml. of pyridine was acetylated with 6 ml. of acetic anhydride. After standing overnight the solution was poured into 30 ml. of water and the precipitate formed was collected by filtration, dried and crystallized from methanol, yielding the 3-acetate, m.p. 207–208°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; CH_3CO, 11.08. Found: C, 70.71, 70.65; H, 7.67, 8.33; CH_3CO, 11.39.

3β-Acetoxy-(5,6)α,(16,17)α-dioxido-21-bromopregnan-20-one (XIX).—This was prepared as described for XII in the allo series above using 0.265 g. (0.000615 mole) of the dioxido compound XVI and 4.43 ml. (0.000615 mole) of a 0.278 *N* bromine solution. The crude product was crystallized from methanol giving 0.07 g. (24.3%) of the 21-bromo compound, m.p. 194–197°. Recrystallization from methanol–methylene chloride raised the melting point to 199–202°; $[\alpha]^{24}D$ −11° (0.61% in chloroform).

Anal. Calcd. for $C_{23}H_{31}BrO_5$: C, 59.10; H, 6.69; Br, 17.10. Found: C, 59.09; H, 6.93; Br, 16.89.

3β,21-Diacetoxy-(5,6)α,(16,17)α-dioxidopregnan-20-one (XX).—The 21-acetate was prepared from 0.07 g. of the above bromo compound by a procedure like that described for compound XIII in the allo series. The product crystallized from methanol, m.p. 192–194°.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.25; H, 7.68. Found: C, 67.46; H, 7.84.

Acknowledgment.—The authors have greatly appreciated the stimulating interest and helpful suggestions of Doctors D. I. Weisblat and A. C. Ott.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

Selective Oxidation of Some Steroid Diols

BY R. E. JONES AND F. W. KOCHER

RECEIVED FEBRUARY 18, 1954

The selective oxidation at C-3 of steroid 3,21-diols by means of N-bromoacetamide has been utilized in an improved synthesis of both 11-dehydro-17α-hydroxycorticosterone and 17α-hydroxycorticosterone.

Both N-bromoacetamide (NBA) and N-bromosuccinimide (NBS) have become generally recognized as excellent oxidizing agents for the conversion of secondary alcohols to ketones. Oxidation by these reagents, first reported by Reich and Reichstein,[1] has been of great utility in the steroid field. Of special interest is the fact that, in many cases, these N-halogenated amides possess a selectivity of attack for secondary as compared with primary hydroxyl groups. Kritchevsky, Garmaise and Gallagher[2] have reported a case in which 3α,-17α,21-trihydroxypregnane,11,20-dione was oxidized selectively to the 3,11,20-trione in high yield.

During our early studies on the partial synthesis of cortisone, we observed the highly selective oxidation of 20-cyano-3α,21-dihydroxy-17-pregnen-11-one (I) to give almost exclusively 20-cyano-21-hydroxy-17-pregnene-3,11-dione (II). The diketone II was identical in all respects with that previously prepared by Sarett[3] *via* another route. This observation is surprising for two reasons. The 21-ol is an allylic alcohol (in contrast to the case reported by Gallagher,[2] *et al.*); as such, it might be expected to oxidize first.[4] Secondly, no addition of the reagent (or of the elements of HOBr) to the 17-unsaturation was experienced. Since this oxidation is completely selective and nearly quantitative, its use in the conversion of I to cortisone represented an improvement over the original procedure.[5] By this present method, the troublesome (21)-monoacetylation of I is obviated and oxidation of an osmate ester at a latter step[5] becomes unnecessary. In the revised sequence, a direct acidic cleavage of the osmate ester to 17α,21-dihydroxypregnane-3,11,20-trione 21-acetate was used.[6] The revised section of the partial synthesis of cortisone is shown in the reaction sequence I → V.

The trione V was converted to cortisone by the procedure described by Sarett[3] and by Mattox and Kendall, also by McGuckin and Kendall.[7,8] The cyanopregnene II was the starting point for a previously described[6] partial synthesis of 17α-hydroxycorticosterone (Kendall's compound F or hydrocortisone).

It is apparent that the cyanopregnene diol I is capable of existing as *cis* and *trans* isomers about the Δ^{17}-double bond. These two isomers have, in fact, been separated.[9] In addition to compound I, "iso" I has been oxidized successfully to "iso" II and acetylated to "iso" III. Since the seat of the isomerism is destroyed by osmium tetroxide hydroxylation of the Δ^{17}-bond, both III and "iso" III afforded V as expected. While the intermediate osmate esters (IV) in both the *normal* and the *iso* series should be expected to be different, characterization of these compounds was not carried out during the course of this work.

Acknowledgment.—The authors are indebted to Mr. R. N. Boos and his associates for the microanalyses and to Mr. F. A. Bacher and his associates for the ultraviolet absorption spectra described in this paper.

Experimental

All melting points were taken in an open capillary, are uncorrected and were taken with uncalibrated Anschütz thermometers. Optical rotations are 1% in acetone.

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