[Contribution from the Research Department, Ciba Pharmaceutical Products, Inc.]

Direct Introduction of Oxygen into the Steroid Nucleus. II. Chromic Anhydride Oxidation of Isoandrosterone Acetate and Androstanediol Diacetate

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The chromic anhydride oxidation method previously described has been applied to two additional steroids. In the case of isoandrosterone acetate two main products were isolated and identified as 3β-acetoxy-6,17-androstanedione and 3β-acetoxy-5-hydroxy-17-androstanone. It has also been found that when 3β,17β-androstanediol diacetate was similarly oxidized 3β,-17β-diacetoxy-6-androstanone and 3β,5,17β-androstanetriol 3,17-diacetate were formed.

In view of the results previously reported on the oxidation of dehydroisoandrosterone acetate dibromide,[1] it seemed desirable to similarly oxidize some saturated steroids to see if substitution could be effected at some position in the nucleus other than C-14. When the reaction was carried out with isoandrosterone acetate four products were isolated by chromatography. The first of these had the empirical formula $C_{21}H_{30}O_4$, indicating that it contained one additional oxygen atom. Attempts to either acetylate the substance or to dehydrate it were unsuccessful. On catalytic reduction two moles of hydrogen were taken up and a tetrahydro derivative was obtained, thus indicating that a diketone might be present, although the original material formed only a monosemicarbazone. A search of the literature revealed that the physical properties of the original oxidation product were quite similar to those reported for 3β-acetoxy-6,17-androstanedione, while the tetrahydro compound correspondingly resembled 3β,6β,17β-androstanetriol 3-acetate.[2] On the basis of this evidence the diketone was synthesized[2] and proved to be identical with the unknown, thus establishing that in this case oxidation had taken place with the introduction of a 6-keto group.

The second oxidation product also contained one additional oxygen atom as shown by the formula $C_{21}H_{32}O_4$. A sample of the material was dehydrated and the resulting product was identified as dehydroisoandrosterone acetate, thus indicating the presence of a hydroxyl group probably at C-5. This supposition was strengthened by the similarity in properties of our oxidation product with those given in the literature for 3β-acetoxy-5-hydroxy-17-androstanone. That this was its structure was confirmed by synthesis.[2]

The third chromatographic fraction from the isoandrosterone acetate oxidation was further purified and yielded small amounts of two as yet unidentified products whose analyses best fit the formulas $C_{23}H_{34}O_6$ and $C_{21}H_{32}O_5$.

When androstanediol diacetate was similarly oxidized three products could be isolated. The first of these analyzed for $C_{23}H_{34}O_5$ which corresponded to one additional oxygen function, which did not seem to be alcoholic since acetylation and dehydration reactions were unsuccessful. In view of the nature of the oxidation products mentioned above, it seemed likely that this compound might also be a 6-ketone. Therefore, it was saponified and then oxidized to yield a triketone which was identified as 3,6,17-androstanetrione. The structure of this oxidation product was finally proved by showing it to be identical with a synthetic sample of 3β,17β-diacetoxy-6-androstanone made by the method used by Heilbron, *et al.*,[3] for the preparation of 6-ketocholestanyl acetate.

The second androstanediol acetate oxidation product had the empirical formula $C_{23}H_{36}O_5$. Its structure was easily shown by proving its identity with 3β,5,17β-androstanetriol 3,17-diacetate, a compound which we had already prepared by the reduction and acetylation of 3β-acetoxy-5-hydroxy-17-androstanone.

The third oxidation product, $C_{23}H_{34}O_5$, was obtained in such a low yield that insufficient material was available for further work.

The results of these experiments show that when positions 5 and 6 of the steroid nucleus are unsubstituted chromic anhydride first reacts with the molecule at these sites. It is interesting that none of the major products were the result of oxidation at C-14.

Experimental[4]

Oxidation of Isoandrosterone Acetate.—Three batches of 20 g. of isoandrosterone acetate were each dissolved in 1000 cc. of glacial acetic acid in a 3-liter 3-necked round-bottom flask equipped with an efficient stirrer and thermometer. The flask was placed in a water-bath so that the temperature was maintained at about room temperature (21–24°). Sixty grams of finely pulverized solid chromic anhydride was added to each flask in one portion. The stirring was continued for one-half hour during which time the internal temperature rose 3–4°.

The solution was then decanted from the excess solid chromic anhydride and that remaining in solution was reduced with 30% sodium bisulfite solution. The reaction mixture was diluted with an equal volume of water and the precipitated material extracted with four portions of 125 cc. each of chloroform. The combined extracts were washed with water, 30% sodium hydroxide solution and finally with water until neutral. The solution was then dried and the solvent removed leaving 45 g. of crude oil.

This was chromatographed in benzene solution on 900 g. of acid-washed alumina and the following crystalline fractions were isolated: 1, benzene to 2% ether in benzene, 15 g., m.p. 113–116°; 2, 20–30% ether in benzene, 5.6 g., m.p. 196–201°; 3, ether to 2% methanol in ether, 8.9 g., m.p. 141–160°; 4, 25% methanol in ether to methanol, 4.9 g., m.p. 200–215°.

Fraction 1 after recrystallization was shown to be starting material, isoandrosterone acetate.

Fraction 4 seemed to be a mixture and was, therefore, rechromatographed yielding two substances which were fur-

(1) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica and C. R. Scholz, This Journal, **74**, 5506 (1952).

(2) L. Ruzicka and A. C. Muhr, *Helv. Chim. Acta*, **27**, 503 (1944).

(3) I. M. Heilbron, H. Jackson, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 102 (1938).

(4) All melting points are uncorrected and were taken by the capillary tube method in an aluminum block. Except where noted all optical rotation measurements were taken in chloroform solution. We are greatly indebted to Mr. Louis Dorfman and his associates of our analytical laboratories for the microanalyses and rotation data.

ther purified by recrystallization from methanol: A, 500 mg., m.p. 234–235°, $[\alpha]^{23}D$ +4°.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 68.0; H, 8.4. Found: C, 68.2; H, 8.5.

B. 400 mg., m.p. 251–252°, $[\alpha]^{23}D$ +38°.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.2; H, 8.9. Found: C, 69.3; H, 9.1.

Isolation of 3β-Acetoxy-6,17-androstanedione.—Fraction 2 of the above chromatogram was repeatedly recrystallized from methanol–water and yielded 2.3 g. (4%) of pure product, m.p. 208–209°, $[\alpha]^{23}D$ +33°; reported[2] m.p. 203–205°, $[\alpha]^{15}D$ +39°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.8; H, 8.7. Found: C, 72.8; H, 8.6.

Semicarbazone, m.p. 247–249°.

Anal. Calcd. for $C_{22}H_{33}O_4N_3$: N, 10.4. Found: N, 10.2.

Several attempts to dehydrate the compound were unsuccessful. Acetylation with acetic anhydride and pyridine resulted in the complete recovery of unchanged starting material.

3β-Hydroxy-6,17-androstanedione.—A 50-mg. sample of the above material was saponified with alcoholic potassium hydroxide by refluxing for three hours. After working up the material in the usual way and recrystallization of the product from methanol–water, 40 mg. of substance was obtained, m.p. 176–178°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.0; H, 9.3. Found: C, 74.9; H, 9.4.

3β,6β,17β-Androstanetriol 3-Acetate.—A 37.8-mg. sample of the above 3β-acetoxy-6,17-androstanedione in 5 cc. of acetic acid was hydrogenated using 30 mg. of platinum oxide catalyst. At the end of an hour 2.02 moles of hydrogen had been absorbed and on working up the product 35 mg. of material, m.p. 206–208°, was obtained after recrystallization from methanol–water; reported[2] m.p. 204–207°.

Synthesis of 3β-Acetoxy-6,17-androstanedione from Dehydroepiandrosterone Acetate.—To a solution of 17 g. of dehydroisoandrosterone acetate in a mixture of 100 cc. of carbon tetrachloride and 500 cc. of ether was added 164 cc. of an ether solution of monoperphthalic acid containing 0.06 g./cc. The mixture was allowed to stand for 48 hours at room temperature. On working up the product[2] and chromatographing the resulting mixture, 4.0 g. of 3β-acetoxy-5β,6β-epoxy-17-androstanone, m.p. 187–189°, and 5.5 g. of the α-epoxide, m.p. 219–223°, were obtained.

Three grams of the β-epoxide was reduced in acetic acid solution with 443 mg. of platinum oxide catalyst and approximately two moles of hydrogen was taken up. The crude reaction product was then oxidized with chromic acid in acetic acid solution. The product was purified by chromatography and yielded 550 mg. of pure material, m.p. 204–207°, $[\alpha]^{23}D$ +33°. In all respects it was identical with that isolated from the chromic acid oxidation of isoandrosterone acetate.

Isolation of 3β-Acetoxy-5-hydroxy-17-androstanone.—Chromatographic fraction 3 obtained as previously mentioned from the oxidation products of isoandrosterone acetate was recrystallized from methanol–water and yielded 4.2 g. (7.3%) of material showing a double melting point, 152–153°, 164–166°, $[\alpha]^{24}D$ +57°; reported[2] m.p. 152–153°, 162–163°, $[\alpha]^{13}D$ +59°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.4; H, 9.3. Found: C, 72.2; H, 9.2.

3β,5-Dihydroxy-17-androstanone.—A 240-mg. sample of the above product was saponified with alcoholic potassium carbonate solution and yielded 195 mg. of product, m.p. 280–282°, $[\alpha]^{23}D$ +88°; reported[2] m.p. 281–282°, $[\alpha]^{14}D$ +92°.

Dehydroisoandrosterone Acetate from 3β-Acetoxy-5-hydroxy-17-androstanone.—The dehydration was carried out by heating a solution of 250 mg. of the diolone in 2.5 cc. of acetic acid with 250 mg. of potassium acid sulfate on the steam-bath for 20 minutes. After cooling, the mixture was allowed to stand 4–5 hours at room temperature with 10 cc. of a saturated sodium chloride solution. The resulting precipitated material was extracted with ether. The ether solution was washed with water and sodium carbonate solution, dried and the solvent removed. After recrystallization of the residue from methanol 165 mg. of product was obtained, m.p. 165–167°. A mixture of this material with an authentic sample of dehydroisoandrosterone acetate showed no depression of the melting point.

Synthesis of 3β-Acetoxy-5-hydroxy-17-androstanone.—A solution of 3.5 g. of 3β-acetoxy-5α,6α-epoxy-17-androstanone, the preparation of which has already been described, in 120 cc. of acetic acid was reduced using 653 mg. of platinum oxide catalyst. The reaction was stopped after one mole of hydrogen had been absorbed and the product worked up and purified by chromatography.[2] After recrystallization from methanol–water 980 mg. of material was obtained, m.p. 152–154°, 164–167°, $[\alpha]^{23}D$ +57°. A mixture of this substance with that isolated from the oxidation of isoandrosterone acetate melted 153–155, 164–165°, thus confirming their identity.

Androstane-3β,5,17β-triol 3,17-Diacetate.—To a solution of 500 mg. of 3β-acetoxy-5-hydroxy-17-androstanone in 5 cc. of methanol was added 250 mg. of sodium borohydride. The solution was refluxed for one hour and then 5 cc. of 1% potassium carbonate solution was added and the refluxing continued for an additional hour. The alcohol was removed by distillation *in vacuo* and the precipitated steroid was extracted with chloroform. The chloroform solution was dried and the solvent removed leaving a semi-crystalline mass which was directly acetylated with acetic anhydride and pyridine. On working up the product 326 mg. of material was obtained, m.p. 183–184°, $[\alpha]^{23}D$ −10°; reported[5] m.p. 180–181°, $[\alpha]^{18}D$ −10°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.4; H, 9.3. Found: C, 70.2; H, 9.5.

Oxidation of Androstanediol Diacetate.—Two batches of 15 g. each of 3β,17β-androstanediol diacetate were separately oxidized in acetic acid solution with solid chromic anhydride as has already been described for the oxidation of isoandrosterone acetate. They yielded a combined neutral fraction of 9.8 g. which was chromatographed on 320 g. of acid-washed alumina in benzene solution. The following crystalline fractions were isolated: 1, benzene, 180 mg., m.p. 115–125°; 2, benzene to 1% ether in benzene, 1.30 g., m.p. 161–172°; 3, 25% ether in benzene to 100% ether, 2.10 g., m.p. 156–166°; 4, ether to 10–20% methanol in ether, 1.0 g., m.p. 208–218°.

Fraction 1 on recrystallization from methanol yielded 90 mg. of starting material.

Fraction 4 on repeated recrystallization from acetone–hexane yielded 123 mg. of product, m.p. 216–217°, $[\alpha]^{23}D$ −1°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.7; H, 8.8. Found: C, 71.0; H, 9.3.

Isolation of 3β,17β-Diacetoxy-6-androstanone.—Fraction 2 of the above chromatogram was recrystallized from methanol and yielded 560 mg. (1.8%) of material, m.p. 177–178°, $[\alpha]^{23}D$ −37°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.7; H, 8.8. Found: C, 70.5; H, 9.0.

3β,17β-Dihydroxy-6-androstanone.—A solution of 200 mg. of the above diacetate in 80% ethanol containing potassium carbonate was heated for three hours on the steam-bath. About 138 mg. of free diol was isolated from the reaction mixture and after recrystallization from aqueous methanol melted at 208–210°.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.5; H, 9.9. Found: C, 74.8; H, 10.1.

3,6,17-Androstanetrione.—A 100-mg. sample of the above diolone was oxidized with chromic anhydride overnight in acetic acid solution at room temperature. On working up the product 50 mg. of trione was obtained, m.p. 193–195°, after recrystallization from ether; reported[6] m.p. 191–192°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.5; H, 8.7. Found: C, 75.6; H, 8.4.

This material was identical with that prepared by a similar oxidation of 3β-hydroxy-6,17-androstanedione.

Synthesis of 3β,17β-Diacetoxy-6-androstanone from 5-Androstene-3β,17β-diol Diacetate.—A solution of 5 g. of 3β,17β-diacetoxy-5-androstene in 20 cc. of acetic acid was treated with 7 drops of a mixture of 30.8 cc. of fuming nitric acid (d. 1.50) and 1.9 cc. of red fuming nitric acid (d. 1.59–

(5) S. A. Julia, Pl. A. Plattner and H. Heusser, *Helv. Chim. Acta*, **25**, 665 (1952).

(6) M. Davis and V. Petrow, *J. Chem. Soc.*, 2563 (1949).

1.60) with stirring at room temperature according to the directions for the preparation of 6-ketocholestanyl acetate.[3] The reaction flask was then cooled in an ice–salt-bath and the remaining nitric acid mixture added with vigorous stirring during one hour. Stirring was continued for an additional half-hour and then the solution was poured into ice and water. The yellow precipitate was filtered, washed well with water and air-dried, m.p. 120–125° (dec.).

The crude nitrate was directly reduced in acetic acid solution (100 cc.) by adding 12.5 g. of zinc dust and heating on the steam-bath for two hours and then under reflux for 10 hours. After dilution with water the product was isolated by ether extraction and the resulting brown oil obtained after removal of the solvent was directly hydrolyzed with alcoholic hydrochloric acid for 1.5 hours. On working up the reaction only 520 mg. of crude oil was obtained, which was purified by chromatography on alumina in 25% benzene–hexane solution. The fraction eluted with 100% benzene gave 190 mg. of material, m.p. 174–175° after recrystallization from aqueous methanol. A mixture of this material with that isolated from the oxidation of androstanediol diacetate (m.p. 177–178°) melted at 173–176°.

Isolation of 3β,5,17β-Androstanetriol 3,17-Diacetate.—Fraction 3 of the previously mentioned chromatogram of the oxidation products of androstanediol diacetate was recrystallized from hexane and 1.6 g. (5.3%) of material, m.p. 180–182°, $[\alpha]^{23}D$ −9°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.4; H, 9.3. Found: C, 70.2; H, 9.5.

Since the physical properties of this compound were the same as those of the androstane-3β,5α,17β-triol 3,17-diacetate previously described, a mixture of the two substances was made and this showed no depression of the melting point.

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NOTES

Reduction of Acyl Cyanides with Lithium Aluminum Hydride

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Acyl cyanides have been hydrogenated to primary amino alcohols in good yields[2] but this method has not enjoyed wide use because of its relatively complicated mode of execution. It has now been observed that the same result can be achieved by reduction with lithium aluminum hydride. By this procedure it is also possible to preserve in the amino alcohols such substituents as aromatic halogen atoms which could be hydrogenolyzed in catalytic methods.

The preparation of amino alcohols from acyl cyanides complements related reduction methods of cyanohydrins which lead to amino alcohols[3–6] or amines.[4,7]

Experimental[8]

2-Phenylethanolamine.—A solution of 7.35 g. (0.056 mole) of benzoyl cyanide[9] in 100 ml. of dry ether was added dropwise to a stirred solution of 10 g. (*ca.* 0.26 mole) of lithium aluminum hydride in 300 cc. of ether so that refluxing was maintained. After another four hours of boiling the mixture was decomposed with water, and a 30% sodium hydroxide solution was added in small portions until a granular precipitate appeared. The latter was filtered, washed with ether, and the oily residue from the combined ether layers was distilled under reduced pressure. It yielded 6.5 g. (86%) of a colorless solid which, after recrystallization from benzene–petroleum ether melted at 56.5–58°.[10]

Anal. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08. Found: C, 69.81; H, 8.32.

When in another run only 30% excess of lithium aluminum hydride was used, the yield was reduced to 30%.

The N-benzoyl derivative crystallized from ethanol, m.p. 148–149°.[10]

***p*-Chlorobenzoyl Cyanide.**—A mixture of 65.5 g. (0.374 mole) of *p*-chlorobenzoyl chloride and 40.5 g. (0.45 mole) of cuprous cyanide was heated at 210–220° for one hour and then distilled under reduced pressure. The yield of colorless solid was 24.9 g. (40%), m.p. 37–40°. Redistillation raised the melting point to 41–42.5°.[11]

Anal. Calcd. for C_8H_4ClNO: C, 58.03; H, 2.44. Found: C, 57.76; H, 2.35.

2-(*p*-Chlorophenyl)-ethanolamine.—Reducing 8.3 g. (0.05 mole) of *p*-chlorobenzoyl cyanide with 10 g. (*ca.* 0.26 mole) of lithium aluminum hydride in a total of 300 ml. of dry ether for three hours, and working the reaction mixture up as described above, 7.7 g. (89%) of a colorless solid was obtained which crystallized from benzene, m.p. 93.5–94.5°.

Anal. Calcd. for $C_8H_{10}ClNO$: C, 55.98; H, 5.87. Found: C, 55.82; H, 5.84.

The benzoyl derivative crystallized from ethanol, m.p. 215.5–217.5°.

Anal. Calcd. for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12. Found: C, 65.15; H, 5.34.

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Tetraethyl Pyrophosphite as a Reagent for the Preparation of Anilides

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Tetraethyl pyrophosphite has been shown to be a useful reagent for forming peptide bonds.[1] We have found that it can be conveniently used to prepare anilides in good yield (Table I).

Experimental

Tetraethyl pyrophosphite was prepared as previously described.[1]

(1) Parke, Davis & Co. Predoctoral Fellow.
(2) K. Kindler and W. Peschke, *Arch. Pharm.*, **269**, 581 (1931).
(3) F. Wolfheim, *Ber.*, **47**, 1440 (1914).
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(5) H. R. Nace and B. B. Smith, *ibid.*, **74**, 1861 (1952).
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(7) W. H. Hartung, THIS JOURNAL, **50**, 3370 (1928).
(8) All melting points are corrected.
(9) T. S. Oakwood and C. A. Weisberger, *Org. Syntheses*, **24**, 14 (1944).
(10) Literature (ref. 9), m.p. 57°; N-benzamide derivative 140°.
(11) M. R. Zimmermann, *J. prakt. Chem.*, [2] **66**, 353, 383 (1902), reports m.p. 40°.
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