resulting oil was oxidized with dichromate in benzene–acetic acid at 25° and the product chromatographed on 5 g. of alumina. Petroleum ether eluates gave 70 mg. of B-norcoprostane-3α,6α-oxide (8), and petroleum ether–benzene (1:1) eluates gave 30 mg. of oily ketone 15. When covered with methanol and let stand at 2–3° the material crystallized in needles (m.p. 60–63°). Recrystallization from methanol raised the m.p. to 64.5–65.5°, α_D +37.1° Chf, λ^{CS_2} 5.82 μ.

Anal. Calcd. for $C_{26}H_{44}O$ (372.61): C, 83.80; H, 11.90. Found: C, 83.33; H, 11.52.

Elution of the column with ether gave 30 mg. of crystalline dione 1.

A purer sample of B-norcoprostane-3-one (15) was obtained by dichromate oxidation of B-norcoprostane-3α-ol (11) in benzene–acetic acid at 25°. Crystallized from methanol, it formed needles, m.p. 70–71°, α_D +20.5° Chf, λ^{CS_2} 5.82 μ (Found: C, 84.01; H, 12.01). The two samples showed no depression in m.p. on admixture, and the infrared spectra were identical.

B-Norcoprostane-3α-ol (11).—A mixture of 700 mg. of B-norcoprostane-3,6-dione 3-ethyleneketal (16), 1.4 g. of potassium hydroxide, 1 ml. of hydrazine, 7 ml. of ethanol and 10 ml. of triethylene glycol was refluxed for 30 min. and the condenser was removed and the solution heated at 200–208° for 1 hr. in a hydrogen atmosphere. The resulting ketal, an oil (680 mg.), was dissolved in 7 ml. of tetrahydrofuran and the solution was treated at 25° with 2.5 ml. of 25% perchloric acid and allowed to stand overnight. The crude product was an oil, but on chromatography on 15 g. of alumina, petroleum ether–benzene (6:4) eluates gave 390 mg. of crystalline ketone (needles). Several crystallizations raised the m.p. only to 60–61°, and hence the material was reduced with lithium aluminum hydride in ether and the mixture of 3-ols was chromatographed on 12 g. of alumina. Petroleum ether–benzene (1:4) eluates gave 130 mg. of crystals of the 3α-ol 11, which on recrystallization from aqueous methanol formed aggregates of fine needles, m.p. 93–94.5° (a companion substance is described below).

Anal. Calcd. for $C_{26}H_{46}O$ (374.63): C, 83.35; H, 12.38. Found: C, 83.41; H, 12.13.

A product identical with the 3α-ol 11 was obtained by lithium aluminum hydride reduction of 50 mg. of the 3-one 15 (m.p. 64.5–65.5°, derived from 14). Chromatography of the crude product gave an oil, a solution of which in methanol when let stand at 2–3° gave crystals, m.p. 70–80°. Recrystallization gave aggregates of small crystals, m.p. and mixed m.p. 92–94.5°. Huang-Minlon reduction of 100 mg. of B-norcoprostane-3α-ol-6-one (10) and chromatography gave an oil of infrared spectrum identical with that of 11 (prepared from 16).

B-Norcholestane-3β-ol (17).—Following the chromatograph fractions affording B-norcoprostane-3α-ol (11), benzene eluates afforded 60 mg. of 17, which crystallized from methanol in needles, m.p. 129–131°.

Anal. Calcd. for $C_{26}H_{46}O$ (374.63): C, 83.35; H, 12.38. Found: C, 83.29; H, 12.24.

Dichromate oxidation of 17 (35 mg.) and digestion of the product with methanol gave the corresponding 3-one, m.p. 85–90°. Recrystallization from methanol yielded needles, m.p. 90–93°, α_D +44°.

CAMBRIDGE 38, MASS.

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

4-Oxasteroid Analogs

BY NORMAN W. ATWATER AND JACK W. RALLS[1]

RECEIVED SEPTEMBER 23, 1959

The keto-acid IIa and lactonol IIIa obtained from ozonization of testosterone benzoate have been transformed into a series of epimeric saturated lactones (V and VI), pseudoesters (VIII) and a pseudoacid chloride (VII). Methods for interconverting the keto-acid and the lactonol are discussed.

As part of a general investigation into the effects of changes in the basic carbon skeleton of steroids on their physiological properties, we have prepared a number of androstane derivatives having an oxygen in place of a carbon at the 4-position. Compounds of this type have been prepared previously as intermediates in the series of reactions leading to the introduction of radioactive carbon into the steroid molecule[2] and in certain total synthetic schemes,[3] but in only one case[2a] have the reactions of these compounds been explored to any extent.

When testosterone benzoate (I) was ozonized according to Turner,[2a] the reported product, m.p. 150.5–151.5°, $[\alpha]_D$ +81°, was obtained in the first experiment but a new isomeric material, m.p. 175–176°, $[\alpha]_D$ +127°, was obtained on all subsequent oxidations. Since the rotations of the substances differed and the infrared spectra were not identical, it was clear that this was not a case of polymorphism. It was found that the lower melting isomer could be converted to the new material by heating it above its melting point. The tautomeric keto-acid IIa and lactonol IIIa structures were assigned to the high and low melting materials, respectively, on the basis of their infrared spectra. Compound IIIa had a lactone carbonyl band (5.74 μ) which was clearly resolved from the ester carbonyl absorption and a highly bonded hydroxyl (3.08 μ), while IIa showed only broad unresolved carbonyl absorption (5.83–5.88 μ) and no discernible band in the hydroxyl region.[4,5]

Further evidence for the tautomeric relationship of the two ozonization products of testosterone benzoate is the identity of the materials obtained from them on further reaction. Treatment of either IIa or IIIa with acetyl chloride and acetic anhydride led to 17β-benzoyloxy-4-oxaandrost-5-en-3-one (IV)[2a] which exhibited a strong infrared

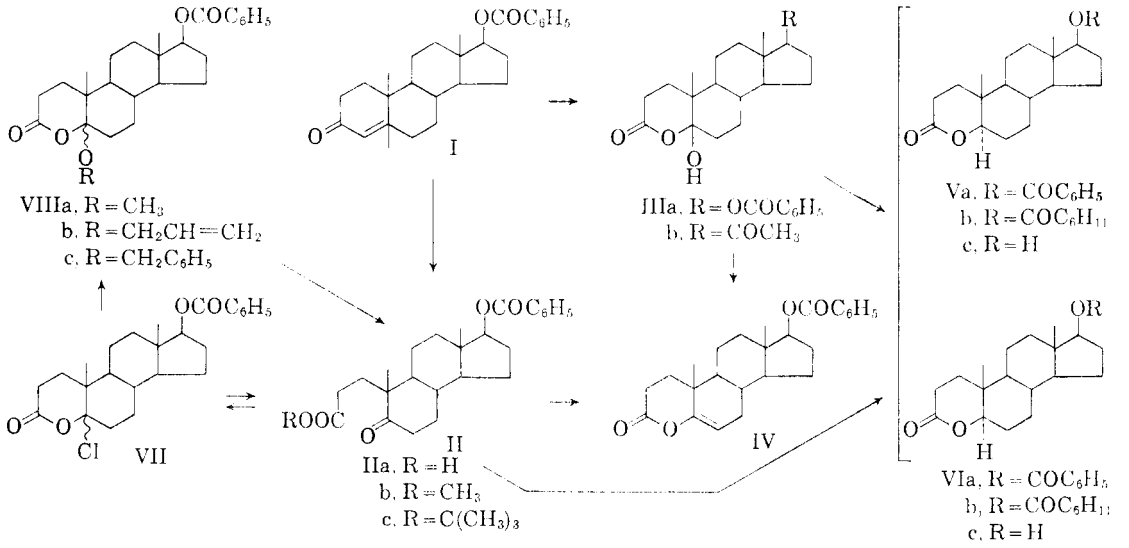
(1) Western Utilization Research and Development Division, Agricultural Research Service, U. S. Dept. of Agriculture, Albany 10, Calif.

(2) (a) R. B. Turner, THIS JOURNAL, **72**, 579 (1950); (b) G. I. Fujimoto, *ibid.*, **73**, 1856 (1951); (c) R. D. H. Heard and P. Ziegler, *ibid.*, **73**, 4036 (1951); (d) M. Uskokovic, R. I. Dorfman and M. Gut, *J. Org. Chem.*, **23**, 1947 (1958).

(3) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952).

(4) Similar ozonizations of cholest-4-ene-3-one (ref. 2a) and 17β-benzoyloxy-19-norandrost-4-en-3-one (A. J. Birch, *Chemistry & Industry*, 615 (1951)) gave products whose spectra indicated that they were in the keto-acid form.

(5) The spectral characteristics of IIIa agree with those reported by Uskokovic, Dorfman and Gut (ref. 2d) for the acidic ozonization product of progesterone to which they have assigned structure IIIb (5β-OH).



band at 5.93 μ due to carbon–carbon double-bond stretching[6] in addition to the expected carbonyl absorptions. Treatment of either tautomer with sodium borohydride produced a mixture of epimeric saturated lactones (Va and VIa) which were only incompletely separated by chromatography on silica. One epimer could be obtained pure in over 50% yield by direct crystallization of the crude reaction product and the second could be separated in low yield by laborious crystallization of the mother liquors.

Exhaustive hydrogenation of IIa over platinum led to a similar mixture of lactones (substituted at C_{17} with the cyclohexanecarboxy group) (Vb and VIb) which were ineffectively separated by chromatography on silica. However, by crystallization of the early chromatography fractions one of the isomers (VIb) could be obtained pure in low yield. The correspondence in configuration at C_5 of VIb with the benzoate VIa was established by the alkaline hydrolysis of both to a common alcohol (VIc). The epimeric cyclohexanecarboxylate Vb was prepared by acylation of Vc obtained in turn by hydrolysis of the benzoate Va.

Assignments of configuration at C_5 have been made on consideration of the fact that Va is the preponderant epimer in the borohydride reduction of the keto-acid IIa. It is well known that metal hydride reductions of unhindered ketones give mainly the equatorial alcohols.[7] Using the optical rotation differences as a basis for comparison, these assignments correspond with those made by Turner[2a] in the cholestane series (on the grounds that the 5α-epimer is obtained on hydrogenation of the enol-lactone).

The pseudoacid chloride VII formed when IIa was treated with thionyl chloride in benzene has spectral characteristics (λ_{max} 5.69 and 13.34 μ) as described[2a,8] for the corresponding cholestane and norandrostane derivatives. It could be readily crystallized to a moderately narrow melting range but slowly decomposed on standing even when the original material was carefully purified. On reaction with alcohols in the presence of pyridine,[9] pseudoesters VIIIa,b,c were formed. The methyl pseudoester VIIIa was obtained in 47% yield but the allyl (VIIIb) and benzyl (VIIIc) compounds were formed in only small yields. The structures of these compounds were assigned on the basis of lactone carbonyl absorption bands (5.71–5.75μ) in their spectra and by the fact that the methyl derivative VIIIa could be converted on mild acid treatment in methanol into the same oily methyl ester IIb obtained by diazomethane treatment of the keto-acid IIa.

As previously mentioned, the lactonol IIIa was produced on only one occasion when testosterone benzoate was ozonized. It could not be obtained from the keto-acid IIa on mild acid treatment or on reprecipitation from basic solution. Attempts were therefore made to hydrolyze the pseudoacid chloride VII directly to the lactonol. On treatment of VII with aqueous pyridine or aqueous dioxane with pyridine added only the keto-acid IIa was obtained but when aqueous *t*-butyl alcohol containing pyridine was employed, a small quantity of the desired ring closed substance IIIa along with a compound identified as the normal *t*-butyl ester IIc resulted.

Compounds Va, VIa and VIIIa have shown a low degree of androgenic and anabolic activity as measured by the modified levator-ani muscle method.[10,11]

Experimental[12]

17β-Benzoyloxy-5-hydroxy-4-oxaandrostan-3-one (IIIa) was prepared by an exact repetition of the published pro-

(6) H. Rosenkrantz and M. Gut, *Helv. Chim. Acta*, **36**, 1000 (1953).

(7) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(8) J. A. Hartman, A. J. Tomasewski and A. S. Dreiding, THIS JOURNAL, **78**, 5662 (1956).

(9) C. D. McCleary, Doctoral Dissertation, Ohio State University, 1940.

(10) L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.*, **83**, 175 (1953).

(11) Bioassays performed in the Division of Biological Research, G. D. Searle and Co., and at the Worcester Foundation for Experimental Biology, Worcester, Mass.

(12) Melting points were determined with a Fisher–Johns apparatus which had been standardized against compounds of known melting point. Ultraviolet spectra were taken in methanol and optical rotations in chloroform at concentrations of 1% and at approximately 23°. Infrared spectra were taken using the potassium bromide disk technique unless noted to the contrary. The term petroleum ether denotes the hydrocarbon fraction boiling between 60 and 70°.

cedure[2a] on double the scale. The yield from 4.50 g. of testosterone benzoate was 2.54 g. (54%), m.p. 142–148°. No attempt was made to improve the yield by treating the neutral product with periodic acid. Recrystallization from methanol–water and chloroform–petroleum ether gave analytical material, m.p. 150.5–151.5°, $[\alpha]_D$ +81°; λ_{max} 3.08, 5.74 and 5.85 μ.

Anal. Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.64; H, 7.75.

17β-Benzoyloxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid (IIa).—Testosterone benzoate (20 g., 0.051 mole) was dissolved in glacial acetic acid (325 ml.) and ethyl acetate (325 ml.), cooled in an ice–salt-bath and treated with oxygen containing ozone (*ca.* 0.18 mole) during 1.25 hours. When the ozonide solution had warmed to room temperature a solution of 30% hydrogen peroxide (20 ml.) in water (40 ml.) was added and the mixture allowed to stand 16 hours. After dilution with ether (2 l.), the acetic acid and excess peroxide were washed out with several portions of water and the acid product taken into 2% sodium hydroxide solution. Acidification of this solution to *p*H 3 with concd. hydrochloric acid gave a gummy precipitate which was extracted into ether. After washing and drying over anhydrous sodium sulfate, the ether solution was evaporated and the residue was crystallized from methanol–water. The yield was 14.90 g. (71%), m.p. 172.5–174.5°. The analytical sample obtained by further crystallization from isopropyl ether melted at 175–176°, $[\alpha]_D$ +127°, λ_{max} 5.83 to 5.88 μ.

Anal. Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.78; H, 7.95.

Other oxidations more closely patterned after the preparation of IIIa with respect to the concentration of the steroid to be ozonized gave IIa as the only product in 60–65% yields without periodic acid treatment of the neutral fraction.

Isomerism of IIIa to IIa.—A small quantity of IIIa was heated to 165° and the melt was then allowed to cool. The resolidified material did not melt when heated again to 165°. Its infrared spectrum was identical to that of IIa. A mixture of IIa and IIIa melted at 173.5–175°.

17β-Benzoyloxy-4-oxa-5α-androstan-3-one (Va). A. From 17β-Benzoyloxy-5-hydroxy-4-oxaandrostan-3-one (IIIa).—The lactonol (IIIa, 1.38 g.) was dissolved in 95% ethanol (100 ml.) and was treated with sodium borohydride (0.39 g.) in water (10 ml.). A flocculent precipitate was caused to redissolve on addition of a further 50 ml. of ethanol and 50 ml. of water. More sodium borohydride (0.15 g.) was added when a test drop of the reaction mixture showed that no excess reducing agent was present. After three hours at room temperature with occasional swirling, the reaction mixture was poured into water, acidified with concd. hydrochloric acid and extracted with ether. The residue remaining after washing, drying and evaporating the ether solution was crystallized from methanol: crop 1, 0.67 g., m.p. 200–205°; crop 2, 0.12 g., m.p. 194–201°; yield (both crops) 59%. Recrystallization twice more from methanol gave the analytical sample, m.p. 206–207.5°, $[\alpha]_D$ +102°, λ_{max} 5.79 and 5.85 μ.

Anal. Calcd. for $C_{25}H_{32}O_4$: C, 75.72; H, 8.14. Found: C, 75.96; H, 8.32.

B. From 17β-Benzoyloxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid (IIa).—The keto-acid (IIa, 2.00 g.) dissolved in 95% ethanol (100 ml.) was treated with sodium borohydride (1.0 g.) in water (10 ml.). The mixture was stirred for 1.25 hours and then was worked up as described above. The gummy product was crystallized from methanol: crop 1, 0.94 g., m.p. 199–204°; crop 2, 0.27 g., m.p. 194–198°; yield (both crops) 63%. Two further recrystallizations from methanol gave analytically pure material, m.p. 207–208.5°, $[\alpha]_D$ +108°. A mixture melting point with the product from reduction of the lactonol IIIa was 206.5–208°. The infrared spectra were identical.

17β-Benzoyloxy-4-oxa-5β-androstan-3-one (VIa).—The keto-acid (IIa, 4.00 g.) was reduced as described above. Recrystallization of the product from methanol gave the following crops: crop 1, 1.92 g., m.p. 204–209°; crop 2, 0.60 g., m.p. 190–200°; crop 3, 0.17 g., m.p. very diffuse up to 200°; crop 4, 0.45 g., m.p. 160–164°; crop 5, 0.02 g., m.p. very diffuse up to 190°. The yield of crop 4 was 12%. An analytical sample was obtained from crop 4 after several recrystallizations from isopropyl ether; m.p. 167–168°, $[\alpha]_D$ +62°, λ_{max} 5.80 to 5.83 μ.

Anal. Calcd. for $C_{25}H_{32}O_4$: C, 75.72; H, 8.14. Found: C, 75.57; H, 8.43.

17β-Cyclohexanecarboxy-4-oxa-5β-androstan-3-one (Vb).—17β-Benzoyloxy-5-oxo-3,5-seco-A-norandrostan-3-oic acid (IIa, 1.50 g.) was dissolved in glacial acetic acid (50 ml.) and shaken under 1 atm. of hydrogen in the presence of prereduced platinum oxide (0.75 g.). At the end of 24 hours 111% of the hydrogen calculated to reduce the ketone and the phenyl ring had been consumed. Filtration of the catalyst and evaporation of the solvent left a solid residue, m.p. 130–160°.

The residue was chromatographed on silica gel (Davidson 80–100 mesh, 160 g.), the solid being eluted with benzene–ethyl acetate mixtures of 49:1 and 19:1. The fractions containing the product graded in m.p. from 186–196° to 141–146° with the middle fractions having wider melting ranges. A total of 0.42 g. (29%) melting above 196.5° was obtained by crystallization of the early fractions from methanol. The analytical sample obtained by further crystallization from methanol had m.p. 200.5–203.5°, $[\alpha]_D$ +12°, λ_{max} 5.78 μ.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.42; H, 9.53.

17β-Hydroxy-4-oxa-5α-androstan-3-one (Vc).—The benzoate (Va, 2.95 g.) in purified dioxane (140 ml.) was refluxed vigorously with a solution of potassium hydroxide (20 g.) in water (140 ml.). The reaction mixture remained biphasic throughout the reflux period. At the end of 3 hours, the mixture was poured into water and acidified with concd. hydrochloric acid. The clear solution resulting was extracted with methylene chloride and the extracts were washed and dried over sodium sulfate. Evaporation under vacuum (to remove extracted dioxane) left a solid residue. Crystallization from acetone–isopropyl ether gave 1.70 g. (78%), m.p. 177.5–179°. Two further recrystallizations from ethyl acetate gave material melting at 178–179°, $[\alpha]_D$ +90°, λ_{max} 2.90 and 5.82 μ.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.06; H, 9.33.

17β-Cyclohexanecarboxy-4-oxa-5α-androstan-3-one (Vb).—A solution of cyclohexanecarboxyl chloride was prepared by refluxing cyclohexanecarboxylic acid (1.0 g.) in thionyl chloride (3 g.) for 1.5 hours. The excess reagent was removed at reduced pressure, then benzene was added and the solution again stripped of solvent. The residual brown oil was made up to 40 ml. with dry benzene.

17β-Hydroxy-4-oxa-5α-androstan-3-one (Vc, 0.239 g.) in 15 ml. of dry benzene was treated with 0.5 ml. of pyridine and 15 ml. of the acid chloride solution prepared above. After standing 16 hours at room temperature the reaction mixture was shaken with water. The organic layer was washed with dil. hydrochloric acid, dil. sodium hydroxide and then with water. The solid residue remaining after drying and stripping the solvent was recrystallized from isopropyl ether and then from chloroform–petroleum ether to give the pure product, m.p. 168–170°, $[\alpha]_D$ +66°, λ_{max} 5.71 and 5.80 μ.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.68; H, 9.53.

17β-Hydroxy-4-oxa-5β-androstan-3-one (VIc). A. From 17β-Cyclohexanecarboxy-4-oxa-5β-androstan-3-one (VIb).—Compound VIb (0.366 g.) in 35 ml. of methanol was refluxed 5 hours with potassium hydroxide (2 g.) in 5 ml. of water. The solution was then allowed to stand at room temperature 16 hours before being poured into water. The precipitated solid was filtered and the filtrate was reduced in volume (under vacuum) and extracted with chloroform. The extracts, after washing and drying, were evaporated to leave a gummy solid. The combined product was crystallized from methanol–water to give 0.194 g. (73%) of material melting at 198–198.5°. Crystallization from ethyl acetate gave the analytical sample, m.p. 198.5–199.5°, λ_{max} 2.87 and 5.79 μ.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.29; H, 9.33.

B. From 17β-Benzoyloxy-4-oxa-5β-androstan-3-one (VIa).—Hydrolysis was accomplished in the same manner as in the case of the epimeric Va. The product was purified by crystallization from acetone–isopropyl ether, m.p. 200.5–202°; mixture with the compound produced from the cyclohexanecarboxylate VIb, m.p. 200.5–202°, $[\alpha]_D$ +9°.

The infrared spectra of VIc from the two sources were identical.

17β-Benzoyloxy-5-chloro-4-oxaandrostan-3-one (VII).—A solution was made of the keto-acid (IIa, 1.03 g.) in benzene (10 ml.) and this was treated at 10° with cold thionyl chloride (5 ml.). The resulting solution was allowed to stand at 2–3° for 2 days and then the solvent and excess reagent were removed under vacuum. Trituration of the residue with a small volume of cold acetone followed by filtration gave 0.83 g. (77%) of a white powder, m.p. 179–182°. Recrystallization from a large volume of acetone gave the analytical sample as stout needles, m.p. 184–189°, $[\alpha]_D$ +61°; λ_{max} 5.69, 5.86 and 13.34 μ.

Anal. Calcd. for $C_{25}H_{31}ClO_4$: C, 69.67; H, 7.25; Cl, 8.23. Found: C, 69.69; H, 7.35; Cl, 8.22.

17β-Benzoyloxy-5-methoxy-4-oxaandrostan-3-one (VIIIa).—The pseudoacid chloride (VII, 0.28 g.) was dissolved with heating in pyridine (5 ml.) and methanol (5 ml.). The solution deposited thick needles on standing at room temperature for 90 hours. The solid was filtered (0.13 g.) and the filtrate was poured into water. The aqueous suspension was ether extracted and the extracts were washed with water, dried over sodium sulfate and evaporated to leave a gummy residue which on trituration with methanol gave more solid (0.06 g.). Two crystallizations of the combined solids from methanol–methylene chloride gave 0.124 g. (47%) of analytically pure material, m.p. 234–238°, $[\alpha]_D$ +72°, λ_{max} 5.75 and 5.85 μ.

Anal. Calcd. for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04. Found: C, 72.95; H, 8.26.

17β-Benzoyloxy-5-allyloxy-4-oxaandrostan-3-one (VIIIb).—The pseudoacid chloride (VII, 0.32 g.) in pyridine (5 ml.) was treated with freshly distilled allyl alcohol (5 ml.) and allowed to stand 3 days at room temperature. No product had precipitated so the reaction was worked up as described for the methyl pseudoester VIIIa. The crude solid which formed on trituration with methanol was combined with that from another run (starting with 0.28 g. of VII) and crystallized from methanol–methylene chloride and petroleum ether–methylene chloride. The product, 0.06 g. (14%), had m.p. 162–164.5°. An analytical sample obtained by a further crystallization showed no improvement of m.p. and had $[\alpha]_D$ +67°, λ_{max} 5.71 and 5.82 μ.

Anal. Calcd. for $C_{28}H_{36}O_5$: C, 74.30; H, 8.02. Found: C, 74.63; H, 7.85.

17β-Benzoyloxy-5-benzyloxy-4-oxaandrostan-3-one (VIIIc).—17β-Benzoyloxy-5-chloro-4-oxaandrostan-3-one (VII, 0.60 g.) was dissolved in pyridine (8 ml.) and benzyl alcohol (8 ml.) with heating and was then allowed to stand 3 days at room temperature. The reagents were removed under vacuum and the residue was taken into ether. The ether solution was washed with water, dried over sodium sulfate and evaporated. The residue on trituration with methanol gave a solid which was crystallized from petroleum ether–methylene chloride to yield 0.04 g. (6%) of product, m.p. 223–227°. A second crystallization gave the analytical sample, m.p. 230–236°, $[\alpha]_D$ +67°, λ_{max} 5.73 and 5.82 μ.

Anal. Calcd. for $C_{32}H_{38}O_5$: C, 76.46; H, 7.62. Found: C, 76.78; H, 7.59.

Acid Hydrolysis of 17β-Benzoyloxy-5-chloro-4-oxaandrostan-3-one (VII).—The pseudoacid chloride (VII, 0.112 g.) and pyridine (0.021 g.) were refluxed in *t*-butyl alcohol (24 ml.) and water (5 ml.) for 2 hours. After standing at room temperature overnight the *t*-butyl alcohol was removed under vacuum until two phases were present. Water was added and the emulsion was ether extracted. The extracts were dried over sodium sulfate and evaporated to leave an oily product. Crystallization from methanol–water gave the following crops: crop 1, 0.042 g., m.p. 129–145°; crop 2, 0.033 g., m.p. 105–108.5°; crop 3, 0.014 g., m.p. 103–105.5°.

Crop 1 after two recrystallizations gave 0.023 g. (21%) of pure *t*-butyl 17β-benzoyloxy-5-oxo-3,5-seco-A-norandrostan-3-oate (IIc), m.p. 154–157°, $[\alpha]_D$ +78°, λ_{max} 5.81 μ (shoulder 5.87).

Anal. Calcd. for $C_{28}H_{40}O_5$: C, 73.65; H, 8.83. Found: C, 73.88; H, 8.62.

Crops 2 and 3 were combined and crystallized from methanol–water. Material melting at 143.5–174.5° was obtained. When placed on the block at 160° it completely melted then resolidified and remelted 173–175.5°. The infrared spectrum was identical to that of 17β-benzoyloxy-5-hydroxy-4-oxaandrostan-3-one (IIIa) obtained directly from ozonization of testosterone benzoate.

Methyl 17β-Benzoyloxy-5-oxo-3,5-seco-A-norandrostan-3-oate (Ib).—The methyl pseudoester (VIIIa, 0.102 g.) was dissolved in methanol (100 ml.) with heating. After cooling to 40°, 1 drop of concd. sulfuric acid was added and the solution was allowed to stand for 22 hours at room temperature. Water was added and the methanol was removed under vacuum. The organic material was extracted into chloroform and the extracts were washed twice with water and evaporated. The gummy product was chromatographed on silica gel (6.4 g.). A colorless oil was eluted with benzene–ethyl acetate 19:1 which had $[\alpha]_D$ +87°; $\lambda_{max}^{CHCl_3}$ 5.84, 7.79, 8.89, 10.47 μ. The infrared absorption spectrum in chloroform was identical with that of the normal methyl ester prepared by diazomethane treatment of 17β-benzoyloxy-5-oxo-3,5-seco-A-norandrostan-3-oic acid (IIa) and distinctly different from that of the starting material.

CHICAGO 80, ILL.

[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY]

The Effect of Cobaltous Ions on Cumene Autoxidation[1]

BY HARRY S. BLANCHARD

RECEIVED AUGUST 20, 1959

The α,α′-azodiisobutyronitrile initiated autoxidation of cumene in acetic acid was studied at 60° in the presence and in the absence of cobaltous ions. Rates of initiation were measured and found to be unaffected by cobaltous ions in the range 0–0.0041 *M*. The over-all rates of autoxidation, however, were increased in this concentration range, indicating that the cobaltous ions catalize either the reaction between cumyl peroxy radicals and cumene or the reaction between cumyl radicals and oxygen. Above 0.0041 *M* the rates of initiation increased and concomitantly the yields of hydroperoxide decreases, suggesting that the increased initiation results from decomposition of the hydroperoxide by the metal ions. In the absence of an added free radical initiator, cumene autoxidation was found to be dependent on the purity of the reagents. The results of the study support the idea that in the presence of metal ions but in the absence of added initiator, initiation results from free radicals formed, either from decomposition of hydroperoxides by the metal ions or from reaction of the metal ions with impurities also resulting in free radicals. The so-called "direct" reaction between hydrocarbon, oxygen and cobaltous ions, at least in the case of cumene, was found to be immeasurably slow under our experimental conditions.

The mechanism of the free radical initiated autoxidation of hydrocarbon has received considerable attention in recent years[2] and as a result is now well understood. The detailed mechanism of how heavy-metal ions affect autoxidizing systems,

(1) Presented in part before the Organic Chemistry Division at the 134th Meeting of the American Chemical Society, Chicago, Ill., September, 1958. A preliminary account of this work appeared in *Chemistry & Industry*, 598 (1959).

(2) (a) J. L. Bolland, *Quart. Rev.*, **3**, 1 (1949); (b) L. Bateman, *ibid.*, **8**, 147 (1954); (c) G. A. Russell, THIS JOURNAL, **77**, 4583 (1955); *ibid.*, **78**, 1047 (1956).