of ether, and the ether extracts evaporated to dryness on the steam-bath. The oily crystals, which contained much acetic acid, were sublimed at 170°, 0.1 mm., to yield 0.70 g. of pasty crystals which, from the infrared absorption spectrum, contained about 90% of 3-methoxyphthalic anhydride.

The crude crystals were dissolved in 10 ml. of 0.5 *N* sodium hydroxide. Fifty grams of 3% sodium amalgam was added. After 48 hours, the aqueous phase was acidified and extracted with four 20-ml. portions of ether. The ether extract was washed with 20 ml. of 5% sodium bicarbonate to remove unreacted methoxyphthalic acid, and the ether layer evaporated to dryness. Distillation of the residue at 120°, 0.1 mm., yielded 20 mg. of 7-methoxy-3-methylphthalide, m.p. 69–72°, mixed m.p. with a sample prepared from terramycin of m.p. 72–74°, not depressed; yield, based on unrecovered starting material, 5%. This identification was confirmed by the identity of the infrared absorption spectra of the two compounds. The yield of this reaction was not markedly improved by the use of a five to one malonic acid–methoxyphthalic anhydride ratio.

When 3-methoxyphthalic anhydride in benzene solution was heated to 100° with excess cadmium dimethyl overnight,[18] only unreacted starting materials were recovered.

2-Acetyl-3-nitrobenzoic acid was prepared in 19% yield by the condensation of 3-nitrophthalic anhydride with malonic acid in pyridine, by a procedure similar to that described by Yale.[7] The product melted at 164–165° (reported 159–160°[10]).

2-Acetyl-3-aminobenzoic Acid.—The reduction of 2.05 g. (9.8 mmoles) of 2-acetyl-3-nitrobenzoic acid in 40 ml. of ethyl acetate over 0.5 g. of 5% palladium-on-charcoal catalyst consumed 670 ml. (30 mmoles) of hydrogen in 1.5 hours and no more in the next 4 hours. The product, which is readily soluble in dilute acid and in bicarbonate, was recrystallized from ethyl acetate, sublimed, and recrystallized from water; m.p. 167.5–168°, yield 1.6 g. (91%).

(18) P. L. DeBenneville, *J. Org. Chem.*, **6**, 462 (1941).

Anal. Calcd. for $C_9H_9O_3N$: C, 60.35; H, 5.05; N, 7.82. Found: C, 60.50; H, 5.54; N, 7.87.

4-Amino-3-methylphthalide resulted from the reduction of 2-acetyl-3-aminobenzoic acid with sodium amalgam. The product, isolated in 52% yield, melted at 122.5–123.5° (reported 121–124°[10]).

4-Hydroxy-3-methylphthalide.—4-Amino-3-methylphthalide (163 mg., 1 mmole) was dissolved in 2 ml. of 10% sulfuric acid and cooled to 0°. One-half ml. of aqueous sodium nitrite (69 mg., 1 mmole) was added. After 5 minutes, the solution was poured into 15 ml. of boiling 1% sulfuric acid, heated for 10 minutes and cooled. The crystalline precipitate, 85 mg., was recrystallized from 1 ml. of ethanol and 3 ml. of water, and sublimed at 160°, 0.1 mm., m.p. 199–200°.

Anal. Calcd. for $C_9H_8O_3$: C, 65.95; H, 4.90. Found: C, 65.92; H, 5.13.

Like I, this material is insoluble in sodium bicarbonate, slowly soluble in cold 10% sodium hydroxide. It gives a pale green ferric chloride test, and a positive aminoantipyrine test. The infrared absorption spectrum in dioxane solution shows a carbonyl peak at 5.68 μ and hydroxyl absorption at 3.13 μ. 4-Methoxy-3-methylphthalide, prepared by the reaction of this hydroxy compound with excess diazomethane, melts at 103–105°. Its infrared spectrum shows carbonyl absorption at 5.70 μ in chloroform solution.

Acknowledgments.—We are indebted to Dr. John Means and the Microanalytical Section of Chas. Pfizer and Co. for the analyses, and to Mr. Glenn Hess for the infrared and ultraviolet absorption spectra. We are grateful to Dr. R. C. Lord for assistance in interpreting the spectra, and to Dr. K. J. Brunings for helpful discussion.

BROOKLYN, N. Y.

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

Introduction of the 11-Keto Function in the Steroids

BY JAMES M. CONSTANTIN AND L. H. SARETT

RECEIVED FEBRUARY 18, 1952

The oxidation of methyl $\Delta^{9,11}$-3α-acetoxycholenate with potassium permanganate in acidic solution yielded two compounds, methyl $\Delta^{9,11}$-3α-acetoxy-12-ketocholanate and methyl 3α-acetoxy-9β,11β-oxidocholanate. The latter compound was converted by hydrogenolysis to methyl 3α-acetoxy-11β-hydroxycholanate, and then by oxidation to methyl 3α-acetoxy-11-ketocholanate. Permanganate oxidation of an A/B *trans*-steroid, $\Delta^{9,11}$-tigogenin acetate, under similar conditions afforded the corresponding 9α,11α-oxido compound.

Because of the increasing interest in both total and partial synthesis of the adrenocortical hormones, the conversion of $\Delta^{9,11}$-steroids to 11-oxygenated derivatives has recently received considerable attention.[1] With this impetus, an investigation initiated by one of us (L.H.S.) in 1942, involving the permanganate oxidation[2] of a $\Delta^{9,11}$-steroid in acidic solution, has recently been extended and brought to fruition with the synthesis of methyl 3α-acetoxy-11-ketocholanate (V).

During the intervening years, one publication appeared[3] reporting the formation of two "oxides" upon oxidation of methyl $\Delta^{9,11}$-3α-acetoxycholenate with potassium permanganate in acetic acid. The so-called "β-oxide," m.p. 115.5–117.5°, was reported to be identical with the oxide obtained by the peracid oxidation of the parent sterol.[4] The higher-melting "oxide," m.p. 146–146.5°, was not completely characterized but was shown to be inert to chromic acid and to perbenzoic acid. Neither "oxide" could be cleaved by catalytic reduction or by treatment with the common mineral acids.

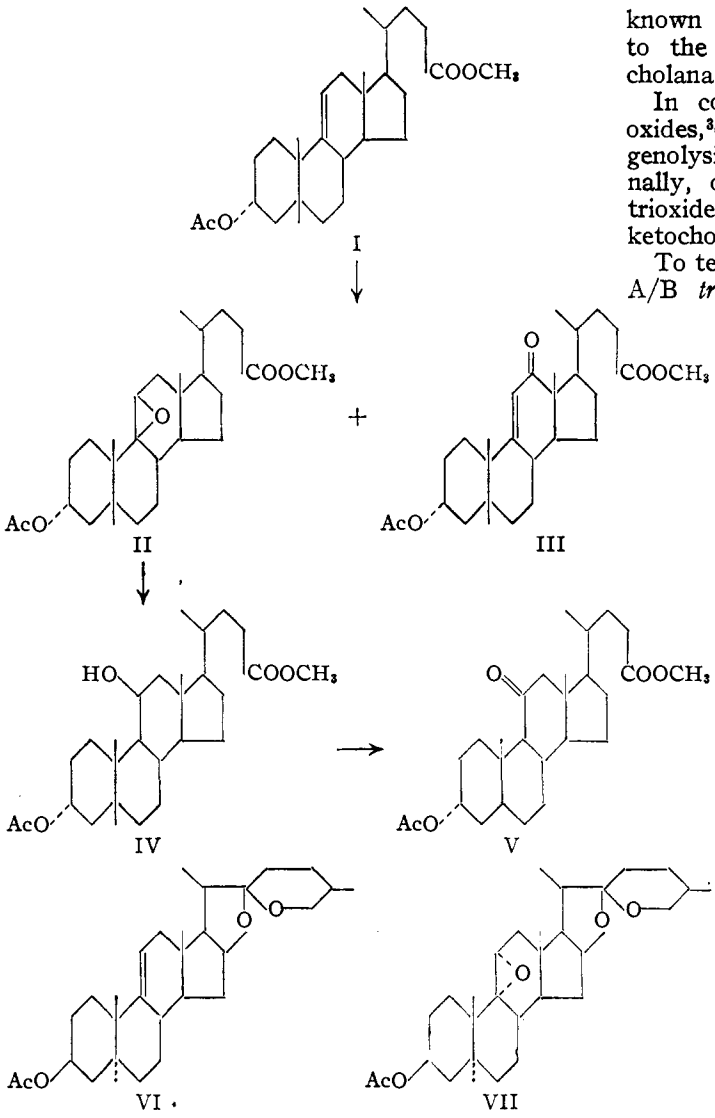
In the course of the present investigation, we also have obtained two compounds from the same oxidation. The higher-melting compound, m.p. 147°, was identified as methyl $\Delta^{9,11}$-3α-acetoxy-12-ketocholenate (III) rather than an epimeric oxide.

(1) (a) E. M. Chamberlin, *et al.*, THIS JOURNAL, **73**, 2396 (1951); (b) G. Stork, *et al.*, *ibid.*, **73**, 3546 (1951); (c) H. Heuser, *et al.*, *Helv. Chim. Acta*, **34**, 2106 (1951); (d) L. F. Fieser and H. Heymann, THIS JOURNAL, **73**, 5252 (1951), and preceding papers.

(2) *Cf.* M. Ehrenstein and M. T. Decker, *J. Org. Chem.*, **5**, 544 (1940).

(3) E. Hicks, C. Berg and E. S. Wallis, *J. Biol. Chem.*, **162**, 645 (1946).

(4) At the time this paper appeared, the oxide obtained by peracid oxidation of a $\Delta^{9,11}$ steroid was thought to be the 9β,11β-oxido compound; and, on the basis of the similarity of physical constants, the oxide obtained in this work was ascribed the β-configuration. Subsequently, however, L. F. Fieser and H. Heymann, ref. 1d, have established the α-configuration for such oxides.



Its structure was elucidated by ultraviolet absorption analysis (λ_{max} 240 mμ, log ε 4.04) and by direct comparison with an authentic sample. The lower-melting compound (II), obtained as the major product in our investigation, showed a pronounced depression of melting point upon admixture with an authentic sample of methyl 3α-acetoxy-9α,11α-oxidocholanate obtained by peracid oxidation of the parent olefin, and its melting point and specific rotation were at variance with those previously reported[5,6,7] for the α-oxide.

Because of the impossibility of obtaining *prima facie* evidence of the existence of the oxide group as such, the structure of this oxide[8] must be inferred from its elemental analysis, which shows an extra oxygen atom in the molecule; its infrared absorption spectrum, which shows no recognizable oxygen-function absorption not previously present in the starting material; from its dissimilarity to the known α-oxide; and finally, from its conversion to the known methyl 3α-acetoxy-11β-hydroxycholanate[9,10] (IV).

In contrast to the inertness of the 9α,11α-oxides,[3,7] the β-oxide readily underwent hydrogenolysis with platinum in acidic solution. Finally, oxidation of this product with chromium trioxide in acetic acid gave methyl 3α-acetoxy-11-ketocholanate (V) in good yield.

To test the scope of this oxidation procedure, an A/B *trans*-steroid, specifically, $\Delta^{9,11}$-dehydrotigogenin acetate (VI), was oxidized under similar conditions, and gave in excellent yield, the same oxide (VII) as that obtained by peracid oxidation. The latter oxide has been assigned the 9α,11α-configuration by Djerassi, *et al.*,[11] and has been reported by these authors to be inert to a variety of reagents, further substantiating the characteristic inertness of the isolated 9α,11α-oxides.

Acknowledgments.—The authors are indebted to Dr. Karl Folkers of these laboratories and to Professor Everett S. Wallis of Princeton University for valuable suggestions in connection with this work. The microanalyses were performed by Mr. R. N. Boos and his associates.

Experimental[12]

Oxidation of Methyl $\Delta^{9,11}$-3α-Acetoxycholenate.—To a cooled solution of 2.00 g. of methyl $\Delta^{9,11}$-3α-acetoxycholenate[13] (I) in 250 ml. of 95% acetic acid was added dropwise 80 ml. of a 5% aqueous solution of potassium permanganate at approximately 10°. After addition was completed, the reaction was stirred for two hours in the ice-bath, and then treated dropwise with a solution of 6.40 g. of sodium bisulfite in 30 ml. of water. The pale yellow solution was diluted with water and extracted thoroughly with ether. Evaporation of the washed ether extract gave 1.99 g. of a white crystalline residue, m.p. 96–106°. Chromatographic separation over acid-washed alumina gave 620 mg. of crystalline methyl 3α-acetoxy-9β,11β-oxidocholanate (II), m.p. 111–117°, and 205 mg. of methyl $\Delta^{9,11}$-3α-acetoxy-12-ketocholenate (III), m.p. 147° (capillary), in addition to a small amount of impure starting material. Repeated recrystallization from methanol afforded pure II, m.p. 115.5–117.5°; $[\alpha]^{25}D$ +58° (*c* 1.0 in acetone).

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.57; H, 9.38.

Pure methyl $\Delta^{9,11}$-3α-acetoxy-12-ketocholenate (III) was obtained by repeated recrystallization from petroleum ether–ether, and melted at 147–150°; $[\alpha]^{25}D$ +103° (*c* 1.0 in acetone).

Anal. Calcd. for $C_{27}H_{40}O_5$: C, 72.93; H, 9.07. Found: C, 72.85; H, 8.81.

Methyl 3α-acetoxy-9β,11β-oxidocholanate (II) upon admixture with an authentic sample of methyl 3α-acetoxy-9α,11α-oxidocholanate[14] melted at 95–110°. Infrared analysis showed only ester carbonyl absorption.

(5) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).
(6) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **73**, 118 (1951).
(7) E. Berner and T. Reichstein, *Helv. Chim. Acta*, **29**, 1374 (1946).
(8) It is of interest to note that the preparation of this oxide represents the first transformation of a steroid to a derivative possessing a substituent at C9 which is unequivocally in the β orientation.
(9) O. Wintersteiner and M. Moore, *J. Biol. Chem.*, **162**, 725 (1946).
(10) R. B. Turner, *et al.*, *ibid.*, **166**, 345 (1946).
(11) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).
(12) Melting points were taken on the Kofler micro hotstage.
(13) Prepared by reduction and hydrogenolysis of methyl $\Delta^{9,11}$-3α-acetoxy-12-ketocholenate using PtO_2 in methanol with a trace of concentrated hydrochloric acid.
(14) Prepared by oxidation of methyl $\Delta^{9,11}$-3α-hydroxycholenate with perbenzoic acid in chloroform followed by acetylation, m.p. 120–121° with sintering at 118°.

Methyl $\Delta^{9,11}$-3α-acetoxy-12-ketocholenate (III) upon admixture with an authentic sample gave no depression, and upon ultraviolet absorption analysis showed a maximum at 240 mμ, log ϵ 4.04.

Methyl 3α-Acetoxy-11β-hydroxycholanate (IV).—A solution of 315 mg. of methyl 3α-acetoxy-9β,11β-oxidocholanate in 30 ml. of glacial acetic acid was treated with 0.1 g. of platinum oxide and hydrogen at room temperature and shaken for 16 hours, at which time 0.75 mole equivalent had been taken up. The catalyst was filtered, the filtrate diluted with water and extracted thoroughly with ether. Evaporation of the washed ether layer gave 295 mg. of a white crystalline residue which after chromatographic purification afforded 80 mg. of crystalline IV. Recrystallization from methanol gave fine needles, m.p. 149.5–151°. Infrared analysis showed hydroxyl absorption at 2.82 μ, and ester carbonyl absorptions at 5.77 and 5.83 μ.

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 72.07; H, 10.02.

Treatment of IV with acetic anhydride and pyridine for three hours on the steam-bath afforded only unchanged starting material.

Methyl 3α-Acetoxy-11-ketocholanate (V).—To a solution of 20.5 mg. of IV in 0.5 ml. of glacial acetic acid and 0.16 ml. of water was added 0.26 ml. of a solution of chromium trioxide in 95% aqueous acetic acid (containing 50 mg. CrO_3/ml.). The reaction was allowed to stand at room temperature for one hour. Careful dilution with water afforded crystalline V which upon recrystallization from methanol melted at 132–134°; $[\alpha]^{24}D$ +66° (*c* 0.99 in acetone). Upon admixture with an authentic sample of methyl 3α-acetoxy-11-ketocholanate, the melting point was not depressed.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.40; H, 9.60.

9α,11α-Oxido-5α,22α-spirostan-3β-ol Acetate (9α,11α-Oxidotigogenin Acetate) (VII).—A solution of 570 mg. of 5a;22a-spirost-9,11-en-3β-ol acetate ($\Delta^{9,11}$-tigogenin acetate) (VI) in 70 ml. of glacial acetic acid was cooled to 15° and treated dropwise with 40 ml. of a 5% aqueous solution of potassium permanganate over a period of one hour. The cooled solution was stirred an additional hour then treated with a saturated aqueous solution of sodium bisulfite until colorless. The reaction mixture was diluted with water and extracted with chloroform. The chloroform extracts were washed thoroughly and dried over anhydrous magnesium sulfate. After evaporation *in vacuo*, the crystalline residue (500 mg.) was chromatographed over acid-washed alumina and yielded 215 mg. of 9α,11α-oxidotigogenin acetate (VII), m.p. 263–265°. Recrystallization from chloroform–methanol gave an analytical sample melting at 264–265°, $[\alpha]^{24}D$ −78° (*c* 1.0 in chloroform). Infrared absorption analysis showed only ester carbonyl and side-chain absorption.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.91; H, 9.61.

Oxidation of $\Delta^{9,11}$-tigogenin acetate with perbenzoic acid essentially according to the procedure of Djerassi, ref. 11, gave, after chromatography, pure 9α,11α-oxidotigogenin acetate, m.p. 263.5–265.5°. The infrared spectrum of this compound was identical with that of the product obtained by permanganate oxidation.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

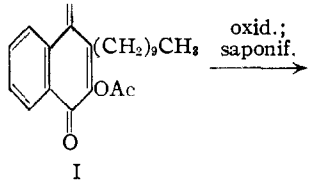
Chromic Anhydride Oxidation of the *n*-Undecyl Side Chain of an Acetoxynaphthoquinone

BY KOJI NAKANISHI[1] AND LOUIS F. FIESER

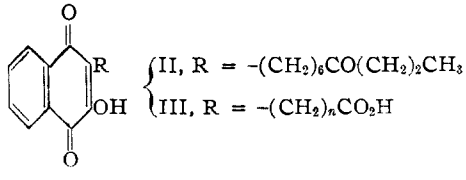
RECEIVED APRIL 4, 1952

A previous study of the oxidation of alkyl side chains has been extended by identification of the acidic products by paper chromatography and by fractionation of the neutral products in a Craig countercurrent machine. Oxidation of the *n*-undecyl side chain gives the acids $-(CH_2)_{1-8}CO_2H$ and the 7′ and 9′-keto derivatives. Oxidation of a synthetic acid with the side chain $-(CH_2)_9CO_2H$ gave, in addition to a series of lower homologous acids, the ketone $-(CH_2)_7COCH_3$, which must have arisen by β-oxidation and decarboxylation.

This investigation is an extension of a research[2] in which it was found that the side chains of 2-alkyl-3-acetoxy-1,4-naphthoquinones are oxidized rapidly at room temperature by a suspension of chromic anhydride in anhydrous acetic acid. Alkyl groups of various types were found to be oxidized to alcoholic, ketonic and acidic derivatives, isolated by differential extraction from ether, before and after hydrolysis of the acetyl group, with aqueous buffers of increasing alkalinity; in one instance separation of a series of homologous acids was effected by countercurrent distribution conducted manually in a series of separatory funnels. Quinone I, with an *n*-decyl side chain, yielded a neutral oxidation fraction, from which the 7′-keto derivative II was isolated, and the series of acids III, n = 2–7. An acetoxy quinone with the side chain $-CH(CH_3)C_6H_{13}$–*n* was likewise found to yield the 7′-keto derivative, $-CH_2CH(CH_3)(CH_2)_4COCH_3$, and the acids $-CH_2CH(CH_3)(CH_2)_nCO_2H$, n = 4,3,1; the 7′-acid $-CH_2CH(CH_3)(CH_2)_4CO_2H$



I



is a product of human metabolic oxidation of the hydroxyalkylnaphthoquinone.[3]

The present work was undertaken with the thought that application of newer techniques of separation and analysis might afford further information on the course and mechanism of the interesting side chain oxidation. The substance

(1) Research Fellow studying under the sponsorship of the Institute of International Education as participant in the Japanese Student Program of the Department of the Army and SCAP.

(2) L. F. Fieser, THIS JOURNAL, **70**, 3237 (1948).

(3) L. F. Fieser, F. C. Chang, W. G. Dauben, C. Heidelberger, H. Heymann and A. M. Seligman, *J. Pharmacol. Exp. Therap.*, **94**, 85 (1948).