[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Structure of Terramycin. IV. 7-Hydroxy-3-methylphthalide

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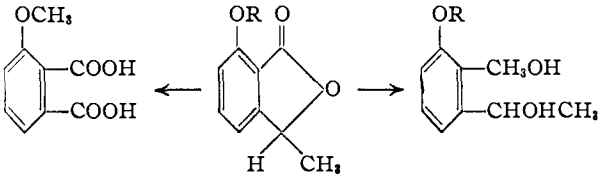
7-Hydroxy-3-methylphthalide has been isolated from the alkaline hydrolysis products of the antibiotic terramycin. The structure of this compound has been established by degradation and confirmed by the synthesis of its methyl ether. The phenolic nature of 7-hydroxy-3-methylphthalide was shown by color reactions, and by the formation of a methyl ether insoluble in cold alkali. Alkaline permanganate oxidation of this ether yielded 3-methoxyphthalic anhydride. Alkali fusion of 7-hydroxy-3-methylphthalide yielded salicylic acid and acetic acid. The five membered ring lactone structure was inferred by salt formation, and is in agreement with the infrared spectrum. 7-Methoxy-3-methylphthalide was synthesized through the pyridine–piperidine catalyzed condensation of 3-methoxyphthalic anhydride and malonic acid, hydrolysis of the 7-methoxy-3-methylenephthalide to 2-acetyl-6-methoxybenzoic acid, and subsequent reduction to the phthalide.

The alkaline hydrolysis of the antibiotic terramycin has been discussed briefly in previous communications from this Laboratory.[1,2] When terramycin is digested with 20% sodium hydroxide in the presence of zinc, the reaction products include terracinoic acid,[3] ammonia and dimethylamine in good yield. Relatively small amounts of two phenolic compounds, $C_{12}H_{12}O_3$, m.p. 172.4–173°, and $C_9H_8O_3 \cdot H_2O$, m.p. 110–112°, may also be isolated. The latter product has now been shown to be a hydrate of 7-hydroxy-3-methylphthalide (I).[4,5]



III I, R = H II, R = CH_3 IV, R = H IVa, R = CH_3

The presence of phenolic group was inferred from the titration curve, which shows a single break corresponding to pK_a 8.5, from the purple ferric chloride test, and from the reaction with diazomethane to yield an alkali stable methyl ether (II) which is only slowly soluble in cold alkali. The monoacetyl derivative was formed with ease. The preparation of a strongly acid *m*-dinitro derivative confirmed the presence of a phenolic hydroxyl.

The presence of a very stable lactone is evident from the behavior of 7-hydroxy-3-methylphthalide in alkaline solution. Although an aqueous solution of I at *p*H 11 is stable for at least 16 hours at 25°, heating to 100° for one hour produced a drop in *p*H to be expected by hydrolysis of a lactone. When a sodium ethoxide solution was heated to 100° for one hour, a sparingly soluble hydrated disodium salt $C_8H_9O_4 \cdot Na_2 \cdot H_2O$ was formed. The original compound, I, was regenerated when an aqueous solution of the salt was acidified. The stability of the lactone excluded from consideration any structure not involving a five- or six-membered lactone ring.

Lithium aluminum hydride reduction of 7-hydroxy-3-methylphthalide (I) yielded one mole of hydrogen, and a phenolic trihydroxy compound, $C_9H_{12}O_3$ (IV). This trihydroxy compound was oxidized by periodate, consuming one mole of periodate rapidly, and additional amounts only very slowly. Formaldehyde was isolated from this oxidation in 10% yield. This behavior, which was at first considered to indicate that IV was a vicinal dihydroxy compound, was also shown to be a property of *o*-hydroxybenzyl alcohol. The methylated product, IVa, resulting from the reaction of hydride with the methyl ether II, is not attacked by periodate.

Permanganate oxidation of 7-methoxy-3-methylphthalide yielded 3-methoxyphthalic acid, III, which was isolated as the anhydride. The position of the substituent groups on the aromatic ring was thus established as being vicinal.

Alkali fusion of I yielded salicylic acid and acetic acid. The ready cleavage of a carbon bonded to an aromatic ring to yield benzoic acids and aliphatic acids on alkali fusion is characteristic of α-alkylphthalides.[6] The position of the phenolic hydroxyl as ortho to the carbonyl group was established by this alkali fusion product and the assignment was confirmed by comparison of the infrared absorption spectrum of I and of its methyl ether II. I shows its carbonyl absorption at 5.75 μ; the methyl ether shows its absorption at 5.67 μ, both in chloroform solution. A shift of this order of magnitude can be most reasonably explained by hydrogen bonding in I, which must presume that the hydroxyl group is ortho to the carbonyl.

The synthesis of 7-methoxy-3-methylphthalide (II) was effected through the pyridine–piperidine condensation of 3-methoxyphthalic anhydride (V) with malonic acid,[7] hydrolysis of the product, and reduction of the resulting 2-acetyl-6-methoxybenzoic acid (VI) with sodium amalgam.[8] The condensation reaction does not proceed readily since the decarboxylation of the malonic acid occurs rapidly under the reaction conditions employed. The identity of II obtained from terramycin with the synthetic 7-methoxy-3-methylphthalide was demonstrated through mixed melting point, and through the identity of their infrared absorption spectra.

Incidental to the synthesis of II, an isomer of I, 4-hydroxy-3-methylphthalide was prepared by the

(1) R. Pasternack, P. P. Regna, R. L. Wagner, A. Bavley, F. A. Hochstein, P. N. Gordon and K. J. Brunings, THIS JOURNAL, **73**, 2400 (1951).

(2) Paper II of this series, R. Pasternack, A. Bavley, R. L. Wagner, F. A. Hochstein, P. P. Regna and K. J. Brunings, *ibid.*, **74**, 1926 (1952).

(3) Paper III of this series, R. Pasternack, L. H. Conover, A. Bavley, F. A. Hochstein, G. B. Hess and K. J. Brunings, *ibid.*, **74**, 1928 (1952).

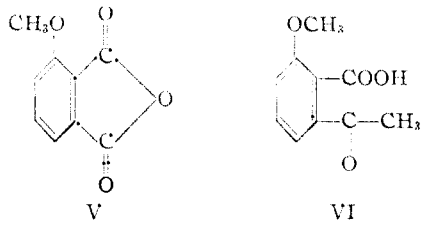
(4) F. A. Hochstein and R. Pasternack, *ibid.*, **73**, 5008 (1951).

(5) R. Kuhn and K. Dury, *Ber.*, **84**, 848 (1951), have recently published an independent proof of the structure of this compound.

(6) R. S. Cahn, *J. Chem. Soc.*, 986 (1930).

(7) H. L. Yale, THIS JOURNAL, **69**, 1547 (1947).

(8) T. Tamura, *J. Agr. Chem. Soc. Japan*, **15**, 685 (1939).



V VI

following route. The Gabriel condensation[9] of 3-nitrophthalic anhydride with potassium acetate yielded 2-acetyl-3-nitrobenzoic acid.[10] (The pyridine-catalyzed condensation of 3-nitrophthalic anhydride with malonic acid yields the same product.) Hydrogenation of this nitro-acid over palladium catalyst in ethyl acetate yields 2-acetyl-3-aminobenzoic acid, which was further reduced by sodium amalgam to 4-amino-3-methylphthalide.[10] Diazotization of the aminophthalide yields 4-hydroxy-3-methylphthalide, melting at 199–200°.

The infrared absorption spectrum of the 4-hydroxy-3-methylphthalide shows a remarkable similarity to that of 7-hydroxy-3-methylphthalide in the 7.5 μ region.

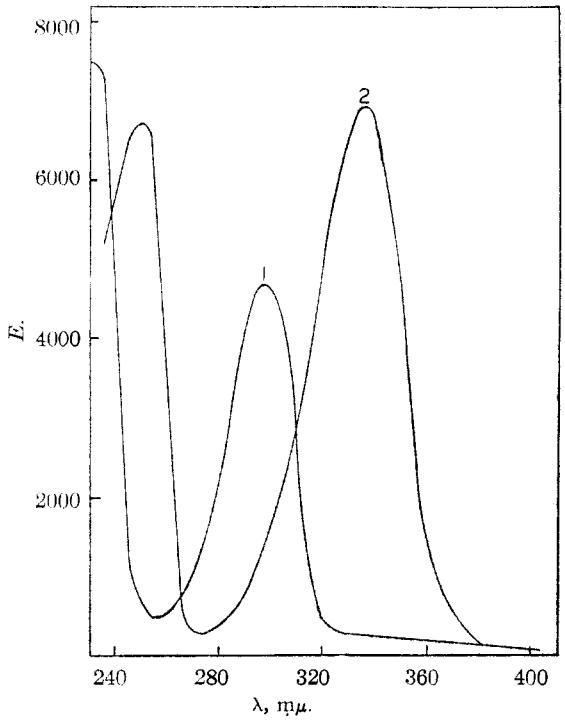


Fig. 1.—Ultraviolet absorption spectrum of 7-methoxy-3-methylphthalide: 1, in methanol; 2, in 0.01 *N* methanolic NaOH.

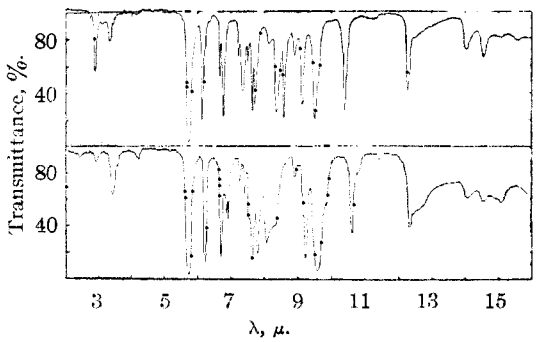


Fig. 2.—Infrared absorption spectra, in chloroform solution: upper, 7-hydroxy-3-methylphthalide; lower, 7-methoxy-3-methylphthalide.

Experimental[11]

Preparation of 7-Hydroxy-3-methylphthalide (I) from Terramycin.—A solution of 75 g. of dihydrated terramycin base (purity, 98%+) in 750 ml. of 25% sodium hydroxide was mixed with 225 g. of granular zinc, and the mixture stirred under reflux in a nitrogen atmosphere for 20 hours. The mixture was cooled, and the aqueous layer poured into a slight excess of sulfuric acid and ice overlayed with 200 ml. of ether. The aqueous layer was then exhaustively extracted with six 200-ml. portions of ether. The ether extract was subsequently extracted with eight 200-ml. portions of 1.0 *M* phosphate buffer, *p*H 5.5 to remove terracinoic acid,[2] and then with nine 200-ml. portions of 2% sodium bicarbonate to remove other acidic fractions. The residual ether soluble fraction was dried over calcium chloride, concentrated to a volume of 20 ml., and diluted with 20 ml. of benzene. A crystalline precipitate of a phenolic substance, $C_{12}H_{12}O_3$, separated, and was removed by filtration. 7-Hydroxy-3-methylphthalide was obtained from the ether–benzene filtrate by evaporation to dryness *in vacuo*, and sublimation at 150–200°, 0.1 mm. The crude oily product was twice resublimed at 125°, 0.1 mm. and finally recrystallized from 50 ml. of boiling water, to yield 0.8 g. of colorless plates, m.p. 110–112°. The compound was dried over $CaCl_2$ (*no* vacuum) for analysis.

Anal. Calcd. for $C_9H_8O_2 \cdot H_2O$: C, 59.33; H, 5.54; H_2O, 9.89. Found: C, 59.32; H, 5.79; H_2O (K.F.), 9.30.

This product can be substantially freed of water by drying over phosphorus pentoxide *in vacuo*, and resublimation. The "anhydrous" product normally distils as an oil which crystallizes only slowly as heavy colorless prisms, m.p. 59–60° (to a turbid liquid which may partly resolidify and become completely clear only above 80°). The analytical data on these preparations have never been entirely satisfactory.

Anal. Calcd. for $C_9H_8O_2$: C, 65.9; H, 4.91; CH_3, 8.95. Found: C, 64.14; H, 5.25; H_2O (K.F.) 0.5, C-methyl (Kuhn–Roth) 11.3.

Titration of the anhydrous product indicates a pK_a of 8.5, equivalent wt. 162 (calcd. 164). When I is heated under reflux with a measured excess of 0.2 *N* aqueous NaOH, the reverse titration curve showed no evidence of a carboxylic acid, but a single break at equivalent wt. 160. The infrared absorption spectra of I hydrate in Nujol mull shows strong bands at 2.87, 2.95, 5.79 and 6.15 μ (Fig. 2). The ultraviolet absorption spectrum (Fig. 1) shows peaks at 232 μ, log ϵ 4.874, 298 μ, log ϵ 4.674, in methanol solution. In 0.01 *N* NaOH in methanol, these peaks are shifted to 250 μ, log ϵ 4.828, and 335 μ, log ϵ 4.844. It reduces Fehling solution, and rapidly reduces ammoniacal silver nitrate.

Disodium Salt of 6-Acetylsalicylic Acid.—When 125 mg. of 7-hydroxy-3-methylphthalide hydrate was dissolved in 2 ml. of 1.25 *N* sodium ethoxide, and heated to 100° for one hour, a crystalline precipitate, only slightly soluble in alcohol, was formed. (No precipitate formed in 5 days at room temperature.) The crystalline product, 0.12 g., was carefully washed with three 1-ml. portions of cold ethanol, and dried at 80°, 0.05 mm. for 2 hours.

Anal. Calcd. for $C_9H_8O_4Na \cdot 2H_2O$: C, 44.30; H, 4.12; Na, 18.79. Found: C, 44.00; H, 4.34; Na, 18.45.

A portion of this disodium salt was dissolved in water, and acidified to yield unchanged starting material, m.p. 108–110°. The infrared absorption spectrum of this salt in Nujol mull shows no absorption in the 5.7–6.1 μ region, but a strong band at 6.37 μ, characteristic of carboxylate ion.

7-Acetoxy-3-methylphthalide was prepared by dissolving 0.10 g. of 7-hydroxy-3-methylphthalide hydrate in 1.0 ml.

(9) D. T. Mowry, E. L. Ringwald and M. Renoll, THIS JOURNAL, **71**, 120 (1949).

(10) C. H. Wang, R. Isensee, A. M. Griffith and B. E. Christensen, *ibid.*, **69**, 1909 (1947).

(11) All melting points are corrected.

of pyridine and 0.25 ml. of acetic anhydride. After 14 hours at room temperature, the reaction mixture was poured into 40 ml. of water, acidified to *p*H 2 with sulfuric acid and extracted with ether. The ether layer, on evaporation to 0.5 ml., yielded 0.1 g. of colorless crystals, m.p. 89–90°, which after two recrystallizations from benzene–ligroin melted at 90.2–90.8°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.03; H, 4.86; mol. wt., 206; acetyl (monoacetyl), 20.81. Found: C, 64.04; H, 5.13; acetyl, 20.67; mol. wt. (Rast), 216; active hydrogen, 0.05.

7-Methoxy-3-methylphthalide (II) was prepared by the reaction of 190 mg. of anhydrous 7-hydroxy-3-methylphthalide with 60 mg. of diazomethane (slight excess) in ether solution for three hours. The viscous product was purified by distillation at 0.1 mm. and had $n^{25}D$ 1.5572, d^{25}_{25} 1.223; yield 190 mg. (90%). This was dissolved in hot water and cooled to yield 130 mg. of crystalline product, m.p. 74–75°. This compound gives negative tests with ferric chloride and with aminoantipyrine. It dissolves very slowly in cold aqueous 10% NaOH. A resublimed sample was analyzed.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.45; H, 5.65; methoxyl, 17.41. Found: C, 67.46; H, 5.76; methoxyl, 18.04.

4,6-Dinitro-7-hydroxy-3-methylphthalide.—In an attempted oxidation, 100 mg. of anhydrous 7-hydroxy-3-methylphthalide in 1 ml. of concentrated nitric acid was heated on the steam-bath for 1 hour. The crystalline precipitate which separated on cooling was recrystallized from 15 ml. of 0.5 *N* hydrochloric acid, and dried at 65°, 0.1 mm. for 1 hour to yield 83 mg. (52%) of colorless product, m.p. 189.2–190.4°. This compound yields an acid-stable red color with sodium cyanide, characteristic of *m*-dinitro aromatic compounds.[12]

Anal. Calcd. for $C_9H_7N_2O_7$: C, 42.53; H, 2.38; N, 11.03; mol. wt., 254. Found: C, 42.66; H, 2.60; N, 11.35; equiv. wt. (titration), 257 (pK_a, 2.57).

Alkali Fusion of 7-Hydroxy-3-methylphthalide.—Anhydrous 7-hydroxy-3-methylphthalide, 0.5 g. (2.75 mmoles), was fused with 2.5 g. of sodium hydroxide and 2.5 g. of potassium hydroxide at 260° for 15 minutes.[6] The cooled melt was dissolved in 15 ml. of water, acidified with 6 *N* sulfuric acid, and extracted with six 30-ml. portions of ether. The ether was extracted with two 10-ml. portions of 5% sodium bicarbonate solution, the aqueous layer evaporated to 1 ml., and acidified with 6 *N* sulfuric acid. Acetic acid, 1.0 mmole (35% yield) was separated by distillation at 0.1 mm., 25°, into a −80° trap, and converted into the *p*-nitrobenzyl ester, m.p. 77–78°, mixed m.p. with an authentic sample not depressed. The non-volatile portion was diluted with 3 ml. of water, the crude salicylic acid removed by filtration, sublimed, and recrystallized from water to yield 90 mg. (25% yield) of salicylic acid, m.p. 158–159°, mixed m.p. with an authentic sample not depressed. This identity was confirmed by comparison of the ultraviolet absorption spectra.

3-Methoxyphthalic Acid (III) from 7-Methoxy-3-methylphthalide.—7-Methoxy-3-methylphthalide, 200 mg., 1.1 mmoles, was suspended in 0.5 ml. of 50% aqueous sodium hydroxide and heated to 120° for 10 minutes. The resulting suspension of crystalline sodium salt was dissolved by the addition of 5 ml. of water. Five ml. of 4% aqueous alkaline potassium permanganate solution was added portionwise to this solution at 5–15° in 15 minutes. Permanganate was still being consumed at this point. The solution was acidified with sulfuric acid, sodium bisulfite added to dissolve the inorganic precipitate, and extracted with five 30-ml. portions of ether. The combined ether extracts were shaken with 5 ml. of 5% sodium bicarbonate, and the ether evaporated to dryness to yield about 100 mg. of unreacted starting material. The bicarbonate layer was acidified, again extracted with ether, and the ether extract sublimed at 160°, 0.1 mm., to yield 7 mg. of 3-methoxyphthalic acid as the anhydride, m.p. 149–151°; mixed melting point with an authentic sample,[13] m.p. 160–161°, not depressed. This material was further characterized by the identity of its infrared absorption spectrum with that of 3-methoxyphthalic anhydride; yield 5%, based on unrecovered starting material.

(12) F. Feigl, "Qualitative Analysis by Spot Tests," Elsevier Press, Inc., New York, N. Y., 1946, p. 323.

(13) A. Girardet, *Helv. Chim. Acta*, **14**, 511 (1931).

Preparation of 1-[2-(Hydroxymethyl)-3-hydroxyphenyl]-ethanol (IV).—Two-tenths gram, 1.1 mmoles of anhydrous 7-hydroxy-3-methylphthalide was dissolved in 25 ml. of ether, and 25 ml. (0.011 mole) of an ether solution of lithium aluminum hydride was added. The mixture was heated under reflux for 5 hours, excess hydride decomposed with a minimum amount of 2 *N* sulfuric acid, and the product extracted from the aqueous phase with ether.[14] Concentration of the ether solution yielded a colorless crystalline product, which, after recrystallization from chloroform, weighed 0.13 g., m.p. 103–104°. It may be sublimed, with decomposition, only slowly at 170°, 0.05 mm. It is moderately soluble in water, gives a positive ferric chloride test, positive aminoantipyrine test, and increases the ionization of boric acid.[15] Titration shows pK_a 9.9, equivalent wt. 166 (calcd. 168).

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.20. Found: C, 64.09; H, 7.28.

With acetic anhydride in pyridine, this substituted α-phenylethanol yielded the triacetyl derivative, as an oil which was purified by distillation at 150°, 0.1 mm., $n^{25}D$ 1.4955, d^{25}_{25} 1.180, *MR*, 72.8.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.18; acetyl, 43.8. Found: C, 61.00; H, 6.20; acetyl, 44.2.

Preparation of 1-[2-(Hydroxymethyl)-3-methoxyphenyl]-ethanol (IVa).—Ten ml. (3 mmoles) of an ether solution of lithium aluminum hydride was added to 100 mg. (0.56 mmole) of 7-methoxy-3-methylphthalide in 10 ml. of ether, and the homogeneous solution left at room temperature overnight. The product was isolated by the procedure described for IV, and recrystallized from chloroform–ligroin. The readily sublimed colorless needles of 1-[2-(hydroxymethyl)-3-methoxyphenyl]-ethanol (IVa) (80 mg.) melted at 122–123°. This substance gives no ferric chloride test, and no color with aminoantipyrine. It is not attacked by potassium periodate in 24 hours at room temperature.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.90; H, 7.75; methoxyl, 17.03; active hydrogens, 2.00. Found: C, 66.10; H, 7.84; methoxyl, 20.5; active hydrogens,[16] 2.00.

Periodate Oxidation of 1-[2-(Hydroxymethyl)-3-hydroxyphenyl]-ethanol.—Twenty ml. of 0.0224 *M* potassium periodate was added to 42.0 mg. (0.25 mmole) of compound in 5.0 ml. of water. Aliquots were removed at intervals, and the unreacted periodate content was determined by addition of potassium iodide and titration with sodium arsenite. After 2 minutes, 1.01 moles of periodate had been consumed, and after 2.5 hours, the consumption was 1.10 moles. The apparent *p*H of the solution, as measured by brom cresol green indicator, remained at 4 to 5 during the whole reaction period, thus indicating that no acid was formed.

In a preparative scale reaction, 170 mg. (1 mmole) was dissolved in 5 ml. of water, 250 mg. of potassium periodate was added, and the mixture shaken until the periodate was dissolved. The aqueous layer was extracted with six 5-ml. portions of ether, the ether layer shaken with 3 ml. of water, and the ether evaporated from the combined layers. The crude 2,4-dinitrophenylhydrazone prepared from the aqueous phase was chromatographed over silicic acid–supercel.[17] Formaldehyde 2,4-dinitrophenylhydrazone, m.p. 164–165°, mixed melting point with an authentic sample not depressed, was isolated in 10% yield (25 mg.). No other product was identified.

The oxidation of *o*-hydroxybenzyl alcohol by periodate followed a course similar to that described above. Formaldehyde was isolated in 5% yield.

7-Methoxy-3-methylphthalide (II).—3-Methoxyphthalic anhydride,[13] 1.0 g. (5.6 mmole) and 1.0 g. (9.6 mmole) of dry malonic acid were powdered together, mixed with 0.7 ml. of pyridine and 0.3 ml. of piperidine, and heated on the steam-bath for 4 hours.[7] The clear solution was diluted with 2 ml. of water, and acidified to *p*H 2.5 with 10% hydrochloric acid. After 48 hours, a crystalline precipitate of 3-methoxyphthalic acid (0.15 g.) was removed by filtration, the mother liquor extracted with eight 20-ml. portions

(14) R. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).

(15) An experimental procedure similar to that of A. C. Cope and E. C. Herrick, *ibid.*, **72**, 983 (1950), was followed.

(16) F. A. Hochstein, *ibid.*, **71**, 305 (1949).

(17) J. D. Roberts and C. Green, *Ind. Eng. Chem., Anal. Ed.*, **18**, 335 (1946).

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.

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Introduction of the 11-Keto Function in the Steroids

BY JAMES M. CONSTANTIN AND L. H. SARETT

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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.