iodide) of progesterone-4-C^{14} (38×10^6 disintegrations/minute/mg.). The infrared spectra of progesterone-4-C^{14} were identical to those of an authentic sample of progesterone. The major absorption bands occurred at 5.86 (C-20 carbonyl), 5.98 (C-3 carbonyl), 6.17 and 7.36 μ.

SALT LAKE CITY, UTAH

[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Synthesis of Degradation Products of Aureomycin. IV[1]

BY J. H. BOOTHE, S. KUSHNER, J. PETISI AND J. H. WILLIAMS

RECEIVED FEBRUARY 18, 1953

One of the degradation products of Aureomycin, 4-chloro-3-hydroxy-7-methoxy-3-methylphthalide has been synthesized by chlorination of 3-hydroxy-7-methoxy-3-methylphthalide. The normal and pseudo esters of these compounds have been prepared and characterized.

During the degradation of Aureomycin,[2] a compound was isolated which was postulated to be 4-chloro-3-hydroxy-7-methoxy-3-methylphthalide (III). This postulation was based partially on the observation that the compound formed two different methyl esters depending on the method of esterification. This fact indicated a normal and a pseudo ester formation which is characteristic for *o*-acyl- or *o*-aroylbenzoic acids[3] or similar compounds in the aliphatic series.[4] It has been postulated that this type of compound exists as an equilibrium mixture of the keto acid and the phthalide type structure. In this paper these acids are named as phthalides rather than as carboxylic acids.

3-Hydroxy-7-methoxy-3-methylphthalide (II) was prepared by hydrolysis of 2-cyano-3-methoxyacetophenone (I)[5] in dilute sodium hydroxide. Hydrolysis of this cyano compound did not go well in acid solution although small yields could be obtained by hydrolysis in boiling 6 *N* hydrochloric acid. Ammonia determinations were run on the hydrolysis mixture to follow the course of the reaction and it was found that after 30 minutes about 35% of the theoretical amount of ammonia was liberated. This figure only increased to about 40% after four hours. The alkaline hydrolysis however gave good yields and a minimum of side reactions.

This acid, 3-hydroxy-7-methoxy-3-methylphthalide (II), on treatment with diazomethane gave a low melting normal ester (IV). The pseudo ester (V) was prepared by acid–methanol esterification or by treating the acid chloride with methanol and pyridine. The normal ester proved to be quite unstable in acid solution and rearranged to the pseudo ester at room temperature in dilute hydrochloric acid. It was also found that some batches of 3-hydroxy-7-methoxy-3-methylphthalide yielded only the pseudo ester on treatment with diazomethane. This unexpected reaction was probably catalyzed by small amounts of mineral acids because after thorough washing of these batches with water, they would then yield the normal ester.

Kuhn and Dury[6] have reported the preparation of "6-methoxy-2-acetylbenzoic acid methyl ester" from the degradation of Terramycin and by a synthetic route different from the one presented here. In each case the esterification was done on a crude mixture with diazomethane. The authors assumed their product was a normal ester as their name for it indicates. However, their reported m.p. is identical with that found by us for the pseudo ester (V). This anomaly might be explained by the presence of small amounts of acidic impurities in their product before esterification as noted in the above paragraph, or perhaps the normal ester is isomerized by distillation.

Chlorination of 3-hydroxy-7-methoxy-3-methylphthalide (II) with chlorine in acetic acid yielded 4-chloro-3-hydroxy-7-methoxy-3-methylphthalide (III). This compound was identical in all respects with the product from Aureomycin degradation as were the various derivatives described below. A normal (VII) and a pseudo ester (VI) were prepared in the same manner as described above for the unchlorinated compound. The normal ester also rearranged to the pseudo ester on treatment with dilute hydrochloric acid.

The position of the entering chlorine atom in these compounds is proved by the fact that they are identical with the degradation product of Aureomycin, since the position of the chlorine in Aureomycin has already been proved.[5]

The ultraviolet absorption data of these acids, normal esters and pseudo esters in methanol are shown in Table I. An inspection of these data shows that in the unchlorinated compounds the acid and the pseudo ester absorb similarly probably

TABLE I

ULTRAVIOLET ABSORPTION DATA

Compound	Maxima			
	mμ	ε	mμ	ε
Acid (II)	232	6940	300	4140
Normal ester (IV)	245	6010	312	3160
Pseudo ester (V)	237	6190	300	5090
Chlorinated acid (III)	235	8610	307	3760
Normal ester (VII)	230	8620	302	3165
	End absorption			
Pseudo ester (VI)	237	9080	312	5240

(1) Portions of this work were presented in a preliminary communication: S. Kushner, *et al.*, THIS JOURNAL, **74**, 3709 (1952).

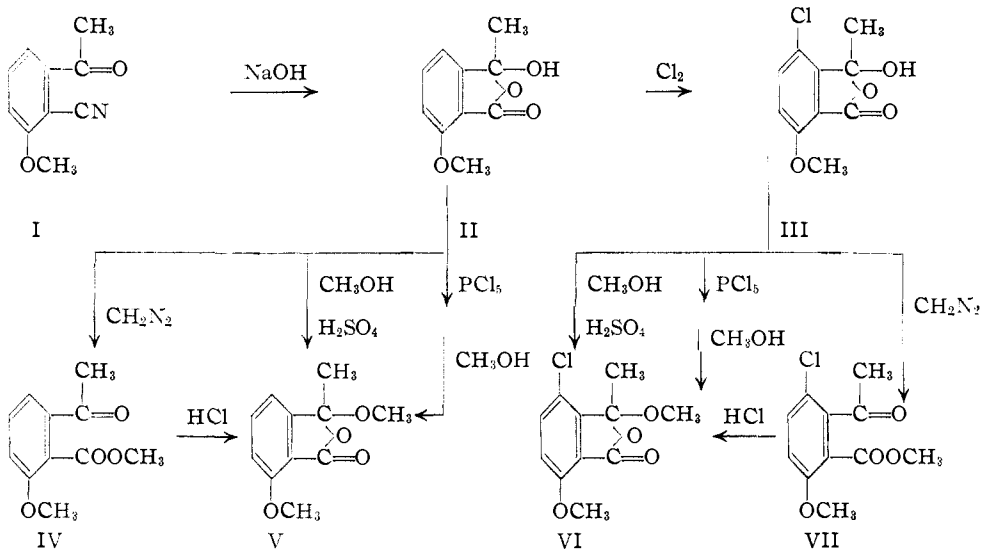
(2) B. L. Hutchings, *et al.*, *ibid.*, **74**, 3710 (1952).

(3) M. S. Newman, *et al.*, (a) *ibid.*, **63**, 1537 (1941); (b) *ibid.*, **66**, 731 (1944); (c) *ibid.*, **73**, 4625 (1952).

(4) R. E. Lutz and A. W. Winne, *ibid.*, **56**, 445 (1934).

(5) S. Kushner, *et al.*, *ibid.*, **75**, 1097 (1953).

(6) R. Kuhn and K. Dury, *Ber.*, **84**, 848 (1951).



indicating that the acid exists predominantly as the phthalide type structure. In the chlorinated series of compounds no such conclusion can be drawn since the absorption maxima of the acid occur about midway between those of the pseudo and normal esters.

The infrared absorption spectra of these compounds confirm the proposed structures. The two normal esters (IV and VII) each show two distinct absorption maxima in the carbonyl region of 5.5–6 microns while the two pseudo esters (V and VI) each show only one maximum in the same region. The two acids (II and III) each show only one maximum in this carbonyl region and in each case there is a slight shoulder on the maximum. These acids also each show an absorption maximum in the hydroxyl region at about 3 microns.

Acknowledgment.—The authors are indebted to Mr. Louis Brancone and staff for the microanalyses and to Mr. William Fulmor for the ultraviolet and infrared data contained herein. Large scale preparation of certain intermediates was carried out by Mr. Willard McEwen and associates.

Experimental[7]

3-Hydroxy-7-methoxy-3-methylphthalide (II).—Ten grams of 2-cyano-3-methoxyacetophenone (I) was refluxed 90 minutes with 200 cc. of 1 *N* sodium hydroxide. The solution was cooled, clarified after adding Norite, and acidified with about 18 cc. of concentrated hydrochloric acid. After cooling well, the product was filtered and dried; weight 9.17 g. A small portion was crystallized once from chloroform; m.p. 164–165°. *Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.8; H, 5.2; OCH_3, 16.0. Found: C, 62.1; H, 5.9; OCH_3, 16.4.

2-Carbomethoxy-3-methoxyacetophenone (IV).—A cold solution of diazomethane in ether (prepared from 24 g. of nitrosomethylurea) was added cautiously to a cold solution of 8 g. of 3-hydroxy-7-methoxy-3-methylphthalide (II) in 60 cc. of methanol. The yellow solution was boiled down to a small volume and the remainder of the solvents was removed *in vacuo*. The residue was dissolved in 50 cc. of methanol, clarified after adding Norite, and the solution was diluted with 250 cc. of water. After cooling well, the product was removed by filtration and dried; weight 7.15 g., m.p. 72–73°. A portion was crystallized from methanol and water and then from petroleum ether (b.p. 90–100°). A small amount was sublimed at 60–63° at 0.15 mm. pressure; m.p. 73–74°. *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.4; H, 5.8; OCH_3, 29.8. Found: C, 63.3; H, 5.9; OCH_3, 29.5.

3,7-Dimethoxy-3-methylphthalide (V). (a).—A solution of 0.46 g. of 3-hydroxy-7-methoxy-3-methylphthalide (II) and 0.1 cc. of concentrated sulfuric acid in 5 cc. of absolute methanol was refluxed one hour. The solution was cooled and after adding 15 cc. of water the product was removed by filtration and dried; weight 0.37 g., m.p. 117–119°. This product was crystallized from heptane and then from methanol and water; m.p. 119–120°. *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.4; H, 5.8; OCH_3, 29.8. Found: C, 63.7; H, 5.9; OCH_3, 30.1.

(b).—A mixture of 5 g. of 3-hydroxy-7-methoxy-3-methylphthalide (II) and 5.6 g. of phosphorus pentachloride in 50 cc. of dry benzene was stirred for one hour. The solution was filtered if necessary and the filtrate was diluted with 150 cc. of dry heptane. After cooling for two to three hours, the product was filtered off and washed with low boiling petroleum ether (b.p. 20–40°); weight 4–5 g. One hundred mg. of this acid chloride was dissolved in 1.5 cc. of methanol and 0.2 cc. of pyridine. After 10 minutes the solution was diluted to about 10 cc. with water and the crystalline product was filtered off; m.p. 117–119°. There was no melting point depression upon admixture with the product from method (a).

(c).—A solution of 0.5 g. of 2-carbomethoxy-3-methoxyacetophenone in 4 cc. of methanol and 5 drops of concentrated hydrochloric acid was allowed to stand at room temperature for two hours. The solution was diluted with 20 cc. of water and the crystalline product was removed by filtration and dried; m.p. 117–119°. There was no melting point depression upon admixture with the products from methods (a) or (b).

4-Chloro-3-hydroxy-7-methoxy-3-methylphthalide (III).—A solution of 0.5 g. of 3-hydroxy-3-methyl-7-methoxyphthalide (II) in 5 cc. of acetic acid was prepared by warming to 75°. The solution was cooled to 40° and 8 cc. of 5.1% solution of chlorine in acetic acid was added. After about four hours at room temperature, the solution was concentrated to dryness *in vacuo*. The residue was crystallized twice from about 50 cc. of benzene; m.p. 204–206°. There was no melting point depression upon admixture with the degradation product from Aureomycin. The infrared absorption spectra of the two compounds also showed they were identical. *Anal.* Calcd. for $C_{10}H_9O_4Cl$: C, 52.4; H, 3.9; Cl, 15.5. Found: C, 52.3; H, 3.9; Cl, 15.4.

2-Carbomethoxy-6-chloro-3-methoxyacetophenone (VII).—A solution of 0.5 g. of 4-chloro-3-hydroxy-7-methoxy-3-methylphthalide (III) in 5 cc. of methanol was treated with an excess of diazomethane as described above for the unchlorinated compound to yield 0.37 g. of ester. It was crystallized twice from methanol and water; m.p. 69.5–

(7) All m.p.'s are corrected and were taken according to U.S.P. specified conditions, *i.e.*, the compounds were put in the bath 30° below the expected m.p. and the temperature was raised at a rate of 3° per minute.

70.5°. *Anal.* Calcd. for $C_{11}H_{11}O_4Cl$: C, 54.5; H, 4.6; OCH_3, 25.6. Found: C, 54.6; H, 4.7; OCH_3, 25.9.

4-Chloro-3,7-dimethoxy-3-methylphthalide (VI).—This compound was prepared by the three methods described above for the unchlorinated pseudo ester; m.p. 190–191°. *Anal.* Calcd. for $C_{11}H_{11}O_4Cl$: C, 54.5; H, 4.6; OCH_3, 25.6. Found: C, 54.4; H, 4.7; OCH_3, 25.7.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Synthesis of Degradation Products of Aureomycin. V[1]

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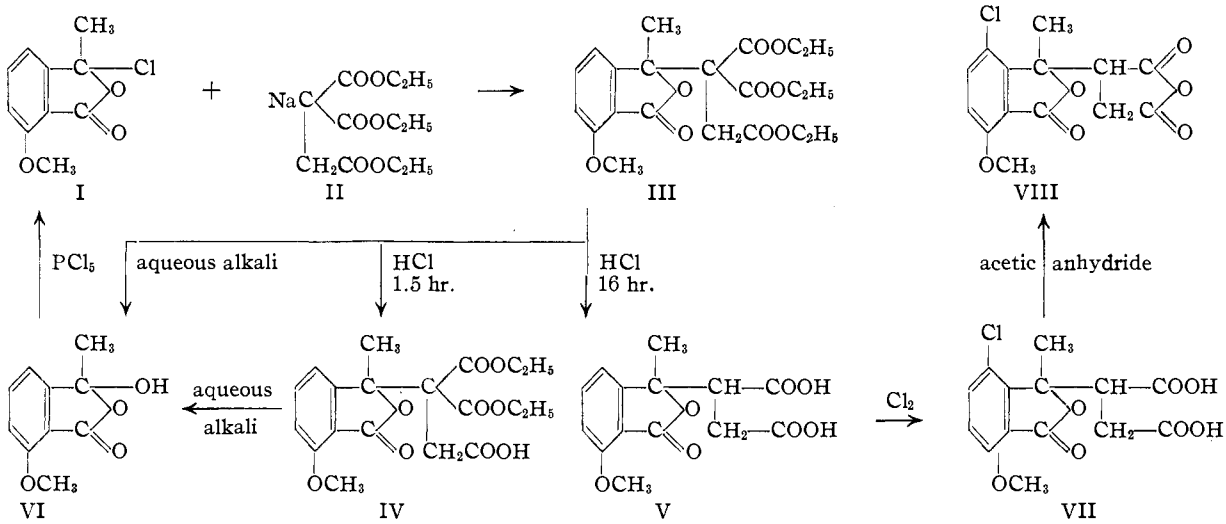
RECEIVED FEBRUARY 18, 1953

One of the degradation products of Aureomycin, 3-(4-chloro-7-methoxy-3-methylphthalidyl)-succinic acid has been synthesized. The synthesis involves a new method of adding substituents to the 3-position of a phthalide by reaction of a pseudo acid chloride with a malonic ester derivative.

One of the degradation products of Aureomycin described in a previous paper[2] was tentatively identified as 3-(4-chloro-7-methoxy-3-methylphthalidyl)-succinic acid. It has already been shown that similar phthalides can be chlorinated easily in the 4-position.[3] Therefore one of the methods considered for preparing a substituted phthalide of this type was the reaction of the pseudo acid chloride, 3-chloro-7-methoxy-3-methylphthalide (I)[4] with a properly substituted malonic ester and subsequent hydrolysis and chlorination.



The coupling reaction was first tried with magnesio malonic ester and successfully yielded diethyl 3-(7-methoxy-3-methylphthalidyl)-malonate. The pseudo acid chloride then reacted with the substituted malonic ester, diethyl carbethoxysuccinate (II) and yielded diethyl α-carbethoxy-α-[3-(7-methoxy-3-methylphthalidyl)]-succinate (III). This compound, however, was found to be quite unstable to alkali, being cleaved to 3-hydroxy-7-methoxy-3-methylphthalide (VI) in dilute sodium hydroxide at room temperature or by refluxing in aqueous sodium carbonate. The compound was somewhat resistant to acid hydrolysis and after refluxing 90 minutes in concentrated hydrochloric acid the recovered product still retained 2 ester groups and was assumed to be monoethyl-α-carbethoxy-α-[3-(7-methoxy-3-methylphthalidyl)]-succinate (IV). Longer refluxing yielded the completely hydrolyzed and decarboxylated product 3-(7-methoxy-3-methylphthalidyl)-succinic acid (V).

Since this compound V has 2 asymmetric centers, it exists in 2 racemic forms or diastereoisomers which were separated by their different solubilities in ethyl acetate. Each racemate was then chlorinated with chlorine in acetic acid to yield the 2 isomeric 3-(4-chloro-7-methoxy-3-methylphthalidyl)-succinic acids. Since one of these racemates more closely resembled the degradation product in infrared absorption spectra it was resolved by means of the brucine salt and the optically active product was identical in all respects with the degradation product.

The anhydride VIII of the above compound was also prepared and found to be identical in all respects with the anhydride of the degradation product.

Acknowledgment.—The authors are indebted to Mr. Louis Brancone and staff for the microanalyses and to Mr. William Fulmor for the ultraviolet and infrared data contained herein. Large scale preparation of certain intermediates was carried out by Mr. Willard McEwen and associates.

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(2) B. L. Hutchings, *ibid.*, **74**, 3710 (1952).
(3) S. Kushner, *ibid.*, **75**, 1097 (1953).
(4) J. H. Boothe, *et al.*, *ibid.*, **75**, 3261 (1953).