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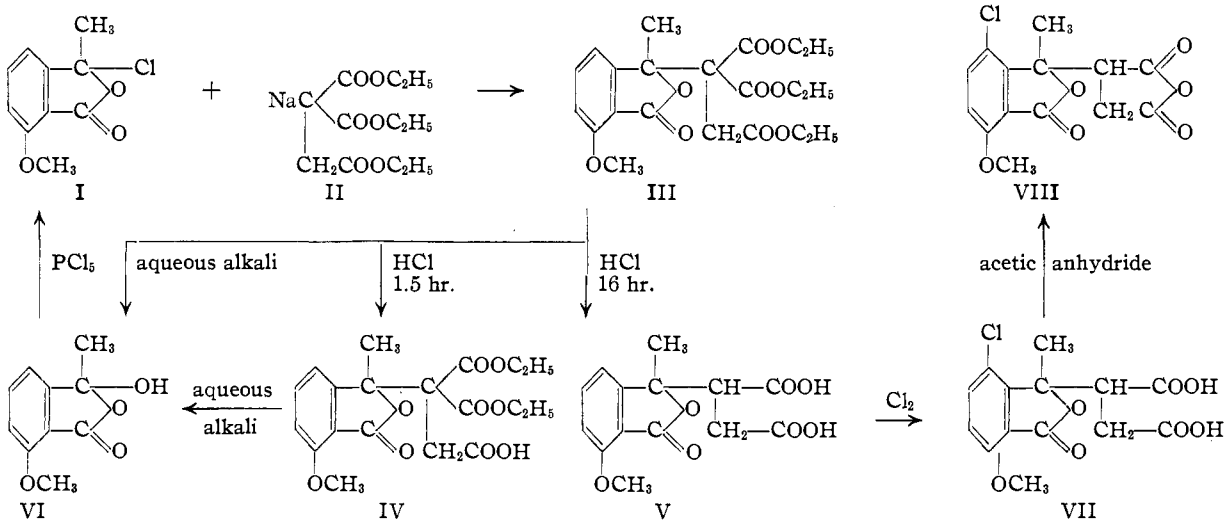
One of the degradation products of Aureomycin, 3-(4-chloro-7-methoxy-3-methylphthalidyl)-succinic acid has been synthesized. The synthesis involves a new method of adding substituents to the 3-position of a phthalide by reaction of a pseudo acid chloride with a malonic ester derivative.

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 carbethoxy-succinate (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.

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

Experimental[5]

Diethyl 3-(7-Methoxy-3-methylphthalidyl)-malonate.—A mixture of 5 g. of 3-hydroxy-7-methoxy-3-methylphthalide (VI) and 5.6 g. of phosphorus pentachloride was stirred in 50 cc. of dry benzene for one hour. The solution was filtered if necessary and the filtrate was diluted with 150 cc. of dry heptane. After cooling for three hours the solid was filtered and washed with low boiling petroleum ether; yield 4–4.5 g. This product is predominantly the pseudo acid chloride, 3-chloro-7-methoxy-3-methylphthalide (I) as shown by its reaction with methanol and pyridine to form the pseudo ether.[4] This pseudo acid chloride was not further purified but was used as such for the further reactions.

A mixture of 5.47 cc. of ethyl malonate and 2.65 g. of magnesium methoxide dimethanolate[6] in 35 cc. of dry benzene was shaken for 3 hours. It was centrifuged clear and evaporated to dryness *in vacuo*. The residue was dissolved in 25 cc. of dry benzene and the chlorophthalide described above was added and stirred for two hours. The mixture was evaporated to dryness *in vacuo* and 25 cc. of water and 1.5 cc. of concentrated hydrochloric acid was added. This mixture was extracted with chloroform and the extracts were dried and evaporated to dryness. The residue was mixed with petroleum ether and after it partially solidified it was filtered off and crystallized from 5 cc. of ethanol; yield 2.44 g., m.p. 120–122°. A portion of the product was crystallized from ethyl acetate and then from ethanol; m.p. 125–126.5°. *Anal.* Calcd. for $C_{17}H_{20}O_7$: C, 60.7; H, 6.0; OCH_3, 27.7. Found: C, 60.6; H, 6.3; OCH_3, 27.5.

Diethyl α-Carbethoxy-α-[3-(7-methoxy-3-methylphthalidyl)]-succinate (III).—A solution of 6 g. of diethyl carbethoxysuccinate and 1.39 g. of sodium methoxide in 35 cc. of dry benzene was evaporated to dryness and the residual sirup was redissolved in 35 cc. of dry benzene. To the stirred solution was added during 20 minutes a suspension of the chlorophthalide I (prepared as described above from 5 g. of 3-hydroxy-7-methoxy-3-methylphthalide) in 40 cc. of dry benzene. The mixture was then refluxed for 30 minutes, cooled, and the insolubles removed by centrifuging. The clear benzene solution was concentrated to dryness *in vacuo* and the yellow oily residue was diluted with 15 cc. of ether. After cooling several hours, the crystalline product was filtered off and dried; wt. 4.55 g., m.p. 80–85°. A portion was crystallized twice from ether; m.p. 83–85°. *Anal.* Calcd. for $C_{21}H_{26}O_9$: C, 59.6; H, 6.2. Found: C, 59.6; H, 6.3.

Hydrolysis with Alkali.—A solution of 422 mg. of the above triester (III) in 3 cc. of ethanol was stirred and 3.1 cc. of 1.0 *N* sodium hydroxide was dripped in over 30 minutes. After 30 minutes more the solution was acidified and a crystalline product slowly deposited; m.p. 160–162°. There was no depression on admixture with 3-hydroxy-3-methyl-7-methoxyphthalide (VI).[4] The same product was obtained by heating on the steam-bath one hour with aqueous 1 *N* sodium hydroxide or by refluxing 18 hours in 0.5 *N* sodium carbonate.

Monoethyl α-Carbethoxy-α-[3-(7-methoxy-3-methylphthalidyl)]-succinate (IV).—A mixture of 0.6 g. of diethyl α-carbethoxy-α-[3-(7-methoxy-3-methylphthalidyl)]-succinate (III) and 12 cc. of concentrated hydrochloric acid was refluxed 90 minutes. The nearly clear solution was diluted with 20 cc. of water, filtered and cooled. The crystalline product was filtered off and recrystallized from 10 cc. of water; m.p. 166–168°, yield about 0.2 g. The product was recrystallized from 8 cc. of benzene; m.p. 169–170.5°. *Anal.* Calcd. for $C_{19}H_{22}O_9$: C, 57.9; H, 5.6; OCH_3, 23.6; equiv. wt., 394. Found: C, 58.1; H, 5.7; OCH_3, 23.5; equiv. wt. (by titration), 387.

Hydrolysis with Alkali.—A solution of 0.2 g. of the above diester IV in 5 cc. of 0.5 *N* sodium hydroxide was allowed to stand at room temperature for three hours. The solution was diluted to 10 cc. and acidified with hydrochloric acid. After cooling, the product was filtered off; m.p. 164–166°. There was no m.p. depression on admixture with 3-hydroxy-3-methyl-7-methoxyphthalide.[4]

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

(6) B. R. Baker, *et al.*, *J. Org. Chem.*, **17**, 78 (1952).

3-(7-Methoxy-3-methylphthalidyl)-succinic Acid (V).—A mixture of 20 g. of diethyl α-carbethoxy-α-[3-(7-methoxy-3-methylphthalidyl)]-succinate (III) and 400 cc. of concentrated hydrochloric acid was refluxed for 16 hours. The solution was concentrated *in vacuo* to about 50 cc. and after cooling well the product was filtered and washed thoroughly with water; yield 7–8 g., m.p. 185–195° with gas. This product contains both racemic diastereoisomers which were separated by the following procedure. The crude product was extracted for 30 minutes with 400 cc. of boiling ethyl acetate and the insoluble residue was filtered off hot; wt. about 2 g., m.p. 204–208° with gas. It was recrystallized once from water; m.p. 207–209.5°. *Anal.* Calcd. for $C_{14}H_{14}O_7$: C, 57.1; H, 4.8; OCH_3, 10.5. Found: C, 57.3; H, 5.2; OCH_3, 9.7.

The 400 cc. of ethyl acetate filtrate on standing 3 days deposited 2.9 g. of crystalline material melting at about 190° with gas. The filtrate from this material was concentrated to 60 cc. and on cooling deposited 1.05 g. of material melting at 186–188° with gas. One-half gram of this material was boiled with 75 cc. of ethyl acetate and a small amount of undissolved residue was filtered off; m.p. 189–191° with gas. The filtrate was cooled and the crystalline material was removed by filtration; m.p. 190–191°. *Anal.* Found: C, 57.1; H, 5.1; OCH_3, 10.8.

3-(4-Chloro-7-methoxy-3-methylphthalidyl)-succinic Acid (VII). (a).—One gram of the low melting isomer of 3-(7-methoxy-3-methylphthalidyl)-succinic acid (V) was dissolved in 50 cc. of acetic acid by heating and then cooled to 40°. A 6.6% solution of chlorine in acetic acid was added (7.2 cc.) and the solution was allowed to stand at room temperature for 3.5 hours. The solution was concentrated to dryness *in vacuo* and the oily residue after stirring with 10 cc. of benzene crystallized. The mixture was cooled and the product filtered off; yield 530 mg., m.p. 178–180° with gas. This product was crystallized twice from ethyl acetate–petroleum ether mixtures (1:1), giving a constant m.p. of 199–200° with gas. *Anal.* Calcd. for $C_{14}H_{13}O_7Cl$: C, 51.1; H, 4.0; Cl, 10.8. Found: C, 51.4; H, 4.4; Cl, 10.9.

(b).—A solution of 0.5 g. of high melting 3-(7-methoxy-3-methylphthalidyl)-succinic acid (V) was chlorinated and worked-up as described above for the low melting isomer. The product was crystallized once from ethyl acetate–petroleum ether and once from water; m.p. 228–229° with gas. *Anal.* Found: C, 51.5; H, 4.3; Cl, 10.7.

Resolution of the High Melting Isomer of 3-(4-Chloro-7-methoxy-3-methylphthalidyl)-succinic Acid (VII).—A solution of 0.5 g. of this compound, m.p. 228–229°, in 10 cc. of ethanol and a solution of 1.2 g. of anhydrous brucine in 10 cc. of ethanol were mixed. On warming and scratching crystals formed and after 30 minutes at room temperature the solid was filtered off; yield 0.51 g. This product was crystallized twice from ethanol; yield 0.4 g. A solution of 0.38 g. of this brucine salt in 10 cc. of water was acidified with 5 drops of concentrated hydrochloric acid and extracted 4 times with 20-cc. portions of ethyl acetate. These extracts were washed with 10 cc. of water, dried and evaporated to dryness *in vacuo*. The 150 mg. of residue was crystallized from 8 cc. of water after treating with norite; yield 110 mg., 209–210.5° with gas, $[\alpha]^{25}D$ −20.4° (5% in ethanol). Under the same m.p. conditions the degradation product from Aureomycin melted at 211–212° with gas and a mixture showed no depression. The ultraviolet and infrared absorption spectra and the rotation of the two compounds were identical.

3-(4-Chloro-7-methoxy-3-methylphthalidyl)-succinic Anhydride (VIII).—A mixture of 0.4 g. of the racemic high melting isomer of 3-(4-chloro-7-methoxy-3-methylphthalidyl)-succinic acid (VII) and 8 cc. of acetic anhydride was heated on a steam-bath for 2.5 hours. The solid went into solution in 20 to 30 minutes. The solution was concentrated to dryness *in vacuo* and the residue was crystallized from 45 cc. of dry benzene; m.p. 202–204°. *Anal.* Calcd. for $C_{14}H_{11}O_6Cl$: C, 54.2; H, 3.6; Cl, 11.4. Found: C, 54.4; H, 3.9; Cl, 11.5.

Fifty mg. of the optically active (resolved) 3-(4-chloro-7-methoxy-3-methylphthalidyl)-succinic acid (VII) was converted to the anhydride as described above; m.p. 200–201°. There was no m.p. depression on admixture with the product from Aureomycin degradation and the infrared absorption spectra were identical.

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