vanadium(III) ions. The possibility of rapid separation-induced exchange brought about when the reaction mixture is added to alcoholic α,α'-dipyridyl is not excluded by these observations. Dodson's work with the iron(II)–iron(III) exchange showed exchange half-times of the order of 15–50 seconds with the reactant species at *ca.* 0.001 *f* each. Reduction of the concentrations of the vanadium reactants may slow the observed rapid exchange rate to a point where kinetic studies could be undertaken, but the techniques used so far have not permitted this because of difficulties with oxidation of both vanadium species in solutions at high dilution by traces of oxygen present.

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SYNTHESIS OF DEGRADATION PRODUCTS OF AUREOMYCIN

Sir:

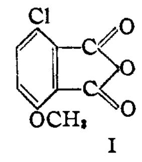
The synthesis of several degradation products[1] of Aureomycin by unequivocal methods has been accomplished. In each case these synthetic products were compared with the degradation products by means of m.p., mixed m.p., ultraviolet and infrared absorption spectra, and other properties to prove their identity.

TABLE I

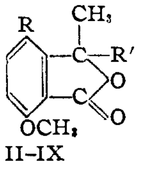
No.	R	R′	M.p., °C.	Theory C	Theory H	Theory OCH_3	Theory Cl	Found C	Found H	Found OCH_3	Found Cl
II	H	—H	73–75	67.4	5.6			66.9	6.0		
III	Cl	—H	113–14	56.5	4.2		16.7	57.0	4.6		16.3
IV	H	—OH	164–65	61.8	5.2	16.0		62.1	5.9	16.4	
V	Cl	—OH	204–206	52.4	3.9		15.5	52.3	3.9		15.4
VI	H	—COOH	168–70	59.5	4.5			59.8	5.2		
VII	Cl	—COOH	199–200	51.5	3.5		13.8	51.7	3.9		13.8
VIII	H	—CH_2COOH | —CH_2COOH	207–209.5	57.1	4.8	10.5		57.3	5.2	9.7	
IX	Cl	CH_2COOH | CH_2COOH	209–210.5	51.1	4.0		10.8	51.4	4.4		10.9

The first of these products is 6-chloro-3-methoxyphthalic anhydride (I) which definitely places the position of the methoxyl and chloro groups in relation to the other 2 substituents on the benzene ring. This compound was prepared from 3-methoxy-6-chloroanthranilic acid[2] by replacement of the amino group by a cyano group through a Sandmeyer reaction and hydrolysis to the phthalic acid derivative, m.p. 187–188°. *Anal.* Calcd. for $C_9H_5O_4Cl$: C, 50.8; H, 2.4; Cl, 16.7. Found: C, 51.5; H, 2.7; Cl, 16.7.

The remaining compounds are phthalides of the following general formula in which R = chlorine and R′ = groups as shown in Table I. These phthalides can be degraded to phthalic or benzoic acid derivatives to prove the position of the chlorine atom as indicated in the previous paper.[1]



I



II–IX

4-Chloro-7-methoxy-3-methyl-phthalide (III) was prepared from 2-amino-3-methoxyacetophenone[3] by reducing the ketone to the alcohol and replacing the amino by a cyano group. On hydrolysis, II was formed which was chlorinated to III with chlorine in acetic acid or with sodium hypochlorite and hydrochloric acid.

4-Chloro-3-hydroxy-7-methoxy-3-methylphthalide (V) was prepared by replacement of the amino by cyano in 2-amino-3-methoxyacetophenone, hydrolysis to IV and chlorination to V. Both IV and V probably exist in equilibrium with the corresponding *o*-carboxyacetophenone structure and both will form "normal" esters with diazomethane and "pseudo" esters with acid–methanol or acid chloride–methanol procedures.

4-Chloro-7-methoxy-3-methyl-3-phthalidecarboxylic acid (VII) was prepared by adding hydrogen cyanide to 2-cyano-3-methoxyacetophenone, hydrolysis of the product to VI and chlorination to VII. The compound was resolved by crystallizing the brucine salt from water; $[\alpha]^{28}D$ +25° (1.2% in ethanol).

3-(4-Chloro-7-methoxy-3-methylphthalidyl)-succinic acid (IX) was prepared by treating IV with phosphorus pentachloride to form the "pseudo" acid chloride which reacted with sodio diethyl carbethoxysuccinate. Hydrolysis and decarboxylation yielded VIII which was chlorinated to IX. Two racemates resulted and the higher melting one, m.p. 228–229° with gas, was resolved by crystallizing the brucine salt from ethanol; m.p. 209–210.5° with gas; $[\alpha]^{25}D$ −20.4° (5% in alcohol).

CONTRIBUTION FROM THE
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[1] B. L. Hutchings, *et al.*, THIS JOURNAL, 74, 3710 (1952).

[2] B. R. Baker, *et al.*, *J. Org. Chem.*, 17, 160 (1952).

[3] J. C. E. Simpson, *et al.*, *J. Chem. Soc.*, 646 (1945).

DEGRADATION OF AUREOMYCIN

Sir:

In a preliminary report[1] certain of the physical and chemical properties of aureomycin were out-

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[1] R. W. Broschard, A. C. Dornbush, S. Gordon, B. L. Hutchings, A. R. Kohler, G. Krupka, S. Kushner, D. V. Lefemine and C. Pidacks, *Science*, 109, 199 (1949).

lined. From the analytical data presented an empirical formula of $C_{22}H_{27}N_2ClO_8$ could be calculated. In the present communication a number of degradation products of aureomycin will be described.

From alkaline fusion of aureomycin 5-chlorosalicylic acid, dimethylamine and ammonia were obtained.[2]

The methylation and subsequent permanganate oxidation of aureomycin resulted in the formation of a number of *p*-chloromethoxybenzene derivatives which were separated by fractional extraction with various buffers and by selective crystallization.

The simplest oxidation product was identified as 6-chloro-3-methoxyphthalic acid, m.p. 186–187°, *anal.* Calcd. for $C_9H_7ClO_5$: C, 46.91; H, 3.06; Cl, 15.37. Found: C, 47.04; H, 3.57; Cl, 15.13. The anhydride of this compound melted at 187–188°.

Further fractionation yielded a monobasic acid, m.p. 199–200° (dec.) $[\alpha]^{25}\mathrm{D}$ +25° (methanol), *anal.* Calcd. for $C_{11}H_9O_5Cl$: C, 51.5; H, 3.54; Cl, 13.8; OCH_3, 12.1; C–CH_3, 5.35. Found: C, 51.5; H, 4.02; Cl, 13.8; OCH_3, 11.9; C–CH_3, 5.18, which readily formed a monomethyl ester, m.p. 96–100°. Infrared absorption spectra showed the presence of carboxyl, lactone, carbonyl, aromatic unsaturation, terminal methyl and aromatic ether absorption. Decarboxylation resulted in the formation of carbon dioxide (one mole) and a neutral compound, m.p. 112–113°. The latter was identified as 4-chloro-7-methoxy-3-methylphthalide, *anal.* Calcd. for $C_{10}H_9O_3Cl$: C, 56.5; H, 4.24; Cl, 16.7. Found: C, 56.6; H, 4.5; Cl, 16.75. Thus, the monobasic acid was 4-chloro-7-methoxy-3-methylphthalide-3-carboxylic acid.

When 4-chloro-7-methoxy-3-methylphthalide was oxidized with alkaline permanganate, 6-chloro-3-methyloxyphthalonic acid or 6-chloro-3-methoxyphthalic acid was obtained, depending on whether the manganese dioxide was filtered off before or after acidification. The former compound melted at 224–227° (dec.), *anal.* Calcd. for $C_{10}H_7O_6Cl$: C, 46.4; H, 2.71; Cl, 13.7. Found: C, 46.8; H, 3.12; Cl, 13.9; C–CH_3, 0.0. If the oxidation was carried out in neutral solution, 3-hydroxy-3-methyl-4-chloro-7-methoxyphthalide, m.p. 198–293°, *anal.* Calcd. for $C_{10}H_9ClO_4$: C, 52.5; H, 3.94; Cl, 15.54; OCH_3, 13.6; C–CH_3, 6.6. Found: C, 52.65; H, 4.47; Cl, 15.26; OCH_3, 10.36; C–CH_3, 6.13, was formed. Methylation of this compound yielded a normal ester, m.p. 69–70°, and a pseudo ester, m.p. 188–190°.

The oxidation residues further yielded a dibasic acid, m.p. 211–212°, $[\alpha]^{25}\mathrm{D}$ −20.2 (ethanol), *anal.* Calcd. for $C_{14}H_{13}O_7Cl$: C, 51.1; H, 3.96; Cl, 10.8; OCH_3, 9.45; C–CH_3, 4.56. Found: C, 51.1; H, 5.54; Cl, 10.7; OCH_3, 9.24; C–CH_3, 4.53. An anhydride, m.p. 209–210°, was readily formed when the dibasic acid was heated in acetic anhydride. Ultraviolet and infrared absorption spectra indicated the presence of the phthalide nucleus in both the acid and the anhydride. The typical absorption bands of the latter compound at 5.3 and 5.6 microns further suggested the presence of a succinic acid moiety. The dibasic acid was postulated to be 4-chloro-7-methoxy-3-methylphthalide-3-succinic acid.

The synthesis[3] of the above compounds unequivocally prove the assigned structures.

Finally, a second dibasic acid, m.p. 203–204°, *anal.* Calcd. for $C_{15}H_{15}O_7Cl$: C, 52.6; H, 4.38; Cl, 10.4; C–CH_3, 4.40; OCH_3, 9.58. Found: C, 52.3; H, 4.81; Cl, 10.5; C–CH_3, 4.89; OCH_3, 9.60, was isolated from the oxidation mixture. The formation of the dimethyl ester, m.p. 108–109.5°, and the anhydride, m.p. 200–201°, established the presence of two carboxylic acid groups. The infrared absorption spectra of the anhydride showed typical bands for glutaric anhydride, in contrast to the bands for succinic anhydride in the previous compound. The ultraviolet absorption spectra of the two dibasic acids were almost identical. The unknown dibasic acid was demethylated with hydrobromic acid to the phenolic acid, m.p. 172.5–175°, and then oxidized with acid permanganate to yield tricarballylic acid. The dibasic acid was, therefore, postulated to be *β*-(4-chloro-7-methoxy-3-methylphthalide-3)-glutaric acid.

Alkaline fusion of the phthalide derivatives, with the exception of 4-chloro-7-methoxy-3-methylphthalide, gave 5-chloro-2-methoxybenzoic acid.

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(2) R. Kuhn and K. Dury, *Chem. Ber.*, **84**, 563 (1951), reported the finding of 5-chlorosalicylic acid and dimethylamine but no ammonia in a similar experiment on aureomycin.

(3) S. Kushner, J. H. Boothe, J. Morton, J. Petisi and J. H. Williams, THIS JOURNAL, **74**, 3710 (1952).

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RECEIVED JUNE 23, 1952

STEROIDS. XXXVII.[1] A TEN STEP CONVERSION OF PROGESTERONE TO CORTISONE

Sir:

Taking advantage of our recently described[2] methods for the introduction of the 11*α*-hydroxy group into ring C unsubstituted steroids we have started a program directed at the chemical synthesis of the 11*α*-hydroxy analogs of the various natural hormones; their application to the case of 11*α*-hydroxyprogesterone (I) has already been reported.[3] The physical constants of the synthetic product proved to be in excellent agreement with those reported by Peterson and Murray[4] for a substance obtained in 10% yield by the microbiological oxidation of progesterone with the mold ***Rhizopus arrhizus*** (their strain RH 176) and assigned the 11*α*-hydroxyprogesterone structure.

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(1) Paper XXXVI, J. Romo, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, in press.

(2) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3546 (1951); C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, *ibid.*, **73**, 4496 (1951); C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *ibid.*, **74**, 1712 (1952); F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952).

(3) O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, in press (1952).

(4) D. H. Peterson and H. C. Murray, THIS JOURNAL, **74**, 1871 (1952).