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.) $[\alpha]^{25}D$ +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°, $[\alpha]^{25}D$ −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.

(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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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 11α-hydroxy group into ring C unsubstituted steroids we have started a program directed at the chemical synthesis of the 11α-hydroxy analogs of the various natural hormones; their application to the case of 11α-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 11α-hydroxyprogesterone structure.

(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).

We now wish to report that by the use of an as yet unidentified fungus of the *Rhizopus* family (our strain SY 152) isolated[5] from a Mexican soil sample (Molino de Bezares, D.F., Mexico) it has been possible to achieve the oxidation of progesterone to its 11α-hydroxy analog I in 45% yield. In striking contrast to the catalytic hydrogenation of 11-keto[6] and 11β-hydroxy[7] steroids which yields predominantly the 5α(*allo*) dihydro derivative, it was observed that catalytic hydrogenation of I with palladized charcoal catalyst in ethanol solution preferably in the presence of potassium hydroxide for 30 minutes yields only small amounts of the *allo* isomer,[8] the main product being the *normal* derivative, pregnane-3,20-dione-11α-ol (II) [m.p. 116–118°, $[\alpha]^{20}D$ +91° (all rotations in chloroform), $\lambda_{max}^{CHCl_3}$ 1700 cm.$^{-1}$ and free –OH; found: C, 75.97; H, 9.92; *acetate*, m.p. 148–149°. $[\alpha]^{20}D$ +65°, $\lambda_{max}^{CHCl_3}$ 1736, 1720 and 1700 cm.$^{-1}$]. This reversal of the stereochemical course of the catalytic hydrogenation of 11-oxygenated Δ^4-3-ketosteroids in the case of the 11α-epimer thus permits the conversion of ring C unsubstituted precursors (progesterone, diosgenin, stigmasterol) to cortisone by way of the desirable 5β(normal) series.

Chromium trioxide oxidation of II furnished pregnane-3,11,20-trione (m.p. 158–160°, [ ]^{20}D +128°, $\lambda_{max}^{CHCl_3}$ 1702 cm.$^{-1}$, identified by comparison with an authentic specimen,[8] m.p. 160–162°, $[\alpha]^{20}D$ +126°) and reduction of the latter with sodium borohydride in *pyridine solution*[9] smoothly yielded the known[8] pregnane-11,20-dione-3α-ol (m.p. 169–171°, $[\alpha]^{20}D$ + 105°, $\lambda_{max}^{CHCl_3}$ 1700 cm.$^{-1}$ and free –OH, identified by comparison with an authentic sample, m.p. 168–171°, $[\alpha]^{20}D$ +103°) and upon acetylation pregnane-11,20-dione-3α-ol acetate m.p. 134–135°, $[\alpha]^{20}D$ +135°). Experimental details of the further transformations of this substance to cortisone have already been recorded.[10] The consistently high yields, the ready availability of the starting materials and the paucity of steps (ten from progesterone or fourteen from diosgenin) appear to make this combined microbiological-chemical route the best yet described synthesis of cortisone.

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(5) This work was aided by the use of a screening technique based on a color reaction specific for 11α-hydroxyprogesterone (A. Zaffaroni, *et al.*, to be published).

(6) C. Djerassi, G. Rosenkranz, J. Pataki, and St. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952).

(7) J. Pataki, G. Rosenkranz and C. Djerassi, *ibid.*, **195**, 751 (1952), and references cited therein.

(8) J. von Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 821 (1944).

(9) In ethanol solution, the product was chiefly the known pregnane-3α,20β-diol-11-one (*cf.* L. H. Sarett, THIS JOURNAL, **70**, 1690 (1948).

(10) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *ibid.*, **74**, 483 (1952).

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ON A PHOSPHO-TRI-ANHYDRIDE FORMULA FOR THE NUCLEIC ACIDS

Sir:

Last year Dr. Edward Ronwin[1] suggested a phospho-tri-anhydride formula for the nucleic acids, with as its core a polymer chain of phosphorus atoms held together by oxygen atoms, each phosphorus atom having five oxygen atoms attached to it, of which three bind it to adjacent phosphorus atoms, one is in a hydroxyl group, and one is in a sugar ester group. We then stated[2] that in formulating a hypothetical structure for a substance one must take care that the structural elements of which use is made are reasonable ones or one must show that there is an overwhelming necessity for a radical proposal, that there is no precedent for a structure in which phosphorus is bonded to five oxygen atoms, that in every one of the scores of quinquepositive phosphorus compounds that have been subjected to complete structural investigation the phosphorus atom is surrounded by four oxygen atoms, and that the ligation of five oxygen atoms about each phosphorus atom is such an unlikely structural feature that the proposed phospho-tri-anhydride formula for the nucleic acids deserves no serious consideration.

Dr. Ronwin has now kindly informed us that he has become aware of earlier references in the literature to compounds to which structures have been attributed involving quinquepositive phosphorus bonded to five oxygen atoms or to a total of five oxygen atoms and similar atoms. Anschütz[3] prepared four compounds to which he assigned structures involving ligation of five oxygen atoms to a phosphorus atom. The synthesis of several compounds described as having one oxygen atom and four NHR groups bonded to a phosphorus atom has been reported by Lemoult,[4] and Autenrieth and Meyer[5] have reported similar compounds with two oxygen atoms, two NHR groups, and one SH group presumed to be bonded to a phosphorus atom.

Although there may be some question about the correctness of the structures attributed to some of these compounds, and although no complete structure determination has been made for any of them, the compounds reported by Anschütz may indeed have the structures suggested by him, involving five oxygen atoms ligated to a quinquepositive phosphorus atom. His suggested formulas for the four substances are $P(OC_6H_5)_5$, $PO_2C_6H_4(OC_6H_5)_3$, $P(OC_6H_5)(O_2C_6H_4)_2$, and $P_2(O_2C_6H_4)_5$, in which $O_2C_6H_4$ is the *o*-phenylene group. Our statement that there is no precedent for a structure in which a phosphorus atom is bonded to five oxygen atoms must accordingly be withdrawn.

It is pertinent to the proposed phospho-tri-anhydride formula for the nucleic acids that the four compounds reported by Anschütz are described by him as being extremely sensitive to moisture, so sensitive as to make it impossible to

(1) E. Ronwin, THIS JOURNAL, **73**, 5141 (1951).

(2) L. Pauling and V. Schomaker, *ibid.*, **74**, 1111 (1952).

(3) L. Anschütz, *Ann.*, **454**, 71 (1927).

(4) P. Lemoult, *Compt. rend.*, **141**, 1241 (1905).

(5) W. Autenrieth and W. Meyer, *Ber.*, **58**, 840 (1925).