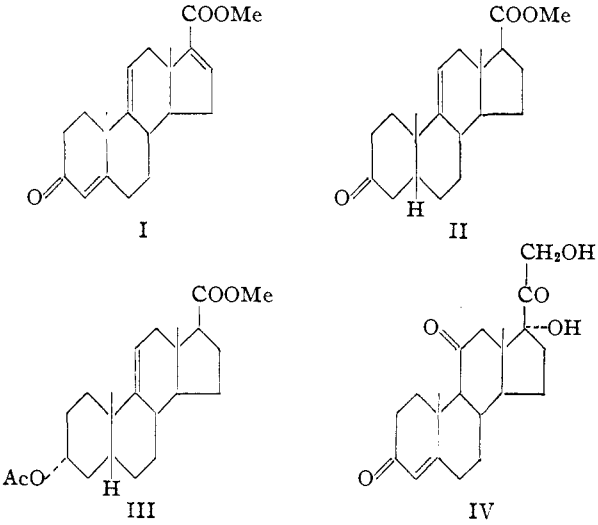
THE TOTAL SYNTHESIS OF CORTISONE

Sir:

We wish to record the completion of the final links in the total synthesis of cortisone.

Methyl *d*-3-keto-$\Delta^{4,9(11)16}$-etiocholatrienate (I)[1] was reduced by hydrogen over palladium on strontium carbonate in neutral media to a mixture containing approximately equal parts of methyl 3-keto-$\Delta^{9(11)}$-etiocholenate (II) and the corresponding *allo* isomer. The crude hydrogenation product was reduced with sodium borohydride in ethanol. The resulting[2] methyl 3(α)-hydroxy-$\Delta^{9(11)}$-etiocholenate and methyl 3(β)-hydroxy-$\Delta^{9(11)}$-etio*allo*cholenate were readily separated through precipitation of the latter by digitonin. Acetylation of the α isomer then gave methyl 3(α)-acetoxy-$\Delta^{9(11)}$-etiocholenate (III), double m.p. 126–128° and 134–136°. An authentic sample had double m.p. 127–128° and 133–136°; on admixture with the synthetic material identical behavior was observed. The infrared spectra of the two samples were identical.

At this point our synthetic work intersects the lines previously laid down in the extensive prior investigations by many groups on the partial synthesis, from natural sources, of cortisone (IV) and other cortical steroids. Thus in an extension of



their elegant method for the transformation of A/B *cis* $\Delta^{9(11)}$ steroids into the corresponding 11-keto compounds,[3] Heymann and Fieser have recently[4] converted the acetoxy-ester (III) into methyl 3,11-diketoetiocholanate (V). Methyl 3(α)-acetoxy-11-ketoetiocholanate has been obtained from (V) by catalytic hydrogenation and acetylation,[5] and converted by the diazoketone method to pregnane-3(α),21-diol-11,20-dione 21-acetate.[6] Introduction of the 17(α) hydroxy group[7] and of the Δ^4 double bond[8] complete the synthesis of cortisone (IV).

(1) Woodward, Sondheimer and Taub, THIS JOURNAL, **73**, 3547 (1951); Woodward, Sondheimer, Taub, Heusler and McLamore, *ibid.*, **73**, 2403 (1951).

(2) *Cf.* Shoppee and Summers, *J. Chem. Soc.*, 687 (1950).

(3) Fieser, Heymann and Rajagopalan, THIS JOURNAL, **72**, 2306 (1950); Heymann and Fieser, *ibid.*, in press.

(4) Heymann and Fieser, *ibid.*, **73**, 4054 (1951).

(5) Lardon and Reichstein, *Helv. Chim. Acta*, **26**, 705 (1943). The catalytic hydrogenation was carried out in glacial acetic acid by the Swiss workers, and the 3(α)-hydroxy compound, as expected under these conditions, was the minor product. We have found that the reduction of (V) by sodium borohydride in ethanol, followed by acetylation and reoxidation, proceeds smoothly to the required methyl 3(α)-acetoxy-11-ketoetiocholanate.

(6) v. Euw, Lardon and Reichstein, *ibid.*, **27**, 1287 (1944).

(7) Sarett, THIS JOURNAL, **70**, 1454 (1948); **71**, 2443 (1949).

(8) Mattox and Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

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THE STABILIZATION OF TERRAMYCIN

Sir:

We have found that traces of cupric ion very markedly increase the rate of decomposition of terramycin solutions. Cyanide ion and other copper sequestrating agents are effective stabilizers. In 0.1 *M* *p*H 7 phosphate buffer at 60° the half-life of a 20 γ per milliliter terramycin solution was 63 minutes in the control, 10 minutes in the presence of 0.5×10^{-4} molar cupric sulfate and 223 minutes when the solution containing copper was made 0.01 *M* with respect to sodium cyanide. In a parallel run without added copper the control half-life was 48 minutes as against 232 minutes with 0.01 *M* cyanide. In another experiment under similar conditions the control was 45 minutes with cupric ion less than 4 minutes and with copper plus 0.1 *M* glutamic acid 53 minutes. Disodium ethylenediamine tetraacetic acid 0.1% prolonged the half-life of terramycin from 48 to 176 minutes. Regna[1] reported a half-life of 26 hours for terramycin in phosphate at *p*H 7 and 37°. We have found under these conditions a half-life of from 13 hours for an old sample assaying 93% and 42 hours for a fresh crystalline sample obtained from Dr. P. Regna. Whether the differences in stability are due to an autocatalytic effect of the decomposition products or variations in the concentration of copper or other heavy metal impurities either in the original samples or the solutions has not yet been determined.

Pasternack, *et al.*,[2] have just reported on the alkaline degradation products of terramycin in the presence of zinc. The role of other trace metals in the decomposition of terramycin and aureomycin has not been evaluated. Womack, *et al.*,[3] observed that the polysaccharide fraction of egg yolk stabilized aureomycin. We found in preliminary experiments that this effect is not marked when the solutions are equimolar with respect to phosphate. At *p*H 6.3 and 37° the half-life of terramycin was 50 hours in citrate and 30 hours in phosphate 0.1 *M* buffers. These results are similar to the observation by Price, *et al.*,[4] that the rapid inactivation of aureomycin in the cylinder plate bioassay could be avoided by the use of citrate instead of phosphate buffers. The effective ionic concentration of copper or other heavy metals in the case of citrate and phosphate buffers and the polysaccharide solutions has not yet been determined.

(1) Regna and Solomons, *Ann. N. Y. Acad. Sci.*, **53**, 229 (1950).

(2) Pasternack, Regna, Wagner, Bavley, Hochstein, Gordon and Brunings, THIS JOURNAL, **73**, 2400 (1951).

(3) Womack, Kass and Finland, *J. Lab. & Clin. Med.*, **36**, 655 (1950).

(4) Price, Randall and Welch, *Ann. N. Y. Acad. Sci.*, **51**, 211 (1948).