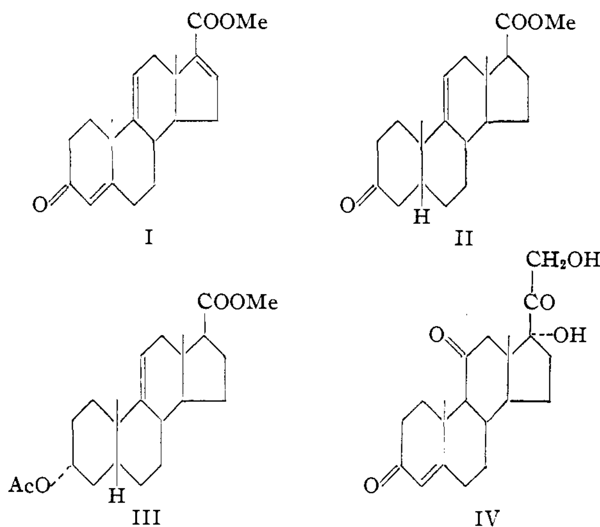
THE TOTAL SYNTHESIS OF CORTISONE

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 $\times 10^{-4}$ 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).

The assay method used was developed in connection with the study of a terramycin-like antibiotic obtained from *Streptomyces griseoflavus* no. 3560.[5] This material has an ultraviolet absorption spectrum similar to that of terramycin and aureomycin. These antibiotics exhibit a characteristic diminution of the peak near 360 mμ when heated for 15 to 30 minutes in *p*H 7 phosphate buffer. For aureomycin the measurements were made at 370 mμ. Spectrophotometric methods for terramycin and aureomycin have just been published[6,7] but our method has the advantage of using a *p*H 7 buffer and hence bioassays can be made on the same dilutions used for spectrographic assays in the range of 2 to 35 γ per ml. New standard curves or corrections have been found to be necessary in the presence of complexing agents or added cupric ion.

(5) Waksman, Kochi and Lechevalier, *Soc. Amer. Bact. Proc.*, P30, (1951).

(6) Hiscox, *J. Am. Pharm. Assocn.* (*Sci. Ed.*), **40**, 237 (1951).

(7) Monastero, Neans, Grenfell and Hedger, *ibid.*, p. 241.

Also the heating period in the assay must be adjusted for special cases since a rise in optical density at 360 occurs on prolonged heating.

Half-lives were determined graphically on semilog paper from two or more points. The rate of decomposition in all cases followed the unimolecular exponential pattern.

It is hoped that this work will have practical applications in the preparation of stable antibiotic solutions and result in reduction of the required dose when the antibiotics are administered orally. Animal experiments with the relatively non-toxic ethylenediamine tetraacetic acid will shortly be carried out.

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BOOK REVIEWS

Advances in Carbohydrate Chemistry. Edited by CLAUDE S. HUDSON, National Institutes of Health, Bethesda, Maryland, and SIDNEY M. CANTOR, American Sugar Refining Company, Philadelphia, Pennsylvania. Volume 5. Academic Press Inc., Publishers, 125 East 23rd Street, New York 10, N. Y., 1950. xi + 322 pp. 16 × 23 cm. Price, $6.80.

Advances in Carbohydrate Chemistry may justly be considered to have come of age as an important weapon in the armamentum of the carbohydrate chemist, as well as a valuable reference work for teachers, students and research workers in related fields. The fifth volume consists of ten expert reviews of chemical, biochemical and industrial interest. Over 800 literature citations are included, but the work is by no means only a compilation of references. The scope of each review is sufficiently limited that the treatment is generally complete, critical and authoritative.

Some of the chapters warrant individual comment:

In the treatment of enzyme specificity Gottschalk has compiled and correlated data from which he develops "principles" which bear on the mechanism of carbohydrase action. While much of the material is thought-provoking, Gottschalk has overlooked pertinent information such as the stereochemistry of reactions at a carbon atom and the physical conformation of sugars, *e.g.* sucrose. His conclusions and speculations, based on arbitrary and questionable assumptions about the spatial relationships of enzymes to substrates, may be rather ephemeral for a volume of this type.

The essay on alpha amylase action by Caldwell and Adams will puzzle the reader in several respects. The time delay between submission (1947) and publication has been too great. Meanwhile, Myrbäck has discussed the same field in this same series (Vol. 3, 1948). No reference is made to Myrbäck's review, and there is a good deal of duplication. For example, Tables X and XII of Myrbäck's review are essentially identical with Tables XI and X in the current volume. It is most annoying that arguments in the text are based upon six legend-less figures, and there is no information either on the figures or in the text which enables one to identify or interpret the various curves without recourse to the original publications.

Nickerson's review on cellulose crystallinity will be read with interest not only by cellulose chemists but also by all who deal with crystalline or partly crystalline natural or synthetic polymers. Correlation of the notion of crystallinity with physical and chemical behavior is presented in a clear fashion. It is hoped that the reader will not be confused on p. 107 where we are informed: "The cellulose molecule is estimated to be about 5 Å. in length."

Other chapters range in scope from the ivory tower of the methyl ethers of glucose (Bourne and Peat) to the brass tacks of the commercial production of crystalline glucose (Dean and Gottfried). On the whole this volume lives up to expectations and the standards set by previous members of the series. Undoubtedly many readers who have not already done so will place standing orders for succeeding volumes of the Advances.

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Histamine Antagonists. By FREDERICK LEONARD AND CHARLES P. HUTTRER, Warner Institute of Therapeutic Research, New York, N. Y. Chemical-Biological Coordination Center Review No. 3. National Research Council, Washington, D. C., 1950. 122 pp. 17 × 24.5 cm. Price, $1.50.

The first one-third of this review (39 pages) covers pharmacological properties, mechanism of activity, evaluation, chemistry, structure–activity relationships and clinical data on histamine antagonists. With the exception of the section on clinical data, the review appears complete. Detailed procedures have been omitted but adequately indexed; *e.g.*, the section on chemistry gives the important reactions used for synthesis of histamine antagonists and refers the reader to original papers for detailed procedures. The section on structure–activity relationships is well organized and for many workers will be the most valuable part of the review. It would be outside the scope of this review to devote more space to clinical results.

The second two-thirds of the review consists of tables of compounds tested, showing the structure, activity and references for each. The compounds have been classified as alkylenediamines, aminoalkyl ethers, alkylamines, haloalkylamines, aminoketones and secondary alcohols, aminoalkyl esters and unclassified compounds. By means of personal communications, the authors have been able to in-