

proteins, forming the peptide bonds under such mild conditions that denaturation does not occur. We have utilized this method with other proteins and other amino acids with essentially similar results. It would seem to be applicable to many amino acid anhydrides and a wide variety of proteins. These studies, as well as an investigation of the relative reactivity of various groups of the protein which may be acylated by the anhydrides, are under investigation. The effects upon the biological activity of enzyme and virus proteins are also being studied.

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### SYNTHESIS OF 11-KETO STEROIDS

Sir:

In an earlier communication<sup>1</sup> we reported a synthesis of *allopregnan-3 $\beta$ -ol-11,20-dione acetate* (I) from ergosterol, stigmasterol, cholesterol and diosgenin. In this communication we wish to present a second, more direct, method for the preparation of the *allo* diketo pregnane (I) from these same raw materials. Heusser and his co-workers<sup>2</sup> have reported the isomerization of the mono-epoxide derived from  $\Delta^{7,9(11),22}$ -ergostatrien-3- $\beta$ -ol acetate<sup>2</sup> by the action of boron trifluoride etherate in benzene solution at room temperature to  $\Delta^{8,22}$ -ergostadien-3- $\beta$ -ol-11-one acetate (II) and we have independently carried out the same reaction in 80% yield; m.p. 131.5–134°;  $[\alpha]_D +110^\circ$  (CHCl<sub>3</sub>);  $\lambda_{max}$  254 m $\mu$ ,  $E_M$  9140 (alc.); found: C, 79.19; H, 10.31. Saponification of II yielded  $\Delta^{8,22}$ -ergostadien-3- $\beta$ -ol-11-one (III); m.p. 171–173°;  $[\alpha]_D +135^\circ$  (CHCl<sub>3</sub>);  $\lambda_{max}$  254 m $\mu$ ,  $E_M$  8920 (alc.); found: C, 81.54; H, 10.45.

As expected, both II and III are inert to reaction with 2,4-dinitrophenylhydrazine. Irrefutable structure proof of these ketones as well as a new and shorter path to I was provided by the reduction of the  $\Delta^8$ -11-ketone (II) with lithium and liquid ammonia in 85–90% yield to  $\Delta^{22}$ -ergostene-3- $\beta$ -ol-11-one (IV), m.p. 168–169.5°;  $[\alpha]_D +23^\circ$  (CHCl<sub>3</sub>). The identity of the lithium-ammonia reduction product of II was conclusively demonstrated by comparison with the product previously obtained by the Wolff-Kishner reduction of  $\Delta^{22}$ -ergostene-3- $\beta$ -ol-7,11-dione acetate.<sup>1</sup>

Similarly diosgenin acetate was converted via the monoepoxide to  $\Delta^8$ -spirostene-3- $\beta$ -ol-11-one acetate (8-dehydro-11-keto tigogenin acetate); m.p. 235–238°;  $[\alpha]_D +57^\circ$  (CHCl<sub>3</sub>);  $\lambda_{max}$  255 m $\mu$ ;  $E_M$  9000 (alc.); found: C, 73.62; H, 8.89; which was likewise reduced by lithium-liquid ammonia to the previously described spirostan-3- $\beta$ -ol-11-one.<sup>1</sup>

(1) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerdar, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *THIS JOURNAL*, **73**, 2396 (1951).

(2) In accordance with the Swiss investigators,<sup>2</sup> we believe the mono-epoxides prepared from *allo*- $\Delta^{7,9(11)}$ -steroids are  $\Delta^{7,9\alpha,11\alpha}$ -epoxides. However, R. C. Anderson, R. Budziarek, G. T. Newbold, R. Stevenson and F. S. Spring regard the epoxide above to be a  $\Delta^{9(11),7,8}$ -epoxide; *Chem. and Ind.*, 1035 (1950). Further discussion of this problem will be forthcoming in a later communication.

(3) H. Heusser, K. Eichenberger, P. Kurath, H. R. Dallenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951).

Of interest to the structure problem of these monoepoxides, as well as their utilization for the synthesis of I, is the fact that acids in aqueous or polar media effect rearrangement to 7-ketones rather than 11-ketones. Thus the mono-epoxide from  $\Delta^{7,9(11),22}$ -ergostatrien-3- $\beta$ -ol; m.p. 188–189°;  $[\alpha]_D -34^\circ$  (CHCl<sub>3</sub>); found: C, 81.25; H, 10.79; (obtained either by the direct action of perbenzoic acid or by alkaline hydrolysis of the 3-acetate) is converted by the action of 0.07 *N* sulfuric acid in aqueous-acetone at 25–30° for ten to thirty minutes to  $\Delta^{9(11),22}$ -ergostadien-3- $\beta$ -ol-7-one (V); m.p. 153.5–154.5°;  $[\alpha]_D -53^\circ$  (CHCl<sub>3</sub>); found: C, 82.10; H, 10.40; end absorption above 220 m $\mu$ ; 3-acetate: m.p. 176–177°;  $[\alpha]_D -43.5^\circ$  (CHCl<sub>3</sub>); found: C, 78.89; H, 9.91.<sup>4</sup> By the action of dilute sulfuric acid on the above mono-epoxide at 50–70° for a few hours, or by treatment of V with alcoholic alkali at room temperature,  $\Delta^{8,22}$ -ergostadiene-3- $\beta$ -ol-7-one (VI) is obtained; m.p. 179–180°;  $[\alpha]_D -43^\circ$  (CHCl<sub>3</sub>);  $\lambda_{max}$  253 m $\mu$ ,  $E_M$  9970 (alc.); found: C, 82.11 H, 10.98. Acetylation of VI yielded the 3-acetoxy derivative, m.p. 213–213.5°;  $[\alpha]_D -59^\circ$  (CHCl<sub>3</sub>); which had been obtained previously in low yield by Stavely and Bollenback<sup>5</sup> from the oxidation of  $\Delta^{7,22}$ -ergostadien-3- $\beta$ -ol acetate by chromic acid. Both V and VI yielded 2,4-dinitrophenylhydrazones.

Complete details of this work will be published later in *THIS JOURNAL*.

(4) Under similar conditions, 0.3 *N* sulfuric acid in aqueous dioxane for three minutes, O. Jeger and his co-workers<sup>3</sup> obtained  $\Delta^{8,22}$ -ergostadien-3- $\beta$ ,7(?) $\alpha$ -triol-3-monoacetate.<sup>1</sup> The sensitivity of the triol to acids suggests that the time allowed for reaction is probably the most critical factor in determining the course of action. The  $\beta$ , $\gamma$ -unsaturated ketone has also been obtained by the action of dilute acids on the triol.

(5) H. E. Stavely and G. N. Bollenback, *THIS JOURNAL*, **65**, 1285 (1943).

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### STEROIDAL SAPOGENINS. XXIII.<sup>1</sup> INTRODUCTION OF THE 11-KETO AND 11 $\alpha$ -HYDROXY GROUPS INTO RING C UNSUBSTITUTED STEROIDS (PART 6). NEW APPROACH TO 11-OXYGENATED STEROIDS

Sir:

Heusser and co-workers<sup>2</sup> reported recently that mono-epoxides of certain steroidal  $\Delta^{7,9(11)}$ -dienes upon treatment with boron trifluoride yield the corresponding  $\Delta^8$ -11-ketones which would constitute a proof for the  $\Delta^7$ -9,11-oxido structure of the starting mono-epoxides. The structure assignment of the unsaturated ketone rested essentially on the non-reactivity of the carbonyl group and the substance's non-identity with the  $\Delta^8$ -7-ketone. We should now like to report certain experiments in the sapogenin series which not only prove un-

(1) Paper XXII, C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, *THIS JOURNAL*, **74**, June (1952).

(2) H. Heusser, *et al.*, *Helv. Chim. Acta*, **34**, 2106 (1951); **35**, 295 (1952).