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.

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF WISCONSIN MARK A. STAHMANN
MADISON, WISCONSIN ROBERT R. BECKER

RECEIVED MARCH 17, 1952

SYNTHESIS OF 11-KETO STEROIDS

Sir:

In an earlier communication[1] we reported a synthesis of *allo*pregnan-3β-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[3] have reported the isomerization of the mono-epoxide derived from $\Delta^{7,9(11),22}$-ergostatrien-3-β-ol acetate[2] by the action of boron trifluoride etherate in benzene solution at room temperature to $\Delta^{8,22}$-ergostadien-3β-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° ($CHCl_3$); λ_{max} 254 mμ, E_M 9140 (alc.); found: C, 79.19; H, 10.31. Saponification of II yielded $\Delta^{8,22}$-ergostadien-3β-ol-11-one (III); m.p. 171–173°; $[\alpha]_D$ +135° ($CHCl_3$); λ_{max} 254 mμ, 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 Δ^8-11-ketone (II) with lithium and liquid ammonia in 85–90% yield to Δ^{22}-ergostene-3β-ol-11-one (IV), m.p. 168–169.5°; $[\alpha]_D$ +23° ($CHCl_3$). 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 Δ^{22}-ergostene-3β-ol-7,11-dione acetate.[1]

Similarly diosgenin acetate was converted via the monoepoxide to Δ^8-spirostene-3-β-ol-11-one acetate (8-dehydro-11-keto tigogenin acetate); m.p. 235–238°; $[\alpha]_D$ +57° ($CHCl_3$); λ_{max} 255 mμ; E_M 9000 (alc.); found: C, 73.62; H, 8.89; which was likewise reduced by lithium–liquid ammonia to the previously described spirostan-3β-ol-11-one.[1]

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

(2) In accordance with the Swiss investigators,[3] we believe the monoepoxides prepared from allo-$\Delta^{7,9(11)}$-steroids are Δ^{7}-9α,11α-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-3β-ol; m.p. 188–189°; $[\alpha]_D$ −34° ($CHCl_3$); 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-3β-ol-7-one (V); m.p. 153.5–154.5°; $[\alpha]_D$ −53° ($CHCl_3$); found: C, 82.10; H, 10.40; end absorption above 220 mμ; 3-acetate: m.p. 176–177°; $[\alpha]_D$ −43.5° ($CHCl_3$); found: C, 78.89; H, 9.91.[4] 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-3β-ol-7-one (VI) is obtained; m.p. 179–180°; $[\alpha]_D$ −43° ($CHCl_3$); λ_{max} 253 mμ, 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° ($CHCl_3$); which had been obtained previously in low yield by Stavely and Bollenback[5] from the oxidation of $\Delta^{7,22}$-ergostadien-3β-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[3] obtained $\Delta^{8,22}$-ergostadien-3β,7(?),11α-triol-3-monoacetate.[1] 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 β,γ-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).

E. SCHOENEWALDT
L. TURNBULL
CONTRIBUTION FROM THE E. M. CHAMBERLIN
RESEARCH LABORATORIES D. REINHOLD
MERCK AND CO., INC. A. E. ERICKSON
RAHWAY, N. J. W. V. RUYLE
J. M. CHEMERDA
M. TISHLER

RECEIVED APRIL 25, 1952

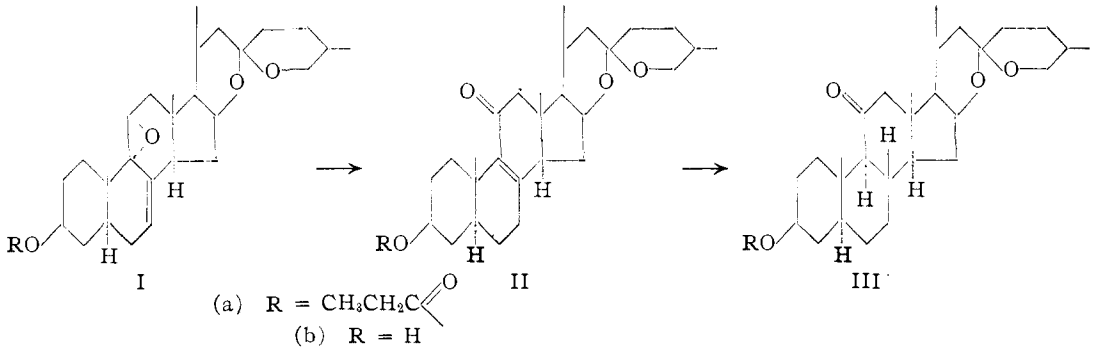
STEROIDAL SAPOGENINS. XXIII.[1] INTRODUCTION OF THE 11-KETO AND 11α-HYDROXY GROUPS INTO RING C UNSUBSTITUTED STEROIDS (PART 6). NEW APPROACH TO 11-OXYGENATED STEROIDS

Sir:

Heusser and co-workers[2] reported recently that mono-epoxides of certain steroidal $\Delta^{7,9(11)}$-dienes upon treatment with boron trifluoride yield the corresponding Δ^8-11-ketones which would constitute a proof for the Δ^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 Δ^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).



equivocally the Δ^8-11-keto structure for the boron trifluoride rearrangement products but also open a new approach to cortisone and related 11-oxygenated steroids.

Esters of $\Delta^{7,9(11)}$-22-isoallospirostadien-3β-ol[3] upon treatment with 1.1 mole of perbenzoic or perphthalic acid afford in excellent yield the corresponding Δ^7-9,11-oxido-22-isoallospirosten-3β-ol[4] (*e.g.* propionate (Ia), m.p. 227–229°, $[\alpha]^{20}D$ −91° (all rotations in chloroform), found: C, 74.39; H, 9.41). Rearrangement of Ia with boron trifluoride in benzene solution[2] led to 70% of Δ^8-22-isoallospirosten-3β-ol-11-one propionate (IIa) (m.p. 194–196°, $[\alpha]^{20}D$ +42°, $\lambda_{max.}^{EtOH}$ 252 mμ, log ϵ 4.08, $\lambda_{max.}^{nujol}$ 1734 and 1656 cm.$^{-1}$) found, C, 74.66; H, 9.35; (free alcohol IIb, m.p. 190–192°, $[\alpha]^{20}D$ +65°, found: C, 75.56; H, 9.24), which upon reduction in ether–dioxane solution with *ca.* three moles of lithium in liquid ammonia followed by alkaline saponification furnished in good yield the known[5,6,7] 22-isoallospirostan-3β-ol-11-one (III) (m.p. 223–225°, $[\alpha]^{20}D$ −29°, identified by infrared comparison). Since this substance (as the acetate, m.p. 224–227°) has already been converted to cortisone,[5,8] the above steps open a new and convenient route to this important hormone. The use of larger amounts of lithium in the *presence of alcohol*[9] in the reduction stage led in good yield to the known 22-isoallospirostan-3β,11α-diol[7] (m.p. 218–220°, $[\alpha]^{20}D$ −78°) thus constituting a convenient synthesis of 11α-hydroxy steroids.

In connection with the above described successful *chemical* reduction of the 8,9-double bond to the desired stereoisomer III, it is pertinent to mention that *catalytic* hydrogenation (5% palladized charcoal, ethanol solution, room temperature, 40 hours) of the Δ^8-11-ketone IIa leads to an 8-epi, 9-epi derivative, most likely 8-epi(α)-9-epi(β)-22-isoallospirostan-3β-ol-11-one propionate (m.p. 211–213°, changed to 224–227° upon rigorous drying, $[\alpha]^{20}D$ −63°, $\lambda_{max.}^{nujol}$ 1730 and 1700 cm.$^{-1}$ found: C, 74.16; H, 9.61) which is not isomerized by alkali. Furthermore, it was observed that the Δ^8-11-ketone IIa could be isomerized very readily at C-14 on boiling with 5% ethanolic potassium hydroxide to produce 14-epi(β)-Δ^8-22-isoallospirosten-3β-ol-11-one (m.p. 239–240°, $[\alpha]^{20}D$ + 113°, $\lambda_{max.}^{EtOH}$ 252 mμ, log ϵ 4.09; found: C, 75.60; H, 9.42; propionate, m.p. 217–219°, $[\alpha]^{20}D$ + 90°, found: C, 74.18; H, 8.88). The details of a number of hydrogenation experiments leading to *epi* derivatives at C-8, C-9 and C-14 together with the interrelationships established among the various series will be published shortly.

RESEARCH LABORATORIES
SYNTEX, S. A.
LAGUNA MAYRAN 413
MEXICO CITY 17, D. F.

F. SONDHEIMER
R. YASHIN
G. ROSENKRANZ
CARL DJERASSI[10]

RECEIVED MARCH 26, 1952

(3) G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951).

(4) G. Rosenkranz, J. Romo and C. Djerassi, U. S. Patent Application No. 191,942 (1950). Such mono-epoxides in the sapogenin series have also been employed in ref. 5, but no physical constants were reported.

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

(6) C. Djerassi, H. J. Ringold and G. Rosenkranz, *ibid.*, **73**, 5513 (1951).

(7) C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *ibid.*, **74**, 1712 (1952).

(8) J. M. Chermerda, E. M. Chamberlain, E. H. Wilson and M. Tishler, *ibid.*, **73**, 4052 (1951); G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, **73**, 4055 (1951).

(9) *Cf.* A. L. Wilds, Abstracts, p. 20M, American Chemical Society Meeting, New York, September, 1951.

(10) Department of Chemistry, Wayne University, Detroit 1, Michigan.