(XXV, Reichstein's Substance E[11]), m.p. 130–132°, identified as the 20,21-diacetate XXVI, m.p. 230–231.5°; $[\alpha]^{23}\text{D}$ +168° (acetone). [Reported[11] m.p. 229–230°; $[\alpha]^{23}\text{D}$ +163° (acetone)]. (*Anal.* Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.69; H, 8.07). That XXIV is the 20α-epimer of Reichstein's Substance E was established by the oxidation of its 21-acetate (XXIII) with manganese dioxide to hydrocortisone acetate (XXVII), m.p. 217–220°, $[\alpha]^{23}\text{D}$ +159° (dioxane), $\lambda^{EtOH}_{max.}$ 243 mμ, ϵ = 15,900. Also, the oxidation of XXIII with chromium trioxide in pyridine yielded cortisone acetate (XXVIII), m.p. 244–248°, identified by its infrared spectrum and paper chromatogram.

The oxidative hydroxylation of XVII in *t*-butyl alcohol–pyridine with phenyl iodosoacetate in the presence of catalytic amounts of osmium tetroxide afforded hydrocortisone acetate (XXVII) in 65% yield.[12] In like manner XXII and XVIII were converted to hydrocortisone acetate (XXVII) and cortisone acetate (XXVIII), respectively.

The methods described have also been applied to progesterone and other 20-ketosteroids.

The authors are indebted to A. Koning, R. W. Kratz, C. D. Wickman and V. R. Shellman for technical assistance, to Dr. J. L. Johnson, Mrs. G. S. Fonken and J. E. Stafford for infrared and ultraviolet absorption studies, to Mr. W. A. Struck and associates for microanalyses and to Mr. L. M. Reineke and associates for paper chromatographic analyses.

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[11] T. Reichstein and J. von Euw, *Helv. Chim. Acta*, **24**, 247E (1941).

[12] K. Miescher and J. Schmidlin, *ibid.*, **33**, 1840 (1950), have described the use of hydrogen peroxide and osmium tetroxide for the oxidative hydroxylation of the steroidal 17,20-double bond. This procedure in the present studies gave hydrocortisone acetate in 35–40% yield when applied to XVII.

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RECEIVED JULY 15, 1955

THE ADRENAL HORMONES AND RELATED COMPOUNDS. II. SYNTHESIS OF 1-DEHYDRO ANALOGS[1]

Sir:

In the previous paper of this series we described the preparation of 21-ethoxyoxalyl-11-ketoprogesterone and its conversion to certain of the adrenal hormones. We now report the preparation of 2,21-di-(ethoxyoxalyl)-11-ketoprogesterone (I) and its conversion to 9α-fluoro-1-dehydrohydrocortisone acetate *via* 1-dehydrohydrocortisone acetate.[2]

11-Ketoprogesterone, prepared by the method of Peterson, Murray, *et al.*,[3] was treated with two moles of diethyl oxalate and sodium methoxide in *t*-butyl alcohol. The yellow disodium salt of I precipitated at once. This slurry was neutralized with acetic acid–methanol and treated with three moles of bromine in the presence of sodium acetate. Subsequent treatment with sodium methoxide in methanol gave a 58.3% yield of methyl 2-bromo-3,11-diketo-4,17(20)-[*cis*]-pregnadien-21-oate (II), m.p. 160–162°; $[\alpha]^{23}\text{D}$ +209° (chloroform); (*Anal.* Calcd. for $C_{22}H_{27}BrO_4$: Br, 18.36. Found: Br, 18.46). Debromination of a sample of II with zinc and acetic acid yielded methyl 3,11-diketo-4,17(20)-[*cis*]-pregnadien-2-oate (III).[1] Dehydrohalogenation of III with collidine or with lithium chloride in dimethyl formamide[4] produced methyl 3,11-diketo-1,4,17(20)-[*cis*]-pregnatrien-21-oate (IV) (70% yield), m.p. 240–243°; $[\alpha]^{24}\text{D}$ +210° (chloroform); (*Anal.* Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.50; H, 7.14). Conversion of IV to the pyrrolidyl enamine followed by reduction with lithium aluminum hydride and removal of the enamine, as previously described,[1] afforded 11β,21-dihydroxy-1,4,17(20)-[*cis*]-pregnatrien-3-one (V), m.p. 174–175°; $[\alpha]^{25}\text{D}$ +110° (chloroform); (*Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.78; H, 8.59. Found: C, 76.98; H, 8.73). The conversion of IV to V also can be effected by blocking the 3-keto grouping as the ethylene ketal instead of the enamine. Acetylation of V gives quantitatively the 21-acetate (VI), m.p. 220–222.5°; $[\alpha]\text{D}$ +122° (chloroform). (*Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.58; H, 8.50). In 65% yield[5] VI is converted by phenyl iodosoacetate in the presence of osmium tetroxide to 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione-21-acetate (VII),[2] m.p. 240–242°; $[\alpha]^{24}\text{D}$ +116° (dioxane); $\lambda^{EtOH}_{max.}$ 242 mμ; ϵ 15,225; (*Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.89; H, 7.52). Saponification of VII produced 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (VIII),[2] (90% yield), m.p. 232–236°; $[\alpha]\text{D}$ +102° (dioxane); (*Anal.* Calcd. for $C_{20}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.79; H, 7.88). Oxidation of VII with N-bromoacetamide in *t*-butyl alcohol–pyridine formed 17,21-dihydroxy-1,4-pregnadiene-3,11,20-trione-21-acetate (IX)[2] (85% yield), m.p. 230–232° (dec.); $[\alpha]_{\text{D}}$ +185° (dioxane); (*Anal.* Calcd. for $C_{23}H_{28}O_5$: C, 68.98; H, 7.05. Found: C, 68.95; H, 6.65). Hydrolysis of IX with potassium bicarbonate in aqueous methanol gave 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione (X)[2] (91% yield), m.p. 230.5–232.5°; $[\alpha]^{23}\text{D}$ +169° (dioxane); (*Anal.* Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.64; H, 7.20). Dehydration of VII with thionyl chloride–pyridine formed 17α,21-dihydroxy-1,4,9(11)-pregnatriene-3,20-dione-21-acetate (XI) (48% yield), m.p. 223–226°; $[\alpha]^{24}\text{D}$ +75° (chloroform); (*Anal.* Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 72.10; H, 7.66). Treatment of XI with N-bromo-

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[1] Preceding paper in this series, THIS JOURNAL, **77**, 4436 (1955).

[2] H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

[3] D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister and H. M. Leigh, THIS JOURNAL, **74**, 5933 (1952).

[4] R. P. Holysz, *ibid.*, **75**, 4432 (1953).

[5] K. Miescher and J. Schmidlin, *Helv. chim. acta*, **33**, 1840 (1950), have described the oxidative hydroxylation of the steroidal 17,20 double bond with hydrogen peroxide and osmium tetroxide. In this work 1-dehydrohydrocortisone acetate was produced in 43% yield from VI by their procedure. Prolonged workup with sodium bisulfite resulted in appreciable hydrolysis to the free alcohol

acetamide in the presence of perchloric acid[6] quantitatively yielded 9α-bromo-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (XII), (XII), m.p. 180–185° (dec.); $[\alpha]^{25}D$ +133° (chloroform); (*Anal.* Calcd. for $C_{23}H_{28}BrO_6$: C, 57.38; H, 6.07; Br, 16.60. Found: C, 57.26; H, 6.56; Br, 16.36). The 9β,11β-oxide (XIII), m.p. 192–195°; $[\alpha]_D$ +67° (chloroform), was obtained in 76% yield by treatment of XII with potassium acetate in acetone, (*Anal.* Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.19; H, 7.29). Opening of the oxide (XIII) with hydrofluoric acid gave 9α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (XIV)[7] (44% yield), m.p. 235–238°; $[\alpha]^{25}D$ +101° (acetone); (*Anal.* Calcd. for $C_{23}H_{29}FO_6$: F, 4.52; Found: F, 4.63).

9α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (XIV) in glycogen deposition potency is 50 times greater than hydrocortisone and in salt retaining potency is 4.6 times greater than desoxycorticosterone acetate (DOCA).[8]

The authors are indebted to A. Koning, R. W. Kratz and V. R. Shellman for technical assistance; to Dr. J. L. Johnson, J. E. Stafford and Mrs. G. S. Fonken for infrared and ultraviolet absorption studies; to Mr. W. A. Struck and associates for microanalyses and to Mr. L. M. Reineke and associates for paper chromatographic analyses.

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[6] J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

[7] R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *ibid.*, **77**, 3166 (1955).

[8] R. O. Stafford, B. J. Bowman, M. M. Meinzinger and L. E. Barnes, *Proc. Soc. Exp. Biol. Med.*, in press.

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AN UNUSUAL ISOTOPE FRACTIONATION EFFECT

Sir:

We are investigating the exchange reaction $CNI + C^{14}N^- \rightleftarrows C^{14}NI + CN^-$ in water and various dioxane–water mixtures. The reaction is followed by precipitation and radioassay of the inorganic cyanide as silver cyanide. The equilibrium constant K is simply the ratio of the specific activities of cyanogen iodide to cyanide after equilibration, S_{CNI}/S_{CN}. A value of 1.05 has been predicted for this constant by statistical thermodynamics.[1] It can be determined experimentally by the relation

$$K = a/b(A_0 - A_e)/A_e$$

In this, a and b are the concentrations of cyanide and cyanogen iodide, A_6 and A_e are the specific activities of cyanide before and after exchange equilibrium, and it is assumed that no fractionation effects result from the separation process. On this basis, the following results have been obtained for K at 30.6° and with an a/b ratio of approximately unity:

% Dioxane in solvent	Number of samples taken	Apparent K (Av. + max. dev.)
0	12	1.08 ± 0.02
20	22	1.15 ± 0.02
28	22	1.18 ± 0.03
40	40	1.28 ± 0.02
60	22	1.29 ± 0.03

The surprising consequence of increased dioxane content of the solvent may be explained in terms of a combined equilibrium and precipitation isotope effect. In experiments in which a solution of labelled sodium cyanide was poured directly into a solution containing silver nitrate and cyanogen iodide, it was found that the precipitated cyanide had undergone complete exchange with the cyanogen iodide. Obviously, the rate of the equilibration reaction is much greater than the rates of the precipitation reactions between silver nitrate and sodium cyanide, labelled and unlabelled. Isotopic equilibrium is thus continuously maintained in the solution during the precipitation procedure.

Letting r be the ratio of the rates of the precipitation reactions and $a/b = f$, a mathematical analysis similar to that employed previously in problems of this type[2] yields the relation

$$S_{CNI}/S_{CN} = f\left(\frac{K}{K+f}\right)^r \Big/ 1 - \left(\frac{K}{K+f}\right)^r$$

If it is assumed that in pure water the precipitation is a rapid ionic process with negligible isotope effect, $r = 1$, and $K = 1.08$ is the true equilibrium constant. In solution of high dioxane content, the precipitation may, however, be a competitive process exhibiting isotope effect. Assigning the reasonable value of $r = 0.9$ under these conditions, the following predictions result, justifying the magnitude of the observed effect:

f	0.5	1.0	2.0	5.0	10.0
S_{CNI}/S_{CN}	1.23	1.25	1.28	1.35	1.42

A full report of this work, which is being supported by the U.S.A.E.C. under Contract No. AT(30-1)-1578, will appear subsequently.

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