rhombohedral with $a \cong 8$ Å. and $\alpha \cong 23.5$ Å. The metal is very soft, has the luster of silver and does not tarnish in air after a month of exposure.

Ytterbium has been prepared by this same method and appears to be more volatile than samarium. X-Ray diffraction studies on this metal indicate that it is face-centered cubic with $a = 5.460$ Å.; Klemm and Bommer reported $a = 5.468$ Å. for this metal.

A more complete description of this work will appear in the future.

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SYNTHESIS OF 17α-HYDROXYCORTICOSTERONE AND ITS 9α-HALO DERIVATIVES FROM 11-EPI-17α-HYDROXYCORTICOSTERONE

Sir:

The ready availability of 11-epi-17α-hydroxycorticosterone (I) by microbiological hydroxylation[1,2,3] of Reichstein's Compound S suggests as an attractive possibility the utilization of I as an intermediate in the synthesis of 17α-hydroxycorticosterone. We wish to report such a synthesis, a distinguishing feature of which is that it dispenses with the protective derivatization of the 3- and 20-keto groups required in previous syntheses[4,5,6] during operations in ring C. Key intermediates in this synthesis are the 9α-haloderivatives of 17α-hydroxycorticosterone, which we have found to be highly active in the rat liver glycogen assay for 11-oxygenated corticoids.[7] Their activities as well as those of the corresponding cortisone derivatives are listed in Table I.

TABLE I

	Activity in rat liver glycogen test, cortisone acetate = 1
9α-Chloro-17α-hydroxycorticosterone acetate	~4.0 ± 0.6
9α-Chlorocortisone acetate	3.5 ± 0.4
9α-Bromo-17α-hydroxycorticosterone acetate	0.28 ± 0.04
9α-Bromocortisone acetate	0.54 ± 0.08
9α-Iodo-17α-hydroxycorticosterone acetate	~0.1

Acetylation of (I) with one mole of acetic anhydride followed by tosylation gave Δ^4-pregnene-11α,17α,21-triol-3,20-dione 21-acetate 11α-tosylate (II), m.p. 165–166° (dec.); $[\alpha]^{23}D$ +106° (*c*, 1.0 in $CHCl_3$); (*Anal.* Calcd. for $C_{30}H_{38}O_8S$: C, 64.51; H, 6.81; S, 5.73. Found: C, 64.55; H, 6.84; S, 5.77), which on treatment with sodium acetate in boiling glacial acetic acid yielded $\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (III) m.p. 236–237°; $[\alpha]D$ +117° (*c*, 1.0 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 238 mμ (ε = 15,500); (*Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.31; H, 7.80). Reaction of (III) with N-bromoacetamide[8] in aqueous dioxane in the presence of perchloric acid[9] afforded Δ^4-9α-bromopregnene-11β,17α,21-triol-3,20-dione 21-acetate (9α-bromo-17α-hydroxycorticosterone acetate) (IV), m.p. 130–131° (dec.); $[\alpha]D$ +133° (*c*, 0.75 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 243 mμ (ε = 14,500); (*Anal.* Calcd. for $C_{23}H_{31}O_6Br$: C, 57.17; H, 6.42; Br, 16.52. Found: C, 57.40; H, 6.56; Br, 16.11). Oxidation of (IV) with chromic acid yielded 9α-bromocortisone acetate, m.p. 219° (dec.); $[\alpha]^{23}D$ +235° (*c*, 0.61 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 237 mμ (ε = 16,100); (*Anal.* Calcd. for $C_{23}H_{29}O_6Br$: C, 57.41; H, 6.03; Br, 16.61. Found: C, 57.30; H, 6.16; Br, 16.15), which on reduction with zinc in acetic acid yielded cortisone acetate identified by comparison with an authentic sample of the latter. IV on treatment with potassium acetate in boiling alcohol gave Δ^4-pregnene-9β,11β-oxido-17α,21-diol-3,20-dione acetate (V),[10] m.p. 210–12°; $[\alpha]^{23}D$ +41° (*c*, 0.69 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 243 mμ (ε = 15,500); (*Anal.* Calcd. for $C_{23}H_{30}O_6$: C. 68.63; H, 7.51. Found: C, 69.02; H, 7.42), which with HBr in acetic acid–carbon tetrachloride reverted to IV. Reaction of V with hydrochloric acid in chloroform at 0° yielded 9α-chloro-17α-hydroxycorticosterone acetate, m.p. 200–201° (dec.); $[\alpha]^{23}D$ +139° (*c*, 0.86 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 241 mμ (ε = 15,800); (*Anal.* Calcd. for $C_{23}H_{31}O_6Cl$: C, 62.93; H, 7.12; Cl, 8.07. Found: C, 63.23; H, 7.41; Cl, 7.70), which on oxidation with chromic acid yielded 9α-chlorocortisone acetate, m.p. 257–58° (dec.); $[\alpha]^{23}D$ +252° (*c*, 1.1 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 236 mμ (ε = 16,600); (*Anal.* Calcd. for $C_{23}H_{29}O_6Cl$: C, 63.22; H, 6.54; Cl, 8.11. Found: C, 62.97; H, 6.61; Cl, 8.13). Reaction of V with hydriodic acid[11] at −20° for 20 minutes gave 9α-iodo-17α-hydroxycorticosterone acetate (VI), m.p. 100–110° (dec.); $[\alpha]^{22}D$ +145° (*c*, 1.05 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 243 mμ (ε = 11,000); (*Anal.* Calcd. for $C_{23}H_{31}O_6I$: C, 52.08; H, 5.89; I, 23.93. Found: C, 52.54; H, 6.44; I, 22.60). Both IV and VI with

(1) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769, July 8, 1952.

(2) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952).

(3) D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, H. C. Murray, H. M. Leigh, A. Weintraub and L. M. Reineke, *ibid.*, **75**, 412 (1953).

(4) N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951).

(5) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(6) R. H. Levin, B. J. Magerlein, A. V. McIntosh, Jr., A. R. Hanze, G. S. Fonken, J. L. Thompson, D. M. Searcy, M. A. Scheri and E. S. Gutsell, THIS JOURNAL, **75**, 502 (1953).

(7) M. L. Pabst, R. Sheppard and M. H. Kuizenga, *Endocrinology*, **41**, 55 (1947). We are indebted to Drs. A. Borman and F. Singer for the liver glycogen assays. The activity ratios are computed on a weight basis.

(8) The reaction of N-bromoacetamide with a $\Delta^{9(11)}$-steroid has been reported by Hicks and Wallis (*J. Biol. Chem.*, **162**, 641 (1946)) and by Stavely (*Fed. Proc.*, **9** (Part 1), 233 (1950)). These authors converted methyl 3α-acetoxy-$\Delta^{9(11)}$-cholenate into methyl 3α-acetoxy-11-keto-cholanate without isolating any of the intermediates.

(9) Using sulfuric acid in this reaction as suggested by Sarett (*J. Biol. Chem.*, **162**, 601 (1946)) gave yields in the vicinity of 45%, the remainder of III having been transformed into a water-soluble substance, presumably the 11β-sulfuric acid ester of IV. The use of perchloric acid in place of sulfuric acid increased the yield to over 90%.

(10) The corresponding 9α,11α-oxide, m.p. 248–249°; $[\alpha]^{23}D$ +99° (*c*, 1.09 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 238 mμ (ε = 16,000); (Found: C, 68.74; H, 7.38) was prepared from III with perbenzoic acid.

(11) D. H. R. Barton, E. Miller and H. T. Young, *J. Chem. Soc.*, 2598 (1951). The longer reaction time recommended by these authors for the opening of a 5β,6β-oxide led in our case mainly to III;

zinc dust in dilute alcohol[12] at room temperature furnished a mixture of III and 17α-hydroxycorticosterone acetate, m.p. 217–20°; $[\alpha]^{23}D$ +156° (c, 0.36 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 241 mμ (ϵ = 16,700); (*Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.47; H, 8.14), identified further by infrared comparison with an authentic sample.

Similarly, 11-epicorticosterone[1,2,13] on monoacetylation, followed by tosylation and elimination of toluenesulfonic acid with sodium acetate in acetic acid yielded the known $\Delta^{4,9(11)}$-pregnadiene-21-ol-3,20-dione 21-acetate,[14] m.p. 160–160.5°; $[\alpha]^{23}D$ +128° (c, 0.76 in acetone), +150° (c, 0.80 in $CHCl_3$); which on treatment with N-bromoacetamide afforded 9α-bromocorticosterone acetate, m.p. 152–53° (dec.); $[\alpha]^{23}D$ +178° (c, 0.94 in $CHCl_3$); (*Anal.* Calcd. for $C_{23}H_{31}O_5Br$: C, 59.10; H, 6.68; Br, 17.10. Found: C, 59.15; H, 6.70; Br, 17.03).

An attractive feature of this synthetic route is that it permits the introduction of radioactive halogen or tritium into the stable 9-position in the final step.

(12) The use of other reagents commonly employed for reductive dehalogenations such as Raney nickel with or without hydrogen, chromous chloride, zinc in acetic acid and others, led to III, V and/or their 4,5-dihydro products. Of particular interest is the reaction of IV with potassium iodide in acetone, which at the boiling point yielded III and V, while at room temperature it afforded in almost quantitative yield $\Delta^{4,6,8(9)}$-pregnatriene-17α,21-diol-3,20-dione acetate, m.p. 188–191°; $[\alpha]^{23}D$ +531° (c, 1.02 in $CHCl_3$); $\lambda_{max.}^{alc.}$ 244 mμ (ϵ = 14,300), 285–300 mμ (ϵ = 3,100), 385 mμ (ϵ = 6,700), *cf.* R. Yashin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 4654 (1951).

(13) S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh, D. A. Lyttle, L. M. Reineke and A. Weintraub, *ibid.*, **75**, 408 (1953).

(14) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 1316 (1943).

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DECATETRAENEDIOIC ACID, A FUMAGILLIN DEGRADATION PRODUCT

Sir:

The antibiotic fumagillin[1,2,3] has been shown to be an acid with an empirical formula of $C_{26-27}H_{34-36}O_7$. We have found that fumagillin can be hydrolyzed under mild alkaline conditions liberating a highly unsaturated acid $C_{10}H_{10}O_4$ with the properties of 2,4,6,8-decatetraenedioic acid.[4]

This appears to be the first isolation of this acid from a natural source. The ultraviolet absorption spectrum shows peaks at 336 mμ and 351 mμ similar to fumagillin. On hydrogenation, fumagillin absorbs about 5 moles of hydrogen. Hydrolysis of hydrogenated fumagillin yields sebacic acid. These facts lead us to the conclusion that fumagillin is a mono-ester of decatetraenedioic acid: $[C_{16-17}H_{25-27}O_3]$—O—CO—$(CH{=}CH)_4$COOH.

Isolation of Decatetraenedioic Acid from Fumagillin.—One gram of fumagillin was suspended in 50 ml. of alcohol, and 12 ml. of N NaOH added. The fumagillin dissolved, and the solution became red. The solution was boiled under reflux for 15 minutes, diluted with 35 ml. of water to redissolve a precipitate, boiled for ten minutes more, filtered, cooled and acidified. The precipitate (305 mg.) was dissolved in 3.5 ml. of N NaOH, treated with Darco G-60, filtered and acidified: yield, 288 mg. of a yellow powder, insoluble in chloroform, alcohol, or water, m. p. 295–297° dec.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.68; H, 5.27.

The infrared spectrum showed bands at 3.65, 3.76 and 3.90 (carboxylic OH), 5.93 (carbonyl), and 6.13 and 6.32 microns (C=C) in Nujol mulls.

The methyl ester[4] was prepared through the acid chloride, m. p. 214–217°; $E_{1\,cm.}^{1\%}$ 3180 at 335 mμ and $E_{1\,cm.}^{1\%}$ 2950 at 351 mμ in alcohol containing 2% chloroform.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.10, 64.88; H, 6.60, 6.43.

This ester was compared directly with a synthetic sample kindly supplied by Prof. R. Kuhn. The two were shown to be identical by mixed melting point, infrared (Nujol mull) and ultraviolet spectra.

Isolation of Sebacic Acid from Hydrogenated Fumagillin.—Fumagillin (10.1 g.) was hydrogenated with Adams catalyst in alcohol at room temperature and three atmospheres pressure. After 15 minutes over 5 molar equivalents of hydrogen had been consumed. The solution was filtered and concentrated with addition of water to remove alcohol. A solution of 1.67 g. (2 molar equivalents) of sodium hydroxide in 250 ml. was added and the solution heated for one hour on a steam-bath. The cooled solution was extracted with ether, evaporated to 50 ml. and acidified. A white solid (3.32 g.) precipitated, m. p. 132–133°, showing no depression with authentic sebacic acid.

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A NEW CLASS OF ANTITUBERCULAR COMPOUNDS

Sir:

During the screening of a large number of substances chosen from a wide range of chemical types, the discovery was made by Dr. R. L. Mayer and co-workers of the Division of Microbiology that 4,4′-diethoxythiocarbanilide (2) had high antituberculous activity in mice infected with the H37RV strain.[1] The synthesis and testing of over 300 thiocarbanilides and related substances revealed the rather specific structural features necessary for activity.

Shortening the 4-substituent to methoxy (1) (see

(1) T. E. Eble and F. R. Hanson, *Antibiotics & Chemotherapy*, **1**, 54 (1951).

(2) I. N. Asheshov, F. Strelitz and E. A. Hall, *ibid.*, **2**, 361 (1952).

(3) Our titration and elementary analyses agree best for $C_{26}H_{34}O_7$, as do the data of Eble and Hanson; Asheshov, *et al.*, however, prefer $C_{30}H_{40}O_8$.

(4) R. Kuhn and C. Grundmann, *Ber.*, **69**, 1757 (1936).

(1) R. L. Mayer, P. C. Eisman and E. A. Konopka, *Proc. Soc. Exp. Biol.*, in press.