one of which involves a surprisingly large amount of energy.

Sub-boric acid, prepared in quantitative yield by the action of water vapor on diboron tetrachloride at room temperature, is a white, microcrystalline solid which starts to lose water at about 90° *in vacuo*.

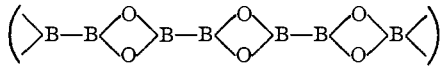
$$B_2(OH)_4 \longrightarrow 2BO + 2H_2O$$

To remove the last traces of water, however, heating for four hours at 220° is required. (1.124 mmoles of $B_2(OH)_4$ treated in this manner liberated 2.278 mmoles of water.) The boron monoxide thus prepared is not light brown as reported by previous workers, but white, and appears substantially unchanged at temperatures up to about 500°. At 650°, *in vacuo*, its color changes to light brown. This latter material, in agreement with previous observation, is only sparingly soluble in water, and solutions thus prepared readily decolorize permanganate.

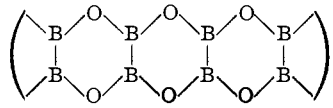
If the white, solid boron monoxide has not been completely dehydrated, its behavior on conversion to the brown form is quite remarkable. Thus, samples which have the approximate composition $BO \cdot {}^1/_{10}H_2O$, when briefly heated to about 400° *in vacuo*, undergo a rapid and spontaneous change, the energy of which is sufficient to heat the entire solid to incandescence. (Using brightness as a criterion, the temperature was estimated at from 700 to 900°.) This behavior has been repeatedly confirmed. The light brown solid which results has the same properties as, and is presumably identical with, the previously prepared light brown material. Also formed are small amounts of hydrogen and a white solid, presumably boric acid but not present in amounts great enough for identification. These latter probably result from thermal decomposition of residual sub-boric acid.

Unlike the white form, the light brown boron monoxide is hard and brittle. Aside from color, the chief observed difference between the two modifications lies in their solubilities in water and methanol, in each of which the white form is readily soluble and the brown form only sparingly so. Prolonged exposure to air does not seem to alter the color or reducing properties of either modification.

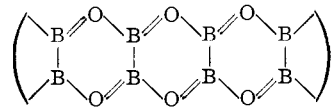
Although arguments for the existence of boron monoxide as B_2O_2 molecules have been presented, its properties do not seem consistent with this interpretation. It seems more likely that boron monoxide, in both modifications, is polymeric. Since one of the forms is white, and the other colored, it may be reasonable to assign to the former the structure



and to the latter the structure



Possible contributions to the latter by quinoid structures, such as



may account for the observed coloration.

The role of water in lowering the temperature of conversion from the white to colored form is not readily explained.

THE PENNSYLVANIA STATE UNIVERSITY
COLLEGE OF CHEMISTRY AND PHYSICS THOMAS WARTIK
UNIVERSITY PARK, PA. EUGENE F. APPLE[3]

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(3) General Electric Co., P. O. Box, 1088, Schenectady, N. Y.

THE ADRENAL HORMONES AND RELATED COMPOUNDS. III. SYNTHESIS OF 2-ALKYL ANALOGS[1]

Sir:

Chemical and microbiological modification of the structures of adrenal cortical hormones by the introduction of 9α-halogen or the 1-double bond has resulted in products of high activity.[2] We now report the synthesis of novel 2-alkyl analogs of the adrenal hormones. This modification has resulted in certain cases in marked enhancement of adrenal cortical activity.

11β,21-Dihydroxy-4,17(20)-*cis*-pregnadiene-3-one 21-acetate (I)[3] was treated with ethyl oxalate and methanolic sodium methoxide in *t*-butyl alcohol to form the sodium enolate of 2-ethoxyoxalyl-11β,-21-dihydroxy-4,17(20)-*cis*-pregnadiene-3-one (II) in essentially quantitative yield. Acidification of an aqueous solution of II with dilute hydrochloric acid precipitated the free enol III as an amorphous solid, m.p. 80–100°. Either II or III, when methylated with methyl iodide and potassium carbonate in acetone, followed by removal of the ethoxyoxalyl group by sodium methoxide in methanol, gave 11β,21-dihydroxy-2-methyl-4,17(20)-*cis*-pregnadiene-3-one (IV), m.p. 162.5–164°. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.64; H, 9.51. Acetylation of IV gave the corresponding 21-acetate V, m.p. 182–184.5°, $[\alpha]_D$ +145° (chl.), λ_{max}^{EtOH} 242 mμ(15,025). *Anal.* Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.32; H, 8.79. The yield from II to V was 33%. It seems likely that the 2-methyl group in V is α-oriented or *quasi-equatorial* both because of its method of preparation and because it was not isomerized by further treatment with sodium methoxide in methanol. Oxidation of V by the method of Miescher and Schmidlin[4] or better with phenyl iodosoacetate[1,3] and a catalytic amount of osmium tetroxide gave a mixture of 11β,17α,21-trihydroxy-2-methyl-4-pregnene-3,20-dione 21-acetate (VI), m.p. 133–

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135°, 171–171.5° or 197–199° (polymorphic forms), $[\alpha]_D$ + 164° (chl.), λ_{max}^{EtOH} 242 mμ (15,125). *Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.84; H, 8.15, and 11β,17α,20α,21-tetrahydroxy-2-methyl-4-pregnene-3-one 21-acetate (VII), m.p. 215–218.5°, $[\alpha]_D$ +67° (diox.). *Anal.* Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.82; H, 8.60. The presence of the 17,20-glycol grouping in VII was shown by a negative Tollens test and periodic acid oxidation to 11β-hydroxy-2-methyl-4-androstene-3,17-dione, m.p. 206–208°, $[\alpha]_D$ +220° (chl.). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.98; H, 9.31. Hydrolysis of VI with potassium bicarbonate in methanol gave 11β,17α,21-trihydroxy-2-methyl-4-pregnene-3,20-dione (VIII), m.p. 237–238°, $[\alpha]_D$ +185° (95% EtOH), λ_{max}^{EtOH} 242 mμ (15,250). *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.14; H, 8.61. N-Bromoacetamide in *t*-butyl alcohol–pyridine oxidized VI to 17α,21-dihydroxy-2-methyl-4-pregnene-3,11,20-trione 21-acetate (IX) in 72% yield, m.p. 205–209°, $[\alpha]_D$ +170° (acetone). *Anal.* Calcd. for $C_{24}H_{32}O_6$: C, 69.25; H, 7.75. Found: C, 68.94; H, 7.69.

Dehydration of the 11β-hydroxyl group of VI with thionyl chloride in pyridine afforded 17α,21-dihydroxy-2-methyl-4,9(11)-pregnadiene-3,20-dione 21-acetate (X), m.p. 220–223°, $[\alpha]_D$ +138° (chl.), λ_{max}^{EtOH} 240 mμ (16,750). *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.05; H, 8.32. Practically quantitative conversion of X to 9α-bromo-11β,17α,21-trihydroxy-2-methyl-4-pregnene-3,20-dione 21-acetate (XI), [m.p. 125–130° dec., $[\alpha]_D$ +146° (chl.). *Anal.* Calcd. for $C_{24}H_{33}O_6Br$: Br, 16.07; Found: Br, 16.27, 16.06] was accomplished with N-bromoacetamide in *t*-butyl alcohol containing aqueous perchloric acid. XI with potassium acetate in acetone gave 9β,11β-epoxy-17α,21-dihydroxy-2-methyl-4-pregnene-3,20-dione 21-acetate (XII), 75% yield, m.p. 185–188°, $[\alpha]_D$ +49° (chl.). *Anal.* Calcd. for $C_{24}H_{32}O_6$: C, 69.20; H, 7.75. Found: C, 69.28; H, 7.90. Hydrofluoric acid converted XII to 9α-fluoro-11β,17α,21-trihydroxy-2-methyl-4-pregnene-3,20-dione 21-acetate (XIII) in about 40% yield, m.p. 236–238°, $[\alpha]_D$ +167° (diox.), λ_{max}^{EtOH} 238.5 mμ (16,150). *Anal.* Calcd. for $C_{24}H_{33}O_6F$: C, 66.03; H, 7.62; F, 4.35. Found: C, 66.12; H, 7.31; F, 3.74. The corresponding 21-alcohol XIV, formed from XIII by potassium bicarbonate hydrolysis, melted at 250–253° dec., λ_{max}^{EtOH} 239 mμ (16,175). *Anal.* Calcd. for $C_{22}H_{31}O_5F$: C, 66.98; H, 7.92; F, 4.82. Found: C, 67.14; H, 7.97; F, 4.47. Oxidation of XIII with chromium trioxide in acetic acid produced 9α-fluoro-17α,21-dihydroxy-2-methyl-4-pregnene-3,11,20-trione 21-acetate (XV), m.p. 227–229°, λ_{max}^{EtOH} 235.5 mμ (15,500), $[\alpha]_D$ +167° (diox.). *Anal.* Calcd. for $C_{24}H_{31}O_6F$: C, 66.34; H, 7.19; F, 4.37. Found: C, 65.79; H, 7.23; F, 3.97.

Alkylation of 2-ethoxyoxalyl-11β,21-dihydroxy-4,17(20)-pregnadiene-3-one (III) with ethyl iodide, followed by removal of the ethoxyoxalyl grouping and acetylation gave 2-ethyl-11β,21-dihydroxy-4,17(20)-pregnadiene-3-one 21-acetate (XVI) in 9% yield, m.p. 149–151°, λ_{max}^{EtOH} 242 mμ (15,000). *Anal.* Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.23; H, 9.17. Oxidation of XVI with hydrogen peroxide and osmium tetroxide produced 2-ethyl-11β,17α,21-trihydroxy-4-pregnene-3,-20-dione 21-acetate (XVII), m.p. 160–168°, isolated as a methanol solvate. *Anal.* Calcd. for $C_{25}H_{36}O_6 \cdot CH_3OH$: C, 67.21; H, 8.67. Found: C, 67.55; H, 8.97.

These compounds were tested in the Department of Endocrinology of the Upjohn Research Division. 2-Methylhydrocortisone acetate (VI) was found to be ten times as active as hydrocortisone in the glycogen deposition assay, while the corresponding 9α-fluoro derivative XIII was thirty-eight times as potent. In the salt retention assay VI and XIII were found to be more potent than DOCA by factors of two and six-tenths and ninety, respectively. More complete biological data will be published.[5]

The preparation of the 2-alkyl analogs of other steroid hormones will be reported at a later date.

The authors are indebted to J. L. Johnson, Mrs. G. S. Fonken and J. E. Stafford for infrared and ultraviolet absorption data, and to W. A. Struck and associates for microanalyses.

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RESEARCH LABORATORIES
THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

J. A. HOGG
F. H. LINCOLN
R. W. JACKSON
W. P. SCHNEIDER

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AN EFFECT OF PYRIDOXAL-5-PHOSPHATE *IN VITRO* ON HEME SYNTHESIS AND CO_2 PRODUCTION FROM GLYCINE-2-C-14[1]

Sir:

Various species of vitamin B_6-deficient animals develop an anemia (dog,[2] pig,[3] rat,[4] duck[5]). The effect of pyridoxal-5-phosphate on heme synthesis was studied with duck blood since ducks have nucleated red cells which are able to synthesize labeled heme *in vitro* from glycine-2-C-14.[6]

Day-old Pekin ducklings were made vitamin B_6-deficient with a diet described by Hegsted and Rao.[5] After 8 days on the diet, the average weights of the control and deficient ducklings were 271 and 89 g., respectively. Two ml. samples of blood removed from the heart of each animal under ether anesthesia were incubated in Warburg vessels with glycine-2-C-14, in the presence and absence of pyridoxal-5-phosphate. The CO_2 released during the incubation was collected in 0.2 ml. of 10% ml. of 10% NaOH contained in the center well. After 2 hours the samples were chilled in ice and 3 ml. of rat blood was added to each vessel to increase the yield of heme. The cells were centrifuged and washed twice with 0.9% saline, and hemin was iso-

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