and a number of 2-pyrrylphosphonate structures are in progress and will be reported in detail.

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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PITTSBURGH
PITTSBURGH 13, PA.

CLAIBOURNE E. GRIFFIN
ROSALYN A. POLSKY

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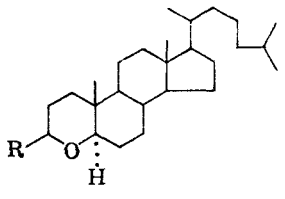
Steroids and Related Natural Products. VI. Diborane Reduction of Lactones to Cyclic Hemiacetals[1,2]

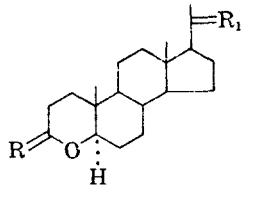
Sir:

Several carbohydrate lactones have been reduced, under carefully controlled conditions, to cyclic hemiacetals by sodium or potassium borohydride.[3] A few examples of lactone → cyclic hemiacetal conversion using lithium aluminum hydride have also been reported.[4]

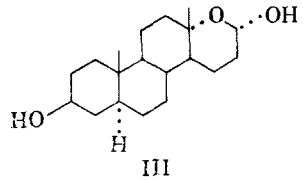
We now wish to report a new and convenient procedure for reducing lactones to cyclic hemiacetals using diborane.[5,6] This useful reduction reaction has been applied to synthesis of several unusual oxasteroids. In a typical experiment, the diborane prepared from sodium borohydride (0.2 g.) and boron trifluoride etherate (1 g.), in diglyme, was passed (over 3 hr.) into a solution of 3-oxo-4-oxa-5α-cholestane (0.39 g.)[7] in tetrahydrofuran at room temperature. Following addition of ethyl ether and water, the crude product was isolated. Chromatographic separation led to 3β-hydroxy-4-oxa-5α-cholestane (Ia, 0.28 g.); m.p. 197–199°, $[\alpha]_D^{22}$, + 106° (chloroform). *Anal.* Calcd. for $C_{26}H_{46}O_2$: C, 79.94; H, 11.87; O, 8.19. Found: C, 79.61; H, 11.52; O, 8.58. The cyclic hemiacetal structure (I) was confirmed by chromic acid oxidation to 3-oxo-4-oxa-5α-cholestane and transformation to 3β-methoxy-4-oxa-5α-cholestane (Ib, m.p. 106–107°, *Anal.* Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96; O, 7.91. Found: C, 80.45; H, 11.85; O, 7.47.) by hydrobromic acid–methanol.



Ia. R = OH
b. R = OCH_3
c. R = H



IIa. R = R_1 = O
b. R = O, R_1 =
c. R = O, R_1 = H_2
d. R = H, OH, R_1 = H_2



III

Conversion of 3,20-dioxo-4-oxa-5α-pregnane (IIa)[8] to 20-ethylene-thioketal derivative IIb (m.p. 237–239°, *Anal.* Calcd. for $C_{22}H_{34}O_2S_2$: C, 66.96; H, 8.69; S, 16.30. Found: C, 66.70; H, 8.58; S, 16.54.), followed by Raney nickel desulfurization gave 3-oxo-4-oxa-5α-pregnane (IIc); m.p. 188–190°, $[\alpha]_D^{23}$, + 107° (chloroform), (*Anal.* Calcd. for $C_{22}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.38; H, 10.33.). Diborane reduction of lactone IIc (0.3 g.) provided hemiacetal IId (0.2 g.); m.p. 161–163°, $[\alpha]_D^{23}$, + 69° (chloroform). *Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18; O, 10.44; Active H, 0.33. Found: C, 77.93; H, 11.11; O, 10.79; Active H, 0.25.

Diborane reduction of 3β-hydroxy-17-oxo-17a-

(1) Part V; G. R. Pettit, B. Green, and W. J. Bowyer, *J. Org. Chem.*, 26, 2879 (1961).

(2) This investigation was supported by PHS Research Grant CY-4074(C2) from the National Cancer Institute, Public Health Service, and National Science Foundation Research Grant G-9585.

(3) These studies have been reviewed by E. Schenker, *Angew. Chem.*, 73, 81 (1961).

(4) *Cf.;* G. E. Arth, *J. Am. Chem. Soc.*, 75, 2413 (1953); J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, 40, 1034 (1957); and H. Obara, *Nippon Kagaku Zasshi*, 82, 58 (1961).

(5) While reaction between diborane and γ-butyrolactone has been observed, the product was not described: H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, 22, 1135 (1957). Interestingly, bis-3-methyl-2-butylborane has been reported to reduce both γ-butyrolactone and γ-valerolactone to hydroxyaldehydes: H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.*, 83, 486 (1961).

(6) Several aspects of diborane chemistry and toxicology have been described by J. Cueilleron and P. Guillot, *Bull. soc. chim. France*, 2044 (1960). The potential value of this interesting substance in organic synthesis is illustrated by a number of recent investigations. For example, see: J. Kollonitsch, *J. Am. Chem. Soc.*, 83, 1515 (1961); H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 83, 1241 (1961); H. C. Brown and C. H. Snyder, *J. Am. Chem. Soc.*, 83, 1002 (1961); H. C. Brown, C. Verbrugge, and C. H. Snyder, *J. Am. Chem. Soc.*, 83, 1001 (1961); W. Jeffers, *Chem. and Ind. (London)*, 431 (1961); R. Köster and G. Griaznov, *Angew. Chem.*, 73, 171 (1961); N. Nöth and G. Mikulaschek, *Chem. Ber.*, 94, 634 (1961); H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 83, 486 (1961); M. F. Hawthorne, *J. Am. Chem. Soc.*, 83, 367 (1961); ref. 3; and a review prepared by H. C. Brown, *Organometallic Chemistry*, H. Zeiss, Ed., Reinhold Publishing Corp., New York, 1960, p. 150.

(7) A. Salamon, *Z. physiol. Chem.*, 272, 61 (1941). Conclusive evidence for the structure and stereochemistry of the lactone prepared by this procedure will be presented in a subsequent communication.

(8) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, 26, 986 (1961).

oxa-5α-androstane (1.25 g.)[9] to hemiacetal III (0.32 g.) was also easily accomplished. A pure specimen melted at 226–228°. *Anal.* Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46; O, 15.56. Found: C, 74.14; H, 10.27; O, 15.73.

We also wish to report that diborane reduction of certain lactones in the presence of boron trifluoride etherate yields the corresponding ether derivative.[10] For example, when reduction of 3-oxo-4-oxa-5α-cholestane (0.39 g.) was repeated employing diborane–boron trifluoride etherate the product was 4-oxa-5α-cholestane[11] (Ic, 0.07 g.).

The stereochemistry assigned hemiacetals Ia, IId, and III received substantial support when each was recovered following equilibration in acidified (hydrochloric acid) tetrahydrofuran or methanol solution.

Several other facets of this unusually mild route to hemiacetals are now under investigation.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MAINE
ORONO, ME.

GEORGE R. PETTIT
T. R. KASTURI
BRIAN GREEN
JOHN C. KNIGHT

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(9) M. F. Murray, B. A. Johnson, R. L. Pederson, and A. C. Ott, *J. Am. Chem. Soc.*, **78**, 981 (1956).

(10) *Cf.*, G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *J. Org. Chem.*, **26**, 1685 (1961).

(11) The 4-oxasteroid (Ic) was identical with an authentic specimen kindly supplied by Dr. J. T. Edward. See, J. T. Edward and P. F. Morand, *Can. J. Chem.*, **38**, 1325 (1960).

17α-Acetoxy-6,16α-dimethylprogesterones

Sir:

In a recent communication[1] we reported the synthesis of a series of 6,16α-dimethylprogesterones.[2] We have now prepared the 17α-acetoxy derivatives of these compounds and find them to be one of the most potent series of orally active progestogens known to date.

A toluene solution of 5,6α-epoxy-16-pregnene-3β-ol-20-one acetate (I) was added to an excess of ethereal methyl magnesium bromide containing powdered cuprous chloride. The magnesium enolate so formed was treated *in situ* with acetic anhydride[3] for periods of up to 3 days to form 6β,16α-dimethyl-17(20)-pregnene-3β,5α,20-triol triacetate (II). The crude compound II on treatment with peracetic acid gave the 17(20)-epoxide which without purification was saponified with methanolic potassium carbonate. The crude 6β,16α-dimethylpregnane-3β,5α,17α-triol-20-one 5-acetate (IIIa) was purified as the 3,5-diacetate (IIIb), m.p. 206.5–208.5°, $[\alpha]_D^{26}$ −27.5°.[4] Saponification of IIIb with potassium bicarbonate in aqueous methanol gave IIIa as a hydrate, m.p. 186–190°, $[\alpha]_D^{26}$ −27.3°, which on oxidation with 8*N* chromic acid–sulfuric acid reagent in acetone gave 6β,16α-dimethylpregnane-5α,17α-diol-3,20-dione 5-acetate (IIIc), m.p. 161–163° (hydrated form), $[\alpha]_D^{26}$ −26.9°. Refluxing a solution of IIIc in ethanol containing hydrochloric acid effected β-elimination together with isomerization at C-6 producing 17α-hydroxy-6α,16α-dimethylprogesterone (IVa).[5] The 17α-acetate (IVb)[6] was prepared in the usual manner.[7] Dehydrogenation of IVa with chloranil in *t*-butanol[8] gave 17α-hydroxy-Δ^6-dehydro-6,16α-dimethylprogesterone (Va) which was also converted to its 17α-acetate (Vb). The Δ^1-dehydro com-

(1) R. P. Graber and M. B. Meyers, *Chem. & Ind.*, 1478, (1960).

(2) 6α,16α-Dimethylprogesterone has been reported recently by (a) S. Bernstein, E. W. Cantrall, and J. P. Dusza, *J. Org. Chem.*, **26**, 269 (1961) and (b) J. Iriarte and M. L. Franco, *J. Org. Chem.*, **26**, 2047, (1961).

(3) K. Heusler, J. Kebrle, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959).

(4) All melting points determined on a micro hot stage; all rotations in chloroform. Satsifactory elemental analyses obtained for all new compounds described herein.

(5) See ref. 2b. Reported m.p. 200–202°, $[\alpha]_D$ + 51.4°, $\lambda_{max}^{C_2H_5OH}$ 240–242 mμ, ϵ 16,600.

(6) See ref. 2b. Reported m.p. 170–172°, $[\alpha]_D$ + 71.1°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, ϵ 13,800.

(7) *Cf.* C. G. Bergstrom, P. B. Sollman, R. T. Nicholson, and R. M. Dodson, *J. Am. Chem. Soc.*, **82**, 2322 (1960).

(8) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960).

TABLE I

Compound	M.P.	$[\alpha]_D$[a]	$\lambda_{max}^{C_2H_5OH}$ mμ(ϵ)	Oral Activity[b]
17α-Hydroxy-6α,16α-dimethylprogesterone(IVa)	203–207°	+53.5°	242(15,400)	0.25
17α-Acetoxy-6α,16α-dimethylprogesterone (IVb)	169–171°	+69.0°	242(15,800)	55
17α-Hydroxy-Δ^6-dehydro-6,16α-dimethylprogesterone (Va)	220.5–229°	+27.9°	290(23,200)	—
17α-Acetoxy-Δ^6-dehydro-6,16α-dimethylprogesterone (Vb)	189.5–195°	+25.6°	288(24,900)	130
17α-Acetoxy-Δ^1-dehydro-6α,16α-dimethylprogesterone (VI)	168–173°	+21.7°	245(15,800)	40
17α-Acetoxy-$\Delta^{1,6}$-bisdehydro-6,16α-dimethylprogesterone (VII)	161.5–163°	−24.2°	228(12,000) 256(8470) 302(11,540)	120

[a] Temperature *ca.* 25°. [b] Clauberg assay; ethinyl testosterone = 1. Assays by Endocrine Laboratories, Madison, Wis.