which does not participate in the myokinase reaction would be expected nonetheless to inhibit the phosphorylation of riboflavin in the presence of $Mg^{++}$. However, as can be seen from Table II, expt. 3, whereas AMP inhibited the synthesis of FMN by 53.5%, no inhibition by adenosine was observed. Thus, on the basis of this analogy, it appears less likely that the absence of $Mg^{++}$ is responsible for the loss of AMP inhibition in the presence of $Zn^{++}$. The higher AMP inhibition noted here as compared to expt. 2 is due to the slightly lower relative ATP concentration and to the use of unpurified ATP solutions which probably already contain some AMP. As expected neither AMP nor adenosine inhibited in the presence of $Zn^{++}$ (Table II, expt. 4).

The experimental results outlined here are highly suggestive that the observed activity of ADP as a phosphate donor in the presence of $Mg^{++}$ is due to contaminating myokinase activity. The remote possibility that ADP acts as a direct phosphorylating agent only in the presence of $Mg^{++}$ has not been excluded. The competitive inhibition of AMP observed in the presence of $Mg^{++}$ can be attributed to a competition with riboflavin for ATP to form ADP which in itself cannot donate phosphate, thus lowering the effective ATP concentration of the reaction mixture.

Although the maximal velocity with ADP in the presence of $Mg^{++}$ is about 50% of that with ATP, this does not constitute an unequivocal argument to conclude that the activity of ADP is direct and not due to its prior conversion to ATP by myokinase. A possible inhibitory effect of ADP on the flavokinase reaction may very well lead to such fortuitous results. Neither does the maximal velocity with ADP equal that with AMP in the activation of crude muscle phosphorylase (Dr. S. P. Colowick, personal communication). Yet with purified muscle phosphorylase ADP does not retain its activating effect, suggesting that its stimulatory effect in the crude system was due to its prior conversion to AMP by myokinase.

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## Cyclopentadienylsilane Derivatives

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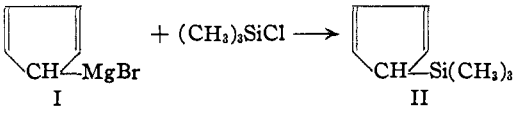
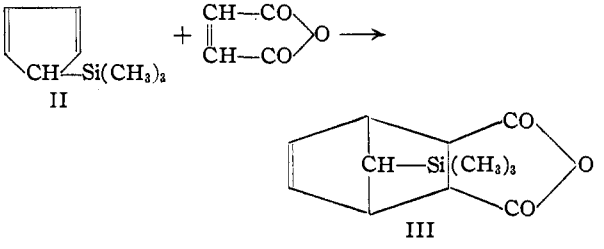
Cyclopentadienylsilane derivatives have hitherto not been reported in the literature. Several routes are possible for the preparation of these derivatives, among them the use of alkali metals to form the corresponding salts which then could react further with chlorosilanes. However, some of these salts are spontaneously inflammable on exposure to air.[1]

The Grignard method offered a convenient and safe way to arrive at these compounds. Cyclopentadienylmagnesium bromide (I) was prepared according to the method of Grignard and Courtot[2] using an exchange reaction between cyclopentadiene and ethylmagnesium bromide. This Grignard compound I then was treated with various chlorosilanes. The reaction of I with trimethylchlorosilane resulted in the formation of cyclopentadienyltrimethylsilane (II).



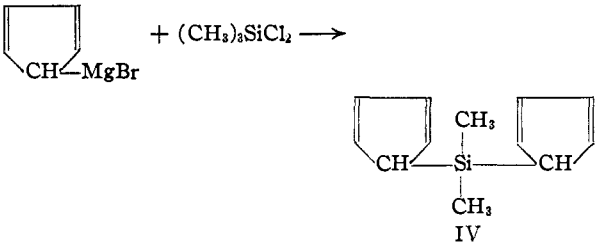

I II

Since a silicon analysis alone was not sufficient to decide between a monomeric or dimeric structure, a molecular weight determination in dioxane indicated the existence of the monomeric form. In addition, a crystalline Diels–Alder adduct III with maleic anhydride gave further proof that the conjugated double bond system in II was still intact




II III

The reaction of cyclopentadienylmagnesium bromide with dimethyldichlorosilane led to the isolation of two products from which bis-(cyclopentadienyl)-dimethylsilane (IV) was identified.




IV

Another product, distilling at 80–83° at 0.7 mm., was obtained in a yield of 11%. It had a silicon content of 16.6% and gave a positive chlorine test. However, no definite structure was assigned as yet to this product.

### Experimental

**Cyclopentadienylmagnesium Bromide (I).**—To an ethylmagnesium bromide solution, prepared from 200 g. of ethyl bromide was added 500 cc. of benzene and the ether removed by distillation.

One hundred twenty-one grams of cyclopentadiene, obtained by slow distillation from dicyclopentadiene, was added slowly to the ethylmagnesium bromide solution. It was then added for 1.5 hours at 60°. Ethane evolution occurred during the heating period. Cyclopentadienylmagnesium bromide formed a dark colored, clear solution.

**Cyclopentadienyltrimethylsilane (II).**—Half of the above Grignard solution was added gradually to a solution of 99.5 g. of trimethylchlorosilane in 150 cc. of benzene. The reaction mixture was then refluxed for 15.5 hours. The inorganic precipitate was filtered off and washed with benzene. The solvent was removed from the filtrate and the residual liquid vacuum distilled. The product distilled at 43–44° at 19 mm. as a colorless liquid which darkened on prolonged exposure to air. The yield was about 45%.

*Anal.* Calcd. for $C_8H_{14}Si$: Si, 20.3; mol. wt., 138. Found: Si, 19.7; mol. wt. 135.

**The 3,6-*endo*-Trimethylsilylmethylene-1,2,3,6-tetrahydrophthalic Anhydride (III).**—Two and two-tenths grams of maleic anhydride was added to a solution of 3.1 g. of cyclopentadienyltrimethylsilane in 10 cc. of benzene at room temperature. An instantaneous exothermic reaction set in. The reaction mixture was allowed to stand at room tempera-

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(1) J. Thiele, *Ber.*, **34**, 68 (1901).

(2) V. Grignard and C. Courtot, *Compt. rend.*, **158**, 1763 (1914).

ture for 2 hours. It was then concentrated using an air blower. It was filtered and 4 g. (78.5% of theory) of a colorless, crystalline material was obtained. Recrystallized from glacial acetic acid, it melted at 105° (uncor.).

*Anal.* Calcd. for $C_{12}H_{16}O_3Si$: Si, 11.86. Found: Si, 11.4.

**Bis-(cyclopentadienyl)-dimethylsilane (IV).**—Half of the above-described cyclopentadienylmagnesium bromide solution was added gradually to a solution of 207 g. of dimethyldichlorosilane in 250 cc. of benzene. The reaction mixture was refluxed for 15.5 hours. It was filtered and the inorganic precipitate washed with benzene. The solvent was removed and the residual material vacuum distilled. The product, a colorless liquid, distilled at 73° at 25 mm. This material gave a negative chlorine test. The yield was about 40%.

*Anal.* Calcd. for $C_{12}H_{16}Si$: Si, 14.89. Found: Si, 14.5.

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## The Kinetics of 20-Keto Reduction in 11α-Acetoxypregnane-3,20-dione by Sodium Borohydride

BY EDWARD R. GARRETT AND DOUGLAS A. LYTTLE

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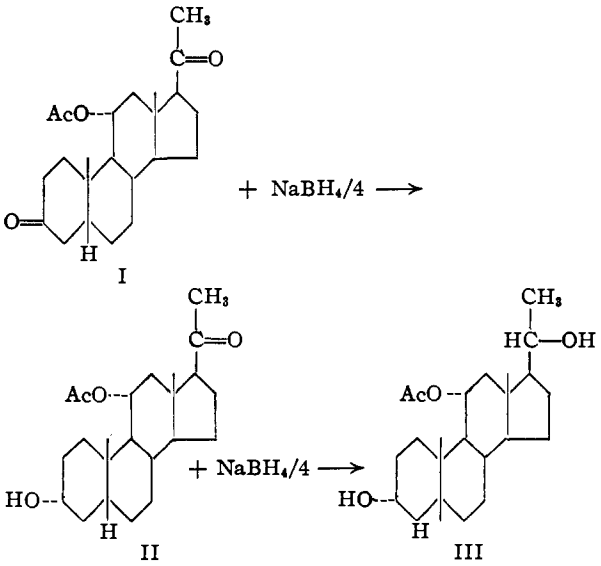
The selective reduction by sodium borohydride of the 3-keto group of pregnane-3,20-diones to the 3α-hydroxy configuration has been reported.[1-3] In the course of studies on the quantitative rates of selective reduction we have found that the reduction of the 3-keto group of the dione I occurred too rapidly for precise measurement under our experimental conditions. Therefore, we have investigated the kinetics of the reduction of the C-20 carbonyl group. The kinetics of borohydride reduction of 3α-hydroxy-11α-acetoxypregnan-20-one (II) are bimolecular with respect to carbonyl and sodium borohydride concentration. The stoichiometry of the reduction requires one mole of sodium borohydride to four moles of carbonyl.




(1) J. A. Hogg, D. A. Lyttle and A. H. Nathan, U. S. Patent 2,647,-134.

(2) O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, THIS JOURNAL, 74, 3711 (1952).

(3) O. Mancera, Howard J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *ibid.*, 75, 1286 (1953).

### Experimental

**Materials.**—The $NaBH_4$ (Metal Hydrides, Inc.) was used as received from the manufacturer. The 11α-acetoxypregnane-11,20-dione[4] melted at 149.5–153.5°. The 3α-hydroxy-11α-acetoxypregnan-20-one[1] melted at 145.5–147.0°. The dioxane was freshly distilled over $NaBH_4$.

**Borohydride Assay.**—The effective borohydride concentration of the solutions used was determined in the following manner: a 5-cc. sample containing up to 15 mg. of $NaBH_4$ was pipetted into a solution of 1 cc. of 2 *N* NaOH and 25 cc. of 0.1 *N* $KIO_3$. To this was added 1 g. of KI, 15 cc. of $CHCl_3$ and 12 cc. of 2 *N* $H_2SO_4$. The released $I_2$ was titrated with 0.1 *N* $Na_2S_2O_3$ using 1% starch indicator. The equivalent weight of $NaBH_4$ is 1/8 molecular weight.[5]

**Rate Studies.**—The ketosteroid was dissolved in dioxane and this solution was added to an aqueous solution of sodium borohydride previously assayed and of known alkalinity. The resulting solvent was 68.5% dioxane. Aliquots were removed at timed intervals and titrated by the procedure given above.

The composition of the solutions studied is given in Table I.

TABLE I

THE REACTION CONDITIONS FOR SODIUM BOROHYDRIDE REDUCTIONS OF KETOSTEROIDS IN 68.5% DIOXANE

| Run no.[a] | Temp., °C. | $NaBH_4$, *M* | NaOH, *M* | *k* (l. mole$^{-1}$ hr.$^{-1}$)[b] for 20-ketone reduction |
|---|---|---|---|---|
| 1[c] | 15 ± 0.5 | 0.00656 | 0.0544 | .. |
| 2 | 25.5 ± .3 | .0502 | .0564 | 0.40 |
| 3 | 56.0 ± .5 | .0533 | .0552 | 3.6 |
| 4 | 57.0 ± 1.0 | .0533 | .0281 | 3.7 |
| 5 | 56.0 ± 0.5 | .0262 | .0555 | 4.2 |
| 6 | 56.5 ± 0.2 | .0389 | .0552 | 3.9 |

[a] Runs 1 through 5 were with 0.0517 *M* 11α-acetoxypregnane-3,20-dione (I). Run 6 was with 0.0517 *M* 3α-hydroxy-11α-acetoxypregnan-20-one (II). [b] The bimolecular rate constant, *k*, is calculated from the product of $2.303/(4A - B)$ and the slope of the linear plot of $\log [(A - x)/(B - 4x)]$ *vs.* time in hours. The initial carbonyl molarity ($B$) is twice the molarity of the diketosteroid and equal to the molarity of the monoketosteroid. The initial molarity of borohydride is $A$ and $x$ is the calculated consumption of borohydride at time $t$. [c] 87% of the $NaBH_4$ was consumed within two minutes.

### Results and Discussion

The relatively instantaneous reduction of the 3-keto group of 11α-acetoxypregnane-3,20-dione under the mildest conditions studied is shown in run no. 1 at 15° and with no borohydride in stoichiometric excess of the 3-keto group (Table I). In the other runs the consumption of a second stoichiometric equivalent proceeded at a measurable rate. Each molecule of borohydride was equivalent to the reduction of four carbonyls.

This is consistent with the proposed mechanism of Chaikin and Brown[6] of a 1:4 adduct prior to hydrolysis. On the postulate that this adduct is formed in four successive steps, 1:1, 1:2, 1:3 and finally, 1:4, and that the first 1:1 adduct formation is rate determining, the over-all rate expression is

$$dx/dt = k(A - x)(B - 4x)$$

where $A$ = $[NaBH_4]$, the initial molar concentration of sodium borohydride, $B$ = $[R_2C{=}O]$, the molar concentration of reducible carbonyl groups,

(4) S. H. Eppstein, D. H. Peterson, H. Marian Leigh, H. C. Murray, A. Weintraub, L. M. Reineke and P. D. Meister, *ibid.*, 75, 421 (1953).

(5) D. A. Lyttle, E. H. Jensen and W. A. Struck, *Anal. Chem.*, 24, 1843 (1952).

(6) S. W. Chaikin and W. G. Brown, THIS JOURNAL, 71, 122 (1949).