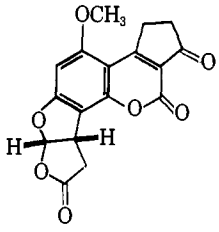
brief exposure to polyphosphoric acid. Hydrolysis of the acetal **15** in aqueous hydrochloric–acetic acid solution gave the lactone carboxylic acid **16**, mp 245–254° dec; ν_{max}^{Nujol} 1787, 1739, 1711 cm^{-1}, with *cis*-fused five-membered rings (acetal proton doublet at 6.79 ppm, J = 6 cps).

Cyclodehydration of this carboxylic acid **16** was effected in methylene chloride solution by consecutive treatments with oxalyl chloride (20°; 24 hr) and aluminum chloride (−15°; 4 hr). Crystallization of the nonacidic portion of the reaction product from chloroform furnished the pentacyclic lactone **17**, mp >320° dec; ν_{max}^{Nujol} 1788, 1760, 1688 cm^{-1}; λ_{max}^{MeOH} 220, 239 (s), 263, 355 mμ (ε 19,400, 12,200, 10,600, 17,700). When the lactone **17** was treated with disiamylborane[9] in



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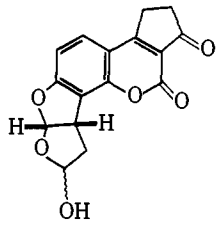

18

diglyme solution it was reduced to a mixture of at least two products from which the desired hemiacetal **18** could be isolated by chromatography. Infrared ($\nu_{max}^{CHCl_3}$ 3580, 3400, 1760, 1685 cm^{-1}) and ultraviolet spectra (λ_{max}^{EtOH} 215, 237 (s), 260, 364 mμ; $\lambda_{max}^{0.01N\ NaOH}$ 248, 292, 407 mμ) of this hemiacetal were identical with those of a sample, mp 223–225°, prepared by trifluoroacetic acid catalyzed addition of water to natural aflatoxin B_1. Treatment of the racemic hemiacetal with acetic acid–acetic anhydride in the presence of toluenesulfonic acid produced the corresponding acetate which without further purification was pyrolyzed (240°) to racemic aflatoxin B_1 identical with natural material **1** in thin layer chromatographic behavior and infrared, ultraviolet, and mass spectra.

Acknowledgment. We are indebted to the National Cancer Institute for financial support and to Dr. Elizabeth Weisburger for encouragement. Drs. J. Berger and A. Brossi kindly provided us with an aflatoxin concentrate which was prepared by Mr. B. Tabenkin in the microbiology pilot plant of Hoffmann-La Roche Inc., Nutley, N. J.

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(10) National Science Foundation, Cooperative Graduate Fellow 1964–1966.

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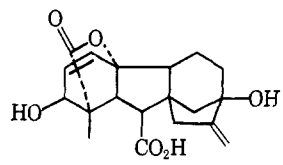
A Model Study of the Synthesis of the A Ring of Gibberellic Acid[1]

Sir:

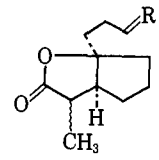
A number of natural products such as gibberellic acid[2] (**1**) and rosenolactone[3] contain a bridged γ-lactone



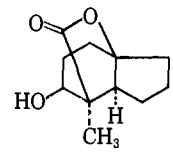
1

as part of their structures. The synthesis of this structural feature is rendered more difficult because the carbonyl group is attached to a quaternary carbon atom. We wish to report a useful synthesis of this structural feature in which the lactone ring is completed before the carbocyclic ring. This synthesis also places a hydroxyl group as found in gibberellic acid.

The action of homoallylmagnesium bromide on ethyl 2-(2-ketocyclopentyl)propionate[4] affords the desired olefinic lactone, bp 135–138° (6 mm) (**2**), in 56% yield after saponification of the crude reaction mixture and lactonization by distillation. It seems quite certain that the lactone ring is fused *cis* to the cyclopentane ring because of the ease of lactone formation, in contrast to the difficulty in obtaining such compounds with *trans* ring junctures.[5] Whereas the olefinic lactone is undoubtedly a mixture of epimers at the carbon atom bearing the methyl group[6], the material shows the expected carbonyl absorption (carbon tetrachloride solution) at 1770 cm^{-1}.



2, R = CH_2
3, R = O



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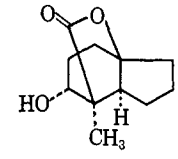

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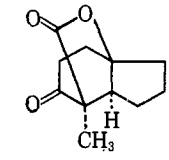

6

Oxidation of the olefinic lactone **2** with osmium tetraoxide–sodium periodate[7] gave the lactone aldehyde **3** after treatment of the crude oxidation product with hydrogen sulfide to remove osmium species. The infrared spectrum (carbon tetrachloride solution) of the lactone aldehyde shows the expected absorption at 2731, 1770, and 1730 cm^{-1}.

Cyclization of the lactone aldehyde **3** with potassium *t*-butoxide in *t*-butyl alcohol afforded a mixture of liquid hydroxy lactones **4** and **5** in 30% yields based on the olefinic lactone **2**. The major hydroxy

(1) The authors gratefully acknowledge financial support from the National Science Foundation (Grant 1266 GP3822) and a Public Health Service career program award (1-K3-NB-28,105) from the National Institute of Neurological Diseases and Blindness.

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(6) The nmr spectrum of the olefinic lactone shows four peaks in the region of τ 8.6–9 indicating two epimeric methyl compounds.
(7) R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

lactone is assigned structure **4** (equatorial hydroxyl) and the minor product is its epimer **5**. These structural assignments are supported by the following observations. The infrared spectra (carbon tetrachloride solution) of both hydroxy lactones show carbonyl absorption at 1770 cm^{-1} and hydroxyl absorption. Their nmr spectra show a sharp peak at τ 8.8 ascribed to the methyl group and complex multiplets in the region of τ 6–7 ascribed to the carbinol proton. Oxidation[8] of the two hydroxy lactones gives the keto lactone **6** which exhibits carbonyl absorption at 1770 and 1720 cm^{-1} (chloroform solution). The 2,4-dinitrophenylhydrazone melts at 218–219°. Exposure of either hydroxy lactone to potassium *t*-butoxide in *t*-butyl alcohol affords a mixture containing about 85% of lactone **4** and 15% of **5**. A similar epimerization is observed for tetrahydrogibberellic acid,[9] and there is little doubt that the more stable hydroxy lactone has the equatorial hydroxyl group.[10]

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(10) Satisfactory combustion analyses were obtained for all new compounds described in this communication.
(11) Alfred P. Sloan Research Fellow.

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Selective Reduction of Steroids by Homogeneous Catalytic Hydrogenation[1]

Sir:

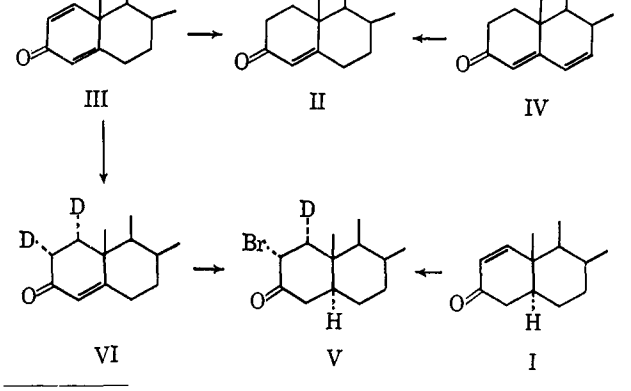
Homogeneous hydrogenation catalysis has recently been introduced by Wilkinson and collaborators[2] for the reduction of aliphatic olefins and acetylenes. Little is as yet known about the scope and limitation of this potentially powerful adjunct to organic chemical methodology, and it is for this reason that we examined the applicability of this technique in the steroid field. The present preliminary report indicates that the method has great promise for selective reductions and should also prove to be of utility in deuterium labeling.

Preparation of 0.005 *M* Catalyst Solution.[3] To a solution of 197 mg (0.75 mmole) of triphenylphosphine in 25 cc of benzene was added an equal volume of ethanol (or methanol) and 48 mg (0.125 mmole) of μ-dichloro-tetraethylenedirhodium.[4] The resulting yellow solution of tris(triphenylphosphine)chlororhodium[5] was filtered through cotton and used directly for the subsequent hydrogenation. The corresponding iodo catalyst (brownish black solution) was prepared by simply adding 1 equiv of sodium iodide to the solution of the chloro complex.

Typical Reduction Procedure. A 100-mg sample of steroid was dissolved in 20–50 cc of 0.005 *M* catalyst solution and stirred at room temperature and atmospheric pressure in a tightly stoppered flask which was first evacuated and filled with hydrogen (or deuterium) several times. After several hours, the solution was evaporated to dryness, and the residue was taken up in a mixture of petroleum ether and methylene chloride and filtered through alumina. Evaporation of the solvent yielded the product.

Results. Unhindered disubstituted olefins such as Δ^1-, Δ^2-, and Δ^3-cholestene were reduced by either the chloro or iodo catalyst to 5α-cholestane in nearly quantitative yield in 1.5–20 hr. More highly substituted olefins such as Δ^4-androstene, Δ^{14}-ergostene, and $\Delta^{8(14)}$-ergostene were recovered during this period of time. More hindered disubstituted olefins seem to react much more sluggishly as indicated in a single experiment with Δ^{11}-5β-pregnene-3,20-dione and the chloro catalyst in benzene–ethanol (1:1) solution (36 hr) which provided 83% of unreacted olefin and 13% of saturated diketone.

Of particular interest is the reduction of α,β-unsaturated ketones by this procedure.[6] In accord with the results on olefins, Δ^1-3-keto 5α-steroids (I) are readily reduced in 6–16 hr, while Δ^4-3-ketones (II) or Δ^5-7-keto 3β-acetates are recovered unchanged.[7] With this information as a background, the selective reduction of dienones was investigated and found to proceed extremely smoothly. Using the chloro catalyst and periods of 16–72 hr, $\Delta^{1,4}$-androstadiene-3,17-dione (III) and $\Delta^{4,6}$-androstadiene-3,17-dione (IV) are converted in 75–85% yield into the Δ^4-3-ketone (II), the remainder of the material being saturated diketone. More careful choice of reduction conditions will probably lead to nearly quantitative yields of Δ^4-3-ketone. This great separation in reactivity of different double bonds toward homogeneous catalytic hydrogenation conditions should be contrasted with the very poor yields of Δ^4-3-ketones, which are generally encountered[8–11] in all selective catalytic hydrogenations of $\Delta^{1,4}$-dien-3-ones (III), and the multiplicity of products that is often generated.



(1) Financial support (Grant No. CA-07195) from the National Institutes of Health of the U. S. Public Health Service is gratefully acknowledged.
(2) J. F. Young, J. A. Osborn, F. H. Jardine, and G. Wilkinson, *Chem. Commun.*, 131 (1965); F. H. Jardine, J. A. Osborn, G. Wilkinson, and J. F. Young, *Chem. Ind.* (London), 560 (1965).
(3) The helpful advice of Professor J. P. Collman of the University of North Carolina is gratefully acknowledged.
(4) R. Cramer, *Inorg. Chem.*, **1**, 722 (1962).
(5) M. A. Bennett and P. A. Longstaff, *Chem. Ind.* (London), 846 (1965).
(6) In the reduction of α,β-unsaturated ketones, a 1:1 ethanol–benzene solution is preferred over 1:1 methanol–benzene because the latter provides the dimethyl ketal of the saturated ketone. For certain synthetic purposes, ketal formation may be advantageous if simultaneous protection of the saturated carbonyl group is required.
(7) After 72-hr exposure to the chloro catalyst, 80% of the enone was still recovered and only 20% of the saturated ketone was formed.
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