can be seen in the concentrated acetone photolysate after 2 and 3 hr.

Steroids. CCCXVII.[1] Photochemical Cycloadducts. III.[2]
Addition of Ethylene and Maleic Anhydride to a Linear Dienone

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Abstract: The photochemical addition of ethylene to 17β-acetoxyandrosta-4,6-dien-3-one (I) gave approximately equal amounts of the $4\beta,5\alpha$- and $4\alpha,5\alpha$-ethylene adducts II and III, and a small amount of the $6\beta,7\beta$ adduct IV. Photochemical addition of maleic anhydride to I produced a mixture of the $4\alpha,5\alpha$, $6\alpha,7\alpha$, and $6\beta,7\beta$ adducts in yields of 15, 19, and 57%, respectively. The 6,7-maleic anhydride adducts were converted *via* the corresponding diacids Vb and VIb to the 6,7-vinylene adducts VIII and IX. A correlation between the maleic anhydride and ethylene additions is described. The structures of the compounds are deduced mainly from their nmr and ORD spectra.

Recently several reports of photochemically induced intermolecular cycloadditions of olefinic compounds to unsaturated carbonyl systems have been published.[4] The method is of considerable utility for the preparation of cyclobutane compounds bearing a wide variety of substituents. In the course of our investigations of the photochemistry of steroids,[2,5] it became of interest to examine the addition of certain olefins to an $\alpha,\beta,\gamma,\delta$-unsaturated ketone. 17β-Acetoxyandrosta-4,6-dien-3-one (I) was chosen as a model unsaturated ketone and ethylene and maleic anhydride as addition substrates. It has been previously reported[6] that dienones of this type will undergo dimerization when irradiated, but the addition of different olefinic compounds has apparently not been studied.

Bubbling a stream of ethylene through an irradiated benzene solution of I, for a period of 6 hr, resulted in a slow cycloaddition to give the *trans*-fused adduct 17β-acetoxy-$4\beta,5\alpha$-ethyleneandrost-6-en-3-one (II) in 7% yield, and the corresponding *cis*-fused adduct, 17β-acetoxy-$4\alpha,5\alpha$-ethyleneandrost-6-en-3-one (III), was isolated in 5% yield. In addition, *ca.* 1% of the 6,7 cycloadduct 17β-acetoxy-$6\beta,7\beta$-ethyleneandrost-4-en-3-one (IV) and *ca.* 30% of recovered starting material were also isolated. The remainder of the material was accounted for by several very polar products whose isolation and characterization were not attempted.

In order to obtain a larger proportion of addition to the γ,δ double bond, we next studied the photochemical addition of maleic anhydride to I, in the expectation that excited maleic anhydride would add preferentially to the more electron-rich 6,7 double bond of the ground-state dienone. Irradiation of an equimolar mixture of I and maleic anhydride under the same conditions as above led to rapid addition with only a trace of starting material being detectable after 40 min. The composition of the resulting mixture of anhydride adducts had to be determined after conversion to the corresponding diesters by mild alkaline hydrolysis followed by diazomethane methylation, since the primary products of addition were too easily hydrolyzed to be chromatographed.

The major product, obtained in 55% yield, was 17β-acetoxy-$6\beta,7\beta$-ethyleneandrost-4-en-3-one-6'-*exo*-7'-*exo*-dicarboxylic acid dimethyl ester (Va). The corresponding $6\alpha,7\alpha$ isomer VIa was isolated in 19% yield, and the product resulting from addition to the 4,5 double bond, 17β-acetoxy-$4\alpha,5\alpha$-ethyleneandrost-6-en-3-one-4'-*exo*-5'-*exo*-dicarboxylic acid dimethyl ester (VII), was obtained in 15% yield, in addition to *ca.* 5% of recovered starting material.

Degradation of the 6,7-anhydride adducts appeared to be a useful route to the epimeric 6,7-vinylene and 6,7-ethylene adducts, as well as providing an opportunity to identify the minor product from photoaddition of ethylene to I, which had not been obtained in large enough amounts or in sufficient purity[7] for conventional structure determination. The diacids Vb and VIb were isolated by preparative tlc of the crude mixture of diacids obtained by mild hydrolysis of the total reaction product[8] from maleic anhydride addition to I. The

(1) Steroids. CCCXVI: L. Cuellar, H. Martinez, and P. Crabbé, *Steroids*, in press.
(2) For part II see P. Sunder-Plassmann, P. H. Nelson, L. Durham, J. A. Edwards, and J. H. Fried, *Tetrahedron Letters*, 653 (1967).
(3) Syntex Postdoctoral Fellow, 1965–1966.
(4) See, for example, E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); R. L. Cargill, J. R. Damewood, and M. M. Cooper, *ibid.*, **88**, 1330 (1966); Y. Yamada, H. Uda, and K. Nakanishi, *Chem. Commun.*, 423 (1966); J. J. McCullough and J. M. Kelly, *J. Amer. Chem. Soc.*, **88**, 5935, (1966).
(5) P. Sunder-Plassmann, J. Zderic, and J. H. Fried, *Tetrahedron Letters*, 3451 (1966).
(6) H. C. Thronsden, G. Carnelli, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2342 (1962); M. B. Rubin, G. E. Hipps, and D. Glover, *J. Org. Chem.*, **29**, 68 (1964).
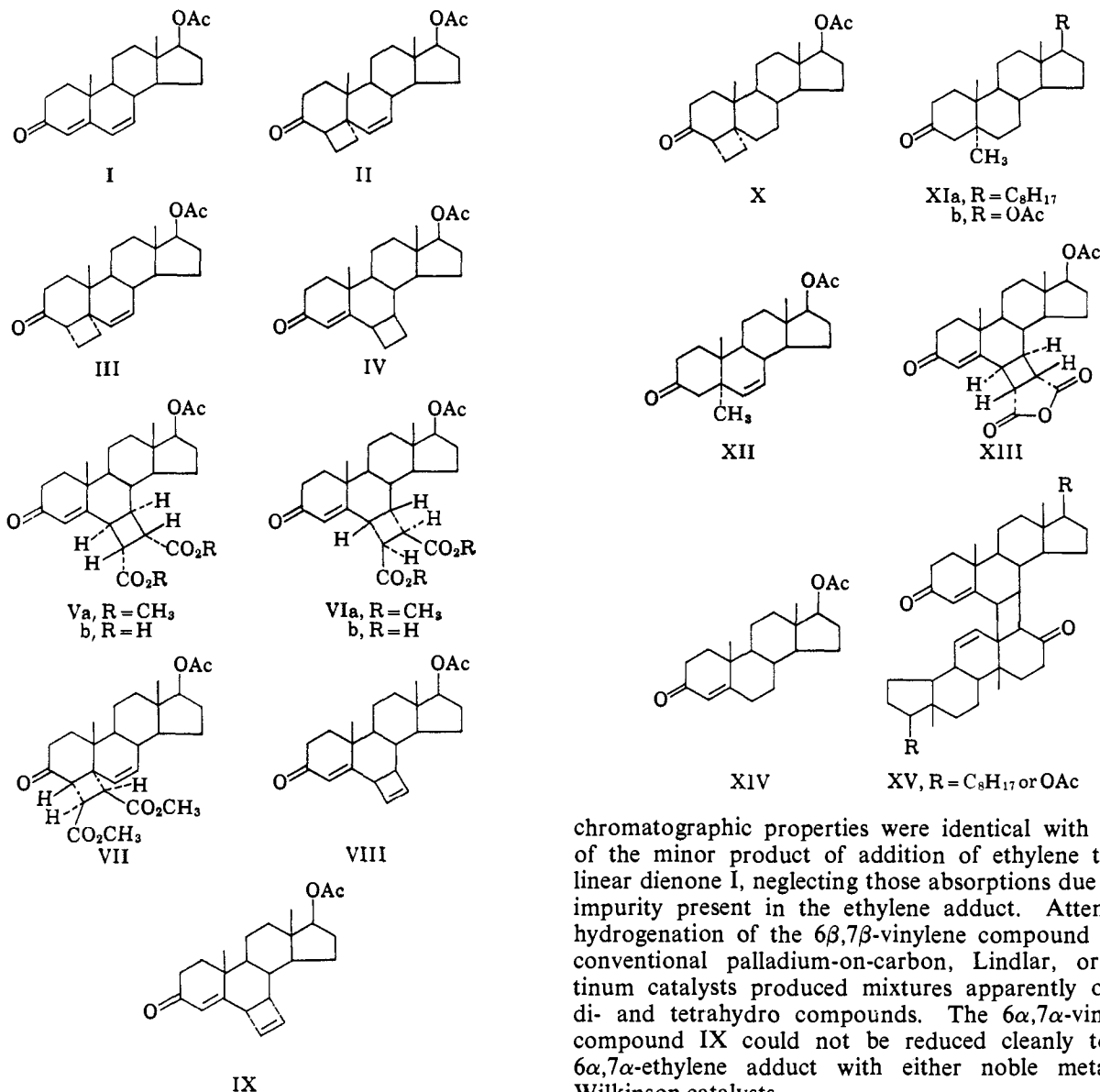
(7) This compound was contaminated with an impurity which could not be removed by recrystallization or chromatography. The nature of the impurity will be discussed later.
(8) The more abundant diacid Va could also be obtained by direct crystallization of the crude hydrolysis mixture, or by hydrolysis of its

I   II

III   IV

Va, R = CH₃ → $Va, R = CH_3$
b, R = H

Va, R = CH₃
b, R = H

VIa, R = CH₃
b, R = H

VII   VIII

IX

X   XIa, R = C₈H₁₇
b, R = OAc

$XIa, R = C_8H_{17}$
$b, R = OAc$

XII   XIII

XIV   XV, R = C_8H_{17} or OAc

separated diacids were each subjected to oxidative decarboxylation by lead tetraacetate in dioxane or tetrahydrofuran at 60–90°,[9] the corresponding 6,7-vinylene compounds VIII and IX being obtained in 30–40% yields. The 6β,7β-vinylene compound VIII was reduced with tristriphenylphosphinerhodium chloride and hydrogen[10] to give compound IV, whose spectral and

anhydride which crystallized directly from the photoaddition mixture in ca. 40% yield.

(9) These solvents were found to give higher yields, a cleaner product, and an easier work-up than those which have been used previously: (a) E. E. van Tamelen and S. P. Pappas, J. Amer. Chem. Soc., 85, 3297 (1963); (b) R. N. McDonald and C. R. Reineke, ibid., 87, 3020 (1965); (c) E. J. Corey and J. Casanova, Jr., ibid., 85, 165 (1963); (d) E. Grovenstein, Jr., D. V. Rao, and J. W. Taylor, ibid., 83, 1705 (1961); (e) C. A. Grob, M. Ohta, and A. Weiss, Angew. Chem., 70, 343 (1958). It was found that the cyclic ethers themselves react with lead tetraacetate to give the corresponding α-acetoxy compounds i and ii which were isolated and characterized by nmr and, in the case of ii,

i   ii

by acid hydrolysis to the known 4-hydroxybutanal. Due to the occurrence of this reaction no excess lead tetraacetate remained after the oxidative decarboxylation, thus greatly simplifying the isolation of the desired product. Compounds i and ii were removed by washing with dilute mineral acid.

chromatographic properties were identical with those of the minor product of addition of ethylene to the linear dienone I, neglecting those absorptions due to an impurity present in the ethylene adduct. Attempted hydrogenation of the 6β,7β-vinylene compound using conventional palladium-on-carbon, Lindlar, or platinum catalysts produced mixtures apparently of the di- and tetrahydro compounds. The 6α,7α-vinylene compound IX could not be reduced cleanly to the 6α,7α-ethylene adduct with either noble metal or Wilkinson catalysts.

The structures of the ethylene addition products were determined by both chemical and physical methods. Compounds II and III were shown to be isomeric 4,5 adducts by their nmr spectra, which showed the resonances of the 6- and 7-vinylic protons, and also by their uv spectra, which had only n–π* carbonyl absorption. The mass spectra of these compounds were identical, presumably due to isomerization in the inlet system, since it was later found that the adduct II could be transformed quantitatively into III either by heating to 230° or by treatment with a catalytic amount of sodium methoxide in methanol at room temperature. These isomerization reactions indicate that the compounds differ in orientation at C_4 and not at C_5. Although thermal epimerization at C_5 could conceivably occur via homolysis of either the C_5–C_5' or C_4–C_5 bonds, base-catalyzed epimerization at C_5 cannot take place. Since the heat-stable adduct III could be catalytically hydrogenated to 17β-acetoxy-4α,5α-ethyleneandrostan-3-one (X) (produced in 78% yield by photochemical addition of ethylene[5] to testosterone

(10) 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).

Table I. Nmr[a] and Uv[b] Spectra of Maleic Anhydride Adducts and Related Compounds

Compound	19-H, ppm	4-H, ppm	4-H half-band width, cps	λ_{max}, mμ	ϵ_{max}
6β,7β-Anhydride XIII	1.41	5.83	2.0	241[d]	20,600
6β,7β-Diacid Vb[c]	1.37	6.43	2.3	247	13,100
6β,7β-Dimethyl ester Va	1.37	5.92	1.8	246	16,500
6β,7β-Vinylene VIII	1.20	5.80	2.5	249	14,200
6β,7β-Ethylene IV	1.41	5.67	2.0	250	14,700
6α,7α-Diacid VIb[e]	1.10	5.72	3.5[e]	246	14,900
6α,7α-Dimethyl ester VIa	1.13	5.80	(doublet, $J_{4,6}$ = 2)	250	11,100
6α,7α-Vinylene IX	1.12	5.77	(doublet, $J_{4,6}$ = 2)	252	13,500

[a] Measured in deuteriochloroform unless otherwise stated. [b] Measured in ethanol unless otherwise stated. [c] In dimethyl-d_6 sulfoxide. [d] In dry dioxane; the dimethyl ester Va had λ_{max} 238 mμ (ϵ 17,100) in this solvent. [e] This half-band width corresponds to a coupling constant ($J_{4,6}$) of approximately 2 cps which was not resolved, probably because of the high viscosity of the dimethyl sulfoxide solution.

acetate), it must be a 4α,5α adduct, and the isomeric compound the 4β,5α-ethylene adduct.

Optical rotatory dispersion (ORD) measurements on the 4α,5α-ethylene adducts III and X support the assignment of α rather than β stereochemistry. Both compounds show a weakly positive curve. The molecular amplitudes, which are smaller than would be expected for a 5α-substituted compound,[11] indicate that ring A is in a boat conformation. In this conformation $C_{4'}$ and $C_{5'}$ lie in a positive octant, their proximity to the 3-carbonyl group evidently just overriding the negative contribution of C_5, which lies in a negative octant. Thus a weakly positive curve is obtained (molecular amplitude a of III is +4 and of X is +26; cf. 5α-methylcholestan-3-one (XIa), a = +73).[11] A much greater amplitude would be expected for these adducts if ring A were in a chair conformation, since carbons 4', 5, 5', 6, and 7 would all lie in a positive octant. A 4β,5β-ethylene adduct would be expected to have a negative Cotton effect of fairly high amplitude since Dreiding models show carbons 4', 5, and 5' to be in a negative octant. The 4β,5α adduct II has a positive Cotton effect with amplitude +265, consistent with a model showing carbons 4', 5, 5', 6, 7, 10, and 19 in a positive octant.

The nmr spectra of the ethylene adducts provide information as to the structures and conformations of these compounds in agreement with the foregoing ORD data.

The 19-H resonances in the 4α,5α-ethylene adducts III and X occur at 0.74 and 0.78 ppm, respectively, compared to calculated values[12] of 1.18 and 1.16 ppm for 17β-acetoxy-5α-methylandrostan-3-one (XIb) and 17β-acetoxy-5α-methylandrost-6-en-3-one (XII), respectively. The relatively large amount of shielding experienced by the 19-H in the adducts is taken to indicate that ring A assumes a boat or a flexible conformation in which the 19-hydrogens are in the shielding zone of the 3-ketone.[13] Examination of Dreiding models supports this conclusion. A model of the extremely strained 4β,5α adduct II indicates a distorted half-boat conformation for ring A in which shielding of the 19-H by the 3-

ketone would not be expected, in accord with the observed position of the 19-H resonance (1.11 ppm) which is only slightly shielded relative to the reference compounds XIb and XII.

The gross structure of the minor product of addition of ethylene to I was deduced from its uv spectrum (λ_{max} 250 mμ (ϵ ca. 10,000)) which indicated a 6,7 adduct, and by its mass spectrum (molecular ion 356 mass units, with a large peak corresponding to loss of C_2H_4). The orientation of addition was not, however, established until the spectra of this compound[14] could be compared with those of authentic IV (see below).

The structures of the maleic anhydride adducts were deduced mainly from their nmr spectra and in particular by the positions of the 19-H resonances and the nature of the 4-H resonances. The relevant data are summarized in Table I, which also summarizes the uv spectra of the adducts and derived compounds.

The relatively low-field positions of the 19-H resonances in the 6β,7β adducts are thought to result from interaction of the quasi-axial 6 and 7 substituents with the 10β-methyl group (a 6β-methyl group produces a downfield shift of 0 08 ppm[12] from the position (1.19 ppm) of the 19-H resonance in testosterone acetate (XIV)). In the 6β,7β-vinylene compound VIII the 19-H is significantly shielded relative to all the other 6β,7β compounds (see Table I). Examination of models shows that in this compound the 10β-methyl group is directly in the shielding zone of the 6,7 double bond.[15]

The 6α,7α compounds, on the other hand, exhibit small upfield shifts relative to the resonance position of the 19-H in testosterone acetate. The observed splitting or broadening of the C_4-H signal in these compounds is also in accord with the assigned 6α,7α stereochemistry, since the measured C_4H-C_6H dihedral angle is larger in these adducts than in the 6β,7β adducts (60° as against 30°) thereby leading to a resolvable coupling in two of the three α adducts.[16]

(11) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1965, pp 103–104.

(12) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, pp 19–24.

(13) J. A. Pople, Proc. Roy. Soc. (London), A239, 541, 550 (1957); L. M. Jackman, "Applications of NMR Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p 124. For use of this effect in conformational analysis see A. D. Cross and I. T. Harrison, J. Amer. Chem. Soc., 85, 3233 (1963); B. B. Dewhurst, D. S. E. Holker, A. Lablache-Combier, M. R. G. Leeming, J. Levisalles, and J. P. Pète, Bull. Soc. Chim. Fr., 3259 (1964).

(14) The identification of this compound was further complicated by the presence of an inseparable impurity whose molecular weight was apparently 2 mass units greater than IV. This contaminant is thought to be the hydroperoxide produced by photoaddition of oxygen to the dienone. This conclusion was supported by the presence of a weak OH band in the infrared spectrum of the impure sample of IV.

(15) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, Tetrahedron, 23, 2357 (1967).

(16) The relationship between allylic coupling constants and the dihedral angle between the relevant C–H bonds has been investigated in some detail. It has generally been found that the coupling constant reaches a maximum when the dihedral angle is 90° (S. Sternhell, Rev. Pure Appl. Chem., 14, 15 (1964)). $J_{4,6}$ in 6-substituted steroidal Δ^4-3-ketones had previously been found to be resolvable only when the 6-hydrogen is in the β (axial) orientation (T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, J. Amer. Chem. Soc., 85, 1699 (1963); D. J. Collins, J. J. Hobbs, and S. Sternhell, Australian J. Chem., 16, 1030 (1963)).

Table II

Protons x–y	J_{xy} for 6β,-7β-diacid Vb	J_{xy} for 6β,-7β-diester Va	Ring B in chair conformation Angle[a] x–y, deg	J_{xy},[b] calcd	Ring B in boat conformation Angle[a] x–y, deg	J_{xy},[b] calcd	J_{xy} for 6β,7β-vinylene VIII	J_{xy} for 6α,7α-vinylene IX
4–6	<1	~1	30[c]		70[c]		~1	2
6–6'	10	10	150	12	90	0	~1	~1
6–7	10	10	25	8	25	8	4	4
7–7'	1	2	110	2	160	14	~1	<0.5
7–8							7	7
6'–7'	10	9	40	6	25	8	<1	<1
6–7'	<1	<1					<1	<1

[a] Measured from Dreiding models to nearest 5°. [b] Calculated to nearest cycle per second.[17,18] [c] This is the angle between the plane of the 4,5 double bond and the C₆ carbon–hydrogen bond.

The spin–spin splitting patterns of the diacid Vb, the diester Va, and the 6,7-vinylene compounds VIII and IX were amenable to a first-order analysis. The coupling constants were confirmed by spin–spin decoupling experiments. In the cases of the diester Va and the diacid Vb it was possible to relate the observed coupling constants to a particular conformation of ring B. Dreiding models indicate that ring B can exist in either a chair or a boat conformation, in which the magnitudes of the corresponding dihedral angles around the cyclobutane ring (particularly the angles C₆H–C₆'H and C₇H–C₇'H) are notably different (see Table II).

It is generally accepted that vicinal coupling constants are minimal when the relevant dihedral angle is near 90°, and maximal near 0 and 180°. It would therefore be expected that the B-ring chair conformer would show a large $J_{6,6'}$ and a small $J_{7,7'}$, whereas the B-ring boat conformer should show a small $J_{6,6'}$ and a large $J_{7,7'}$. The observed coupling constants, $J_{6,6'}$ = 12 cps and $J_{7,7'}$ = 2 cps, clearly indicate the B-ring chair conformation.

It is noteworthy that in the cases of Va and Vb, coupling constants calculated by means of the Williamson and Johnson modification of the Karplus equation,[17] which was empirically derived from a study of 2-substituted 3-keto steroids, are in excellent quantitative agreement with the observed values. This agreement is presumably fortuitous, since it has been demonstrated that both angle strain and the relative orientation of polar substituents[18] have an effect on the magnitudes of coupling constants. The relevant data are summarized in Table II, which also shows the observed J values for the vinylene compounds VIII and IX.

In spite of detailed examination of the nmr spectra of all other adducts, in both deuteriochloroform and benzene-d_6, a complete assignment of the cyclobutane protons was possible only in the case of the 4α,5α-ethylene-4',5'-dicarboxylic acid dimethyl ester adduct VII. The protons at C₄, C₄', and C₅' formed a simple splitting pattern with coupling constants of 4 and 11 cps. By analogy with the 6,7 adducts, in which $J_{6',7'}$ was 10 cps, the 11-cps coupling can be assigned to $J_{4',5'}$, leaving $J_{4,4'}$ = 4 cps.

Within a given series of adducts (i.e., 6α,7α or 6β,7β) the ORD curves of the compounds in Table I show obvious similarities, so that an unknown compound could empirically be assigned the correct stereochemistry, although a detailed analysis is not possible. The

main difference between the two series of adducts is the presence of a positive peak or well-defined shoulder at approximately 270–300 mμ in the 6β,7β adducts. It is of interest to note that the cyclobutane ring causes a significant bathochromic shift in the uv spectra of both series of adducts (see Table I).

Mechanism

The photoreactions described in this paper were conducted in Pyrex apparatus, which excludes all wavelengths below approximately 280 mμ. Thus, transitions occurring at wavelengths below this value need not be considered.

It has been assumed in the following discussion that only one reactant is electronically excited, in view of the short lifetimes of excited species in solution[19] and the consequent low probability of a collision between two excited species.

The proportions of different adducts are summarized in Table III. The most striking feature of these results

Table III. Isomer Ratios in the Photoadditions to I

Addition substrate	Solvent	% 4,5 adducts	% 6,7 adducts	6α,7α/ 6β,7β
Ethylene	Benzene	12	1	
Maleic anhydride	Benzene	15	75	0.33
Maleic anhydride	Dioxane	16	75	0.8

is the predominance of 4,5 addition of ethylene and 6,7 addition of maleic anhydride.

Since ethylene cannot be excited under the reaction conditions used, its photoaddition to the dienone must occur by reaction of an excited dienone molecule with an ethylene molecule in the ground state. It therefore appears that the reactive sites in the excited dienone molecule are at C-4 and C-5.

Addition of maleic anhydride can occur by excitation of either the dienone or the anhydride. If the dienone were the excited component, then by analogy with the ethylene addition a predominance of 4,5 adducts would be expected. Hence, the observation that 6,7 addition was favored over 4,5 addition by a factor of about 5:1 implies that the cycloaddition proceeds by excitation of the maleic anhydride.[20,21] It is not

(17) M. Karplus, J. Chem. Phys., 30, 11 (1959); K. L. Williamson and W. S. Johnson, J. Amer. Chem. Soc., 83, 4623 (1961).
(18) P. Laszlo and P. Schleyer, ibid., 85, 2709 (1963); K. L. Williamson, ibid., 85, 516 (1963); M. Karplus, ibid., 85, 2870 (1963).

(19) See, for example, R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, pp 10–12.
(20) The preferred addition to the more electron-rich 6,7-double bond suggests that the excited maleic anhydride molecule is electrophilic in character.
(21) Benzene and maleic anhydride form a photochemical adduct (H. J. F. Angus and D. Bryce-Smith, Proc. Chem. Soc., 326 (1959);

possible from the available evidence to determine which of the reactants is excited in the formation of the 4,5-maleic anhydride adduct, though it is tempting to ascribe this product to a reaction between the excited dienone and unexcited maleic anhydride by analogy with the observed products of ethylene addition. The observed[6] dimerization of $\Delta^{4,6}$-3-ketones to give a single product XV can be explained by an analogous mechanism, the excited dienone, reactive at positions 4 and 5, adding to the 6,7 double bond of a ground-state dienone.

The preponderance of β-face attack on the 6,7 double bond would, a priori, seem to be at variance with steric hindrance indications. Thus epoxidation[22] and addition of difluorocarbene[23] to $\Delta^{4,6}$-3-ketones give mainly the $6\alpha,7\alpha$ addition products. However, the Dreiding models of the reactants indicate that perpendicular approach of the maleic anhydride molecule on the α side, to form a four-center transition state, is impeded by the 9α-hydrogen. This interference is presumably not so acute when the attacking group is a smaller species such as a peracid or difluorocarbene, especially as reaction in these cases proceeds via the sterically less demanding three-center transition state. The model also shows that the 6,7 double bond is bent slightly downward out of a plane of the steroid molecule, thereby reducing the hindrance to β-face attack usually exerted by the 10β-methyl group and normally observed in substitution reactions at C-6 and C-7.

The larger proportion of $6\beta,7\beta$ to $6\alpha,7\alpha$ products when benzene is used as solvent apparently indicates that the β face is better able to accommodate the larger steric requirement of the benzene–maleic anhydride complex.

Dreiding models of the reactants indicate that in cycloaddition to 4,5 and 6,7 double bonds the maleic anhydride should add such that the anhydride ring is in the exo orientation relative to the steroid molecule. The spectral properties of the products (in particular, the nmr spectra) strongly support this indication.

The formation of the trans-fused $4\beta,5\alpha$-ethylene adduct II has many analogies in the addition of olefins to simple α,β-unsaturated ketones.[4] The initial step in the formation of this adduct is thought to be the addition of the excited enone system to the olefin to form one new carbon–carbon bond. The resulting diradical possesses a large amount of excess energy, some of which can be absorbed in the formation of the highly strained trans-fused system. The possibility that this compound is formed from an excited state of the enone in which the α and β substituents are trans oriented has been suggested by Corey, et al.[4] The photochemical isomerization of cis-cycloheptenone to short-lived trans-cycloheptenone[24] is consistent with this postulate.

This study does not establish conclusively whether or not the cis-fused $4\alpha,5\alpha$ adduct III is a primary reaction product or whether it results from isomerization of the trans-fused adduct. However, as the cis compound is observable by tlc analysis of a sample of the reaction mixture during photoaddition, it seems likely that it is a primary photochemical product.

Dreiding models of the dienone I show no geometrical abnormality; the dienone system is essentially planar, and it therefore seems that such an excited state may be usual in other linear dienones. A useful selectivity of photochemical addition may therefore be obtainable by a suitable choice of addition substrates.

Experimental Section[25]

Irradiation Experiments. A 200-W Hanovia 654-A-36 medium-pressure mercury lamp was used as the source of ultraviolet light. The lamp was enclosed in a specially designed irradiation apparatus (Figure 1).

Efficient stirring was provided by passage of either ethylene or nitrogen through the apparatus. During photoadditions samples of the reaction solution could be removed through the gas outlet. The apparatus was enclosed in aluminum foil during reactions.

Photochemical Addition of Ethylene to 17β-Acetoxyandrosta-4,6-dien-3-one (I). A solution of I (1.0 g) in dry benzene (80 ml) was irradiated for 6 hr while a stream of dry ethylene was passed through the solution. The solvent was removed at room temperature, and the residue chromatographed on preparative tlc plates (0.25 mm, hexane–ethyl acetate, 3:1). In order of increasing polarity, the following compounds were obtained: (a) 17β-acetoxy-$4\alpha,5\alpha$-ethyleneandrost-6-en-3-one (III) [55 mg, 5%, mp 140–142° (ether–hexane); $[\alpha]D$ $-24°$; ORD $[\Phi]_{600}$ $-10°$, $[\Phi]_{350}$ $-95°$, $[\Phi]_{334}$ $-25°$, $[\Phi]_{310}$ $-621°$, $[\Phi]_{280}$ $\pm0°$, $[\Phi]_{246}$ $+14°$, $[\Phi]_{229}$ $+856°$; nmr 0.74 (19-H), 0.83 (18-H), 5.45, 5.97 ppm (6-H, 7-H,[26] AB pattern, $J_{6,7}$ = 9 cps); mass spectrum: m/e 356 (molecular ion) 328, 323, 306, 296, 286, 273, 272, 268, 253. Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.50; H, 8.99. Found: C, 76.67; H, 9.61], (b) 17β-acetoxy-$4\beta,5\alpha$-ethyleneandrost-6-en-3-one (II) [71 mg, 7%, mp 178–180° (ethyl acetate–hexane); $[\alpha]D$ $-71°$; ORD $[\Phi]_{600}$ $-406°$, $[\Phi]_{380}$ $-406°$, $[\Phi]_{350}$ $\pm0°$, $[\Phi]_{314}$ $+7560°$, $[\Phi]_{305}$ $+4660°$ (inflection), $[\Phi]_{300}$ $\pm0°$, $[\Phi]_{286}$ $-13,500°$, $[\Phi]_{256}$ $-18,900°$ (broad shoulder), $[\Phi]_{220}$ $-66,100°$; nmr 0.82 (18-H), 1.11 (19-H), 3.23 (triplet, $J_{4,4'}$ = 8 cps, 4-H), 5.85, 6.08 ppm (AB pattern, $J_{6,7}$ = 9 cps, 6-H and 7-H);[26] mass spectrum identical with that of III above. Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.50; H, 8.99; O, 13.50. Found: C, 77.32; H, 9.12; O, 13.35], (c) impure 17β-acetoxy-$6\beta,7\beta$-ethyleneandrost-4-en-3-one (IV) [9 mg, mp 165–175° (ethyl acetate–hexane); λ_{max} 250 mμ (ϵ ca. 10,000); ν_{max} (Nujol) 3300–3500 (weak), 1735, 1680, 1600 cm^{-1}; nmr 0.83 (imp),[27] 0.87

J. Chem. Soc., 4791 (1960); G. O. Schenck and R. Steinmetz, Tetrahedron Letters, 1, (1960); see also ref 9d) presumably by excitation of an intermediate π complex (W. G. Barb, Trans. Faraday Soc., 49, 143 (1953); L. J. Andrews and R. M. Keefer, J. Am. Chem. Soc., 75, 3776 (1953)). The production of this adduct would not, however, be expected under the conditions of the present experiments, as prolonged irradiation in quartz apparatus at 60° is necessary for significant reaction to occur.

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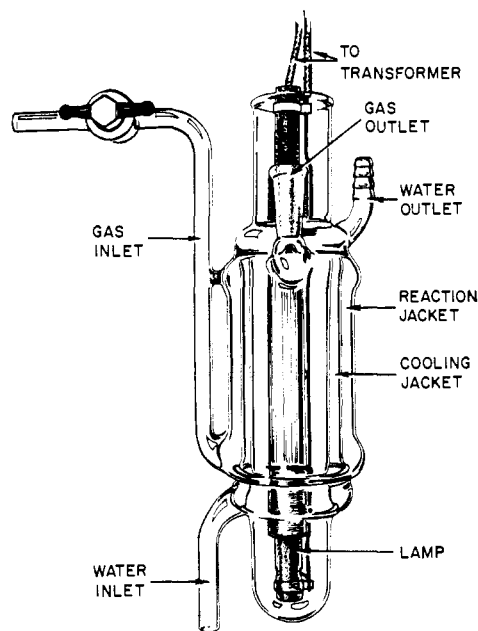(24) E. J. Corey, M. Tada, R. LeMaheiu, and L. Tibit, J. Amer. Chem. Soc., 87, 2052 (1965).

Figure 1.

(18-H), 1.08 (imp), 1.41 (19-H), 5.53 (imp), 5.67 (4-H), 5.88, 6.13 (imp); mass spectrum: m/e 360 (? molecular ion of impurity) 356 (molecular ion), 328, 316 (imp), 298 (imp), 286, 284, 268, 253].

Conversion of 4β,5α-Ethylene Adduct II into the 4α,5α Adduct III. (a) Thermal Isomerization. 17β-Acetoxy-4β,5α-ethylenandrost-6-6-en-3-one (10 mg) was heated to 230° under nitrogen. The progress of the reaction was followed by tlc. After 10 min, ~50% conversion to III had occurred; after 30 min, the reaction was complete. The pale brown product was recrystallized from ethyl acetate–hexane to give a compound identical (melting point, mixture melting point, tlc, ir) with III.

(b) Base-Catalyzed Isomerization. The trans-fused adduct II (10 mg) was dissolved in methanol (3 ml) and added to a methanol solution (1 ml) in which a small (ca. 0.1 mg) piece of sodium had been dissolved. The solution was stirred under nitrogen for 15 min, and then poured into water. The product was extracted with ethyl acetate, and after isolation was recrystallized from ethyl acetate–hexane. The resulting compound was found to be identical (melting point, mixture melting point, tlc, ir) with the authentic cis-fused adduct III.

Photochemical Addition of Ethylene to 17β-Acetoxyandrost-4-en-3-one (XIV). Testosterone acetate (2.0 g) in dry distilled benzene (70 ml) was irradiated while passing dry ethylene through the solution. After 4 hr, tlc showed only a trace of starting material to remain. The solvent was removed at room temperature, and the resulting solid was recrystallized from hexane–methylene chloride to give 17β-acetoxy-4α,5α-ethyleneandrostan-3-one (X) [1.44 g, 78%, mp 197–203° dec; [α]D +62°; ORD [Φ]$_{600}$ +209°, [Φ]$_{343}$ +1190°, [Φ]$_{318}$ +2380°, [Φ]$_{313}$ +2230°, [Φ]$_{303}$ +2300°, [Φ]$_{300}$ +1670° (inflection), [Φ]$_{282}$ ±0°, [Φ]$_{274}$ −242°, [Φ]$_{264}$ ±0°, [Φ]$_{218}$ +3450°; nmr 0.78 ppm (18-H and 19-H). Anal. Calcd for C$_{23}$H$_{34}$O$_3$: C, 77.03; H, 9.51; O, 13.66. Found: C, 77.00; H, 9.49; O, 13.40].

Hydrogenation of 17β-Acetoxy-4α,5α-ethyleneandrost-6-en-3-one (III). A 16-mg sample of the above compound was reduced using prehydrogenated 10% palladium on carbon with ethanol as solvent, in a microhydrogenation apparatus[28] until 1 equiv of hydrogen had been absorbed. The catalyst was filtered off using Celite, and the product was recrystallized from methanol to give a compound identical (melting point, mixture melting point, tlc, ir, nmr) with 17β-acetoxy-4α,5α-ethyleneandrostan-3-one (X).

Photoaddition of Maleic Anhydride to 17β-Acetoxyandrosta-4,6-dien-3-one in Benzene. A solution of the dienone (1.05 g, 3.3 mM) and maleic anhydride (305 mg, 3.3 mM) in dry benzene (65 ml) was irradiated for 30 min. After removal of the benzene the resulting mixture of adducts was treated in several ways according to the purpose of the experiment.

(1) Conversion into Dimethyl Esters to Determine Composition of Product. The mixture (1.4 g) was refluxed for 1 hr in a mixture of methanol (50 ml) and dioxane (30 ml). Removal of the solvents then gave a mixture of acid methyl esters, which was dissolved in ethyl acetate and treated with an excess of ethereal diazomethane. The dimethyl esters were separated by preparative tlc (0.25 mm thickness, ethyl acetate–hexane, 1:1) to give, in order of increasing polarity, the following compounds: (a) recovered starting material (98 mg, 8%), (b) 17β-acetoxy-4α,5α-ethyleneandrost-6-en-3-one-4'-exo-5'exo-dicarboxylic acid dimethyl ester (VII) [188 mg, 15%, mp 215–216° (ether–hexane); [α]D +91°; ORD [Φ]$_{600}$ +437°, [Φ]$_{348}$ +1218°, [Φ]$_{324}$ +600°, [Φ]$_{300}$ +3640°, [Φ]$_{250}$ +11,800°, [Φ]$_{230}$ +22,800°, [Φ]$_{213}$ ±0°, [Φ]$_{212}$ −4540°; nmr 0.79 (19-H), 0.83 (18-H), 3.00 (two doublets,[29] 4'-H), 3.23 (doublet, 5'-H), 3.60, 3.75 (two methoxyl groups), 3.93 (doublet, 4-H), 5.53, 6.04 ppm (AB pattern, 6-H and 7-H;[28] $J_{6,7}$ = 10 cps, $J_{6,8}$, $J_{7,8}$ = 2.0, 2.5 cps). Anal. Calcd for C$_{27}$H$_{36}$O$_7$: C, 68.62; H, 7.62; O, 23.73. Found: C, 68.92; H, 7.71; O, 23.30], (c) 17β-acetoxy-6α,7α-ethyleneandrost-4-en-3-one-6'-exo-7'-exo-dicarboxylic acid dimethyl ester (VIa) [250 mg, 19%, mp 158–159° (ethyl acetate–hexane); [α]D +85°; ORD [Φ]$_{600}$ +420°, [Φ]$_{450}$ +734°, [Φ]$_{390}$ +893°, [Φ]$_{360}$ +514° (inflection), [Φ]$_{356}$ +318°, [Φ]$_{340}$ +1370°, [Φ]$_{280}$ +6930°, [Φ]$_{228}$ +31,500°, [Φ]$_{216}$ ±0°, [Φ]$_{214}$ −15,700°; nmr 0.81 (18-H), 1.12 (19-H), 3.05–3.55 (multiple resonance, 6-H, 6'-H and 7'-H), 3.63, 3.69 (two methoxyl groups), 5.78 ppm (doublet,[29] 4-H). Anal. Calcd for C$_{27}$H$_{36}$O$_7$: C, 68.62; H, 7.62; O, 23.73. Found: C, 68.58; H, 7.55; O, 23.93], (d) 17β-acetoxy-6β,7β-ethyleneandrost-4-en-3-one-6'-exo-7'-exo-dicarboxylic acid dimethyl ester (Va) [750 mg, 57%; needles from ether–hexane change to prisms, mp 143–145°; prisms from ethyl acetate–hexane, 185–186°;[30] [α]D +51°; ORD [Φ]$_{600}$ +204°, [Φ]$_{451}$ +610°, [Φ]$_{381}$ +2640°, [Φ]$_{368}$ +2270° (shoulder), [Φ]$_{351}$ ±0°, [Φ]$_{326}$ −2400°, [Φ]$_{286}$ −1250°, [Φ]$_{266}$ −2560°, [Φ]$_{250}$ ±0°, [Φ]$_{239}$ +13,500°, [Φ]$_{227}$ +17,900°, [Φ]$_{215}$ ±0°, [Φ]$_{212}$ −1635°; nmr 0.87 (18-H), 1.39 (19-H), 3.06 (two doublets, 7'-H), 3.52 (two doublets, 6'-H), 3.68 and 3.71 (two methoxyl groups), 3.78 (two doublets, 6-H[29]), 5.92 ppm (4-H). Anal. Calcd for C$_{27}$H$_{36}$O$_7$: C, 68.62; H, 7.62; O, 23.73. Found: C, 68.78; H, 7.74; O, 23.71].

(2) Isolation of 6β,7β-Anhydride XIII and 6β,7β-Diacid Vb. The major product of the photoaddition, 17β-acetoxy-6β,7β-ethylene-androst-4-en-3-one-6'-exo-7'-exo-dicarboxylic anhydride (XIII), was isolated by direct crystallization of the crude reaction mixture from dry benzene. The isolated anhydride was recrystallized from dry benzene [yield ca. 40%, mp 280–290°; [α]D +4°; ORD [Φ]$_{600}$ +15°, [Φ]$_{450}$ +450°, [Φ]$_{385}$ +1890°, Φ]$_{371}$ +1715° (shoulder), [Φ]$_{356}$ ±0°, [Φ]$_{327}$ −2740°, [Φ]$_{281}$ ±0°, [Φ]$_{254}$ +16,500°, [Φ]$_{251}$ ±0°, [Φ]$_{250}$ −9290°, [Φ]$_{241}$ −45,400°, [Φ]$_{230}$ ±0°, [Φ]$_{221}$ +44,200°, [Φ]$_{210}$ +23,600°; ν_{max} (Nujol) 1850, 1770, 1720, 1660, 1600 cm^{-1}; nmr 0.88 (18-H), 1.41 (19-H), 3.1–3.7 (complex absorption, 6-H, 6'-H, 7'-H), 5.84 ppm (4-H). Anal. Calcd for C$_{25}$H$_{30}$O$_6$: C, 70.41; H, 7.04; O, 22.55. Found: C, 70.61; H 7.27; O, 22.35].

This anhydride (0.5 g) was hydrolyzed to the corresponding diacid by stirring at room temperature for 3 hr in dioxane (30 ml) containing 1 ml of 3% aqueous sodium bicarbonate. The solution was then poured into dilute hydrochloric acid and the product salted out and extracted with ethyl acetate. The isolated diacid was dissolved in the minimum amount of hot dioxane and the solution diluted with ether, whereupon 17β-acetoxy-6β,7β-ethylene-androst-4-en-3-one-6'-exo-7'-exo-dicarboxylic acid (Vb) crystallized out [mp 265–270°; [α]D +50°; ORD [Φ]$_{600}$ +222°, [Φ]$_{450}$ +605°, [Φ]$_{381}$ +2620°, [Φ]$_{367}$ +2240° (shoulder), [Φ]$_{352}$ ±0°, [Φ]$_{324}$ −3010°, [Φ]$_{288}$ −2280°, [Φ]$_{264}$ −5150°, [Φ]$_{257}$ −1620°, [Φ]$_{245}$ ±0°, [Φ]$_{237}$ +15,700°, [Φ]$_{234}$ +13,600°, [Φ]$_{2-8}$ +19,600°, [Φ]$_{216}$ ±0°, [Φ]$_{212}$ −7680°; nmr (dimethyl-d_6 sulfoxide), 0.82 (18-H), 1.32 (19-H), 2.96 (two doublets,[29] 7'-H), 3.47 (two doublets, 6'-H), 3.65 (two doublets, 6-H), and 5.71 ppm (4-H). Anal. Calcd for C$_{25}$H$_{30}$O$_6$: C, 70.41; H, 7.04; O, 22.55. Found: C, 70.61; H, 7.27; O, 22.35]. This diacid can also be obtained in ca. 40% yield by direct crystallization of the mixture of diacids obtained by subjecting the crude photoaddition mixture to the hydrolysis described above. The mother liquors from this crystallization were chromatographed (0.25-mm tlc plates, 99% ether, 1% formic acid) to give additional quantities of the diacid Vb and also ca. 15% of 17β-acetoxy-6α,7α-ethyleneandrost-4-en-3-one-6'-exo-7'-

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(29) Further details of the nmr spectrum of this compound are to be found in the text.

(30) The possibility that the dimorphism exhibited by this compound was due to a chemical reaction (e.g., isomerization) was excluded by the observation that the nmr spectra of the two crystalline forms were identical.

exo-dicarboxylic acid (VIb) which was recrystallized from ethyl acetate–ether [mp 195–197°; [α]D +60°; ORD [Φ]₆₀₀ +186°, [Φ]₃₈₆ +700°, [Φ]₃₇₀ +339°, [Φ]₃₆₃ +443°, [Φ]₃₅₇ ±0°, [Φ]₃₅₄ −41°, [Φ]₃₅₃ ±0°, [Φ]₃₄₆ +790°, [Φ]₃₄₂ +690°, [Φ]₂₅₀ +13,500°, [Φ]₂₄₈ +11,200°, [Φ]₂₂₇ +27,400°, [Φ]₂₁₆ ±0°, [Φ]₂₁₂ −14,800°; ν_max(KBr) 3600–2400, 1735, 1640 cm⁻¹; nmr 0.79 (18-H), 1.09 (19-H), 2.9–3.65 (multiple resonance, 6′-H, 7′-H), 5.72 ppm (broad singlet,²⁹ 4-H). *Anal.* Calcd for C₂₅H₃₂O₇: C, 67.55; H, 7.21; O, 25.22. Found: C, 67.62; H, 8.08; O, 25.21].

Photoaddition of Maleic Anhydride and I in Dioxane. The dienone (1.0 g) and maleic anhydride (305 mg) were dissolved in dry dioxane (50 ml) and irradiated for 40 min. Aqueous sodium bicarbonate (3%, 5 ml) was added to the solution, and the resulting mixture was stirred at room temperature for 3 hr. The solution was then acidified, and most of the dioxane was removed at the pump. Water and ethyl acetate were added, and the separated organic layer was dried and treated with excess ethereal diazomethane. An aliquot of the product was chromatographed as described in 1 above to give I (6%), VII (16%), VIa (33%), Va (42%), and 4% of a noncrystalline highly polar compound.

Oxidative Decarboxylation of Diacids Vb and VIb. The 6β,7β-diacid Vb (1.0 g) was dissolved in dry dioxane (60 ml), and finely powdered vacuum-dried lead tetraacetate (10 g) was added. The reaction mixture was heated to 80–90° and stirred vigorously under nitrogen for 90 min, by which time a drop of the solution when added to water did not produce a brown precipitate, indicating that all the lead tetraacetate had been consumed. Water and ethyl acetate were added and the separated organic layer was washed (2 N hydrochloric acid and water), dried, and evaporated. The semicrystalline residue (650 mg) was chromatographed (1.3-mm tlc plate, hexane–ethyl acetate, 2:1) to give 17β-acetoxy-6β,7β-

vinyleneandrost-4-en-3-one (VIII) [290 mg, 36%; mp 112–115° dec (ether–hexane); [α]D −61°; ORD [Φ]₆₀₀ −177°, [Φ]₃₉₄ ±0°, [Φ]₃₇₈ +872°, [Φ]₃₅₈ ±0°, [Φ]₃₂₀ −6250°, [Φ]₂₉₃ −8470° (shoulder), [Φ]₂₈₀ −29,400°, [Φ]₂₄₂ ±0°, [Φ]₂₂₇ +56,000°, [Φ]₂₁₁ +44,300°; nmr 0.85 (18-H), 1.22 (19-H), 2.74 (two doublets,²⁹ 7-H), 3.68 (doublet, 6-H), 5.78 (4-H), 6.1 ppm (narrow multiplet, 6′-H, 7′-H). *Anal.* Calcd for C₂₃H₃₀O₃: C, 77.95; H, 8.47; O, 13.56. Found: C, 77.37; H, 8.66; O, 13.93].

The 6α,7α-diacid VIb was decarboxylated in the same manner to give a 38% yield of 17β-acetoxy-6α,7α-vinyleneandrost-4-en-3-one (IX) [mp 138–139° (ether–hexane); [α]D +73°; ORD [Φ]₆₀₀ +180°, [Φ]₄₄₅ +558°, [Φ]₃₈₂ +1280°, [Φ]₃₅₄ +256°, [Φ]₂₉₄ +788°, [Φ]₂₈₀ +13,700°, [Φ]₂₅₇ +30,400°, [Φ]₂₄₂ ±0°, [Φ]₂₁₁ −55,900°; nmr 0.85 (18-H), 1.11 (19-H), 3.20 (two doublets,²⁹ 7-H), 3.67 (two doublets, 6-H), 5.74 (doublet, 4-H), 6.00 ppm (narrow multiplet, 6′-H and 7′-H). *Anal.* Calcd for C₂₃H₃₀O₃: C, 77.95; H, 8.47. Found: C, 77.24; H, 8.46].

Reduction of 17β-Acetoxy-6β,7β-vinyleneandrost-4-en-3-one (VIII). Tristriphenylphosphinerhodium chloride¹⁰ (150 mg) was added to ethyl acetate (5 ml) and benzene (5 ml) and the mixture shaken in a hydrogen atmosphere for 15 min. The 6β,7β-vinylene compound VIII (60 mg) was added, and the shaking continued for 30 min. The solution was filtered and the filtrate evaporated. The residue was chromatographed (0.25-mm tlc plates, hexane–ethyl acetate, 2:1) to give starting material (27 mg) and 17β-acetoxy-6β,7β-ethyleneandrost-4-en-3-one [25 mg, 42%, mp 175–177° (ether–hexane); [α]D +2°; ORD [Φ]₆₀₀ ±0°, [Φ]₄₅₀ +133°, [Φ]₃₇₇ +187°, [Φ]₃₆₇ +123°, [Φ]₃₅₉ +123° (shoulder), [Φ]₃₅₄ ±0°, [Φ]₃₁₀ −4150°, [Φ]₂₄₂ ±0°, [Φ]₂₂₃ +23,400°, [Φ]₂₀₆ +12,200°; nmr 0.88 (18-H), 1.41 (19-H), 5.67 ppm (4-H); mass spectrum *m/e* 356 (molecular ion) 328].

Alkaline Reactions of Glucose 6-Phosphate

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Abstract: Glucose 6-phosphate in aqueous alkaline solutions, above pH 7 and up to 5 N sodium hydroxide, undergoes a series of consecutive and parallel reactions. The first step seems to involve an equilibrium of the dianion of the substrate with its conjugate base, which may be the 1,2-enediol. This in part rearranges irreversibly to the relatively stable 6-phosphoglucometasaccharinic acid, and in part undergoes reversible epimerization to fructose 6-phosphate. Fructose 6-phosphate splits by a reversed aldol condensation to glyceraldehyde 3-phosphate (and presumably dihydroxyacetone), which is hydrolyzed rapidly to lactic acid and orthophosphate. All the above phosphate esters, as well as lactic acid, were identified by paper chromatography and electrophoresis. The rate of disappearance of glucose 6-phosphate in alkaline media, measured by glucose 6-phosphate dehydrogenase, follows first-order kinetics. On the other hand, the rate of release of orthophosphate does not obey first-order kinetics. In the pH range 8.7–9.7, the observed first-order rate constant for the disappearance of glucose 6-phosphate is linearly related to the OH⁻ concentration. The bimolecular rate constant at 100.0° is 29.1 ± 0.7 l. mol⁻¹ sec⁻¹. But in 1–5 M sodium hydroxide, the increase in rate levels off, possibly due to rapid conversion of the substrate into the 1,2-enediolate of glucose 6-phosphate. The alkaline reactions of glucose 6-phosphate are not a hydrolysis, because no glucose is formed. The partial similarity between the pathways for alkaline degradation of glucose 6-phosphate and the anaerobic metabolism of carbohydrate in muscle and in yeast is noted.

In contrast to sugar phosphates in which the reducing group is protected, sugar phosphates having a free aldehyde or ketonic group are labile to alkali. Thus, glucose 1-phosphate and ribose 1-phosphate are stable in alkali, while glucose 6-phosphate and ribose 5-phosphate undergo rapid degradation.¹ It has been proposed that an enediol is involved as an intermediate in the degradation of the alkali-labile sugar phosphates.²

However, relatively little is known about the mechanism of these reactions, and several pieces of contradictory data appear in the literature. For instance, fructose 1,6-diphosphate is reported to liberate orthophosphate quantitatively in 0.2 M alkali at 100°,¹ᵇ but a recent investigation has shown that only part of the orthophosphate is released and that alkali-resistant 6-phosphoglucosaccharinic acid is also formed.³ Also, the hy-

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