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The Preparation of $\Delta^{7,9(11)}$-*allo*-Steroids by the Action of Mercuric Acetate on Δ^{7}-*allo*-Steroids

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The preparation of a number of $\Delta^{7,9(11)}$-*allo*-steroids from Δ^{7}-*allo*-steroids by the action of mercuric acetate is described. A mechanism for the action of mercuric acetate on Δ^{7}-*allo*-steroids is proposed.

In the early phase of research on the synthesis of cortisone from ergosterol, diosgenin and stigmasterol,[1] the prerequisite $\Delta^{7,9(11)}$-*allo*-steroids were conveniently prepared by the action of mercuric acetate on Δ^{7}-*allo*-steroids using a modification of the original procedure for the conversion of $\Delta^{7,22}$-ergostadiene-3β-ol acetate (I) to $\Delta^{7,9(11),22}$-ergostatriene-3β-ol acetate (II).[2] In this communication the details of this improved process are discussed, together with information of interest to the mechanism of the mercuric acetate dehydrogenation of Δ^{7}-*allo*-steroids.

Windaus and his co-workers[2] assumed that two moles of mercuric acetate reacted with one mole of I to yield an equivalent amount of mercurous acetate and II. Repetition of their original experiment, in which I was refluxed with mercuric acetate in alcohol together with a small amount of acetic acid, led to the formation of II in poor yield, although mercurous acetate was formed in considerable quantity. Some improvement in the yield of II was effected by carrying out the dehydrogenation of I in chloroform–acetic acid at room temperature but further study indicated that factors other than temperature and solvent medium were equally important.

A better understanding of the variables involved in the mercuric acetate conversion of I to II (and the conversion of Δ^{7}-*allo*-steroids to $\Delta^{7,9(11)}$-*allo*-steroids in general) was achieved through the correlation of rough kinetic data with typical preparative experiments. The desired quantitative data were readily secured in view of the ease of analysis for mercuric acetate, mercurous acetate and one of the organic components, II.[3] In Table I are described several kinetic experiments which are of interest to the subsequent discussion.

On mixing a solution of mercuric acetate in acetic acid with a solution of I in chloroform, a homogeneous mixture is obtained from which mercurous acetate is soon deposited.[4] In a run under typical preparative conditions (run A, Table I), the mercury balance can be accounted for in terms of mercurous acetate and unreacted mercuric acetate in the early phase of the reaction (up to three hours).

TABLE I

REACTION OF MERCURIC ACETATE AND $\Delta^{7,22}$-ERGOSTADIEN-3β-OL ACETATE (I)

Run A: initial concentration, 0.153 *M* $Hg(OAc)_2$ and 0.064 *M* $\Delta^{7,22}$-diene (I) in 41% HOAc–59% $CHCl_3$ (room temperature)

Time, hr.	HgOAc[a], mole	$Hg(OAc)_2$, mole	Total Hg, mole[b]	$\Delta^{7,9(11),22}$-Triene (II), mole
0.5	0.057	0.095	0.152	0.009
1.5	.096	.056	.152	.017
3.5	.121	.031	.152	.021
7.5	.136	.013	.149	.026
15.5	.144	.003	.147	.032
31.5	.147	.001	.148	.040

Run B: initial concentration, 0.194 *M* $Hg(OAc)_2$ and 0.033 *M* $\Delta^{7,22}$ diene (I) in 20% $CHCl_3$–80% HOAc (room temperature)

0.5	0.043	0.151	0.194	0.007
1.0	.060	.134	.194	.010
3.0	.079	.113	.192	.013
6.0	.095	.093	.188	.014
24.0	.137	.040	.177	.016

Run C: initial concentration, 0.066 *M* $Hg(OAc)_2$ and 0.129 *M* $\Delta^{7,22}$-diene (I) in 41% $CHCl_3$–59% HOAc (room temperature)

0.5	0.053	0.013	0.066	0.010
1.0	.063	.003	.066	.012
2.5	.066	.000	.066	.013
8.0	.066	.000	.066	.014
22.0	.066	.000	.066	.017

Run D: initial concentration, 0.127 *M* $Hg(OAc)_2$ and 0.063 *M* $\Delta^{7,22}$-diene (I) in 44% HOAc–56% $CHCl_3$ (0°)[c]

7.75	0.039	0.089	0.128	0.008
24	.086	.039	.125	.017
48	.110	.017	.127	.021
140	.123	.002	.125	.028
196	.125	.001	.126	.033

[a] HgOAc = 2 × amount of $Hg_2(OAc)_2$ in moles. [b] Total Hg = HgOAc + $Hg(OAc)_2$ in moles. [c] On mixing solutions at 0°, partial precipitation of mercuric acetate occurred.

Later in the reaction (after the first three hours), a small but significant deficit in the mercury balance is observed which amounts to *ca.* 2–3%. The residual mercury is associated with the steroid reactants and can be found in the chloroform-soluble fraction. On increasing the ratio of mercuric acetate to I (run B, Table I) a greater deficit is observed. Thus after 24 hours in run B, 8% of the total mercury is associated with the steroid, whereas 92% of the original mercury is present either as mercurous acetate or unreacted mercuric acetate. On the other hand by maintaining an excess of I

(1) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951); J. M. Chemerda, E. M. Chamberlin, E. Wilson and M. Tishler, *ibid.*, **73**, 4052 (1951).

(2) A. Windaus, K. Dithmar, H. Mürke and F. Suckfüll, *Ann.*, **488**, 91 (1931).

(3) The analysis of these reaction mixtures and the methods employed for the kinetic studies are described in detail in the experimental section.

(4) In all of the experiments at room temperature, the insoluble phase is pure mercurous acetate which was identified by virtue of its behavior with dilute hydrochloric acid and by a C–H analysis.

relative to mercuric acetate, all of the mercuric acetate is converted to mercurous acetate (run C, Table I).

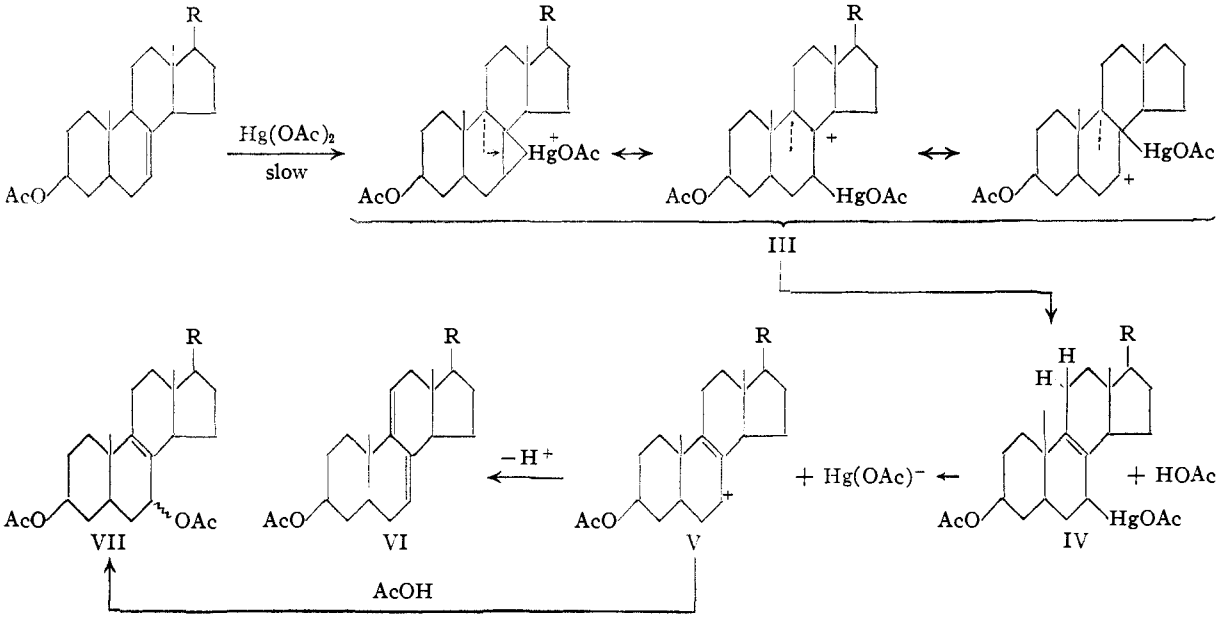
The deficit in mercury balance is apparently of little significance to the intrinsic conversion of I to II. The behavior of II with mercuric acetate under similar conditions suggested a rational explanation for the observed deficit. Thus, the $\Delta^{7,9(11),22}$-triene (II) reacts with mercuric acetate (more slowly than I) to yield mercurous acetate and a complex steroidal reaction product which contains in part a mercurated steroid derivative. The stoichiometry of the reaction of II with mercuric acetate is complex. Upon utilization of two moles of mercuric acetate, 77% is converted to mercurous acetate, about 20% is associated with the steroid and some II is still unreacted judging from the ultraviolet absorption spectrum. Complete elimination of II is effected by the utilization of four moles of mercuric acetate in which case 71% is converted to mercurous acetate, 14% is present as mercuric acetate and the remaining mercury (15%) is present in the ill-defined steroid reaction product. The nature of the steroid reaction product was not studied further except to verify the presence of mercury. Confirmation of the role of II with regard to the mercury deficit is provided by the results of run C, Table I in which mercuric acetate is quantitatively converted to mercurous acetate by virtue of the high relative concentration of I at all times. These experiments indicate that a mercurated complex of I is present at too low a concentration to be measured and that, if formed, it possesses a transitory existence.

In all of the instances in Table I, the formation of mercurous acetate is likewise accompanied by the appearance of the $\Delta^{7,9(11),22}$-triene (II). However, even in the early phase (up to three hours) of run A (Table I) or in the case of the relatively uncomplicated conditions of run C the amount of II is not equivalent to the amount of mercurous acetate formed or the amount of mercuric acetate utilized. Moreover, even after the consumption of sufficient mercuric acetate for complete conversion of I to II (three hours), only 30–50% of the expected II is present. On standing and without further significant utilization of mercuric acetate (*cf.* especially run C, Table I), more of the $\Delta^{7,9(11),22}$-triene (II) is formed although the rate is significantly less than in the early phase of the reaction. Thus it is apparent that the $\Delta^{7,9(11),22}$-triene (II) arises not only by the direct action of mercuric acetate on I but by the decomposition of a non-mercurated transformation product of I as well.

Preparative experiments confirmed this supposition and likewise suggested a method for the determination of the stoichiometry of the reaction of I and mercuric acetate. It had been observed that despite the utilization of similar conditions for the mercuric acetate dehydrogenation of I (concentration, solvent media and reaction periods), the yield of II varied erratically. Correlation of these results with the method of isolation revealed that higher yields always resulted whenever the mercury-free reaction liquors were subject to temperatures of 70–100° for several hours during the work-up procedure. Examination of aliquots from runs A, B and C (Table I), for which accurate data on mercury balance and initial concentration of II were available, confirmed the fact that additional II could be obtained without the agency of mercuric acetate. In each instance, the concentration of II was increased from its initial value at room temperature by refluxing the mercury-free aliquot in chloroform–acetic acid. Thus in the case of run C, the 22-hour aliquot originally contained 1.7×10^{-2} mole of II, whereas after a reflux period, the amount of II was increased to 3.0×10^{-2} mole. Hence, in the absence of the side-reaction of II with mercuric acetate, the primary reaction at room temperature involves the utilization of two moles of mercuric acetate by one mole of I to yield one mole of mercurous acetate and an equivalent amount of a mixture composed of II and a non-mercurated precursor of II.

Further characterization of the thermally labile non-mercurated precursor of II proved difficult but was aided considerably by ancillary data arising from the study of the reaction of mercuric acetate with methyl Δ^{7}-3-acetoxybisnor*allo*cholenate, Δ^{7}-*allo*pregnen-3β-ol-20-one acetate and Δ^{7}-5α,22a-spirosten-3β-ol acetate. In each of the instances above, despite the absence of kinetic studies, the reaction of mercuric acetate is undoubtedly mechanistically identical to the conversion of I to II judging from the yield of mercurous acetate and effect of temperature on the yield of $\Delta^{7,9(11)}$-*allo*-steroid. In the case of the Δ^{7}-*allo*-steroids, reaction with mercuric acetate in chloroform–acetic acid at room temperature followed by isolation of the steroid reaction product under mild conditions leads to the expected $\Delta^{7,9(11)}$-*allo*-steroids and a new series of derivatives which possess end absorption in the ultraviolet above 220 mμ. Ultimate analyses of these non-absorbing compounds correspond to molecular formulas derived from the $\Delta^{7,9(11)}$-*allo*-steroids plus the elements of acetic acid. The instability of these derivatives was discerned by their behavior on melting. In one instance, encountered in the preparation of $\Delta^{7,9(11)}$-5α,22a-spirostadien-3β-ol acetate, acetic acid was obtained in quantitative yield upon fusion, together with an equivalent amount of the $\Delta^{7,9(11)}$-*allo*-steroid. Upon heating the mercury-free reaction liquor prior to isolation, none of these derivatives is obtained and a correspondingly greater yield of $\Delta^{7,9(11)}$-*allo*-steroid results. Hence these thermally labile crystalline by-products are evidently typical non-mercurated $\Delta^{7,9(11)}$-*allo*-steroid precursors similar to the substance observed in the transformation of I to II.

Further study of one of these derivatives (encountered in the preparation of $\Delta^{7,9(11)}$-*allo*-pregnadien-3β-ol-20-one acetate) led to the characterization of these substances as disecondary diol diacetates. In the specific instance mentioned, the pregnene derivative is hydrolyzed to a diol which is reacetylated to the parent ester by pyridine–acetic anhydride. Since the 3β-acetoxyl is common to both the $\Delta^{7,9(11)}$-*allo*-steroid and the precursor, the new acetoxyl group must reside in a labilizing olefinic environment to accommodate the ready forma-



tion of the $\Delta^{7,9(11)}$-function. On the basis of these considerations and the mechanism proposed later, these derivatives were formulated as Δ^{8}-3β,7ξ-dihydroxy-*allo*-steroid diacetates.

Conclusive evidence for the structure of these non-mercurated $\Delta^{7,9(11)}$-*allo*-steroid precursors is provided in the case of the conversion of I to II. Although the non-mercurated precursor of II could not be isolated from the usual preparative experiments, the utilization of the conditions of run C led to the desired goal. When the reaction of mercuric acetate with excess I is interrupted after three hours and II and excess I removed without undue heating, the non-mercurated precursor is readily separated as the diol after hydrolysis of the residual oil. The $\Delta^{8,22}$-ergostadien-3β,7ξ-diol stereoisomer obtained proved to be identical with the product prepared by the reduction of $\Delta^{8,22}$-ergostadien-3β-ol-7-one with lithium aluminum hydride. Both the reduction product of the Δ^{8}-7-ketone and the diol isolated from the mercuric acetate dehydrogenation of I are converted to II on heating in acetic acid. Thus there remains little doubt that in the primary reaction of Δ^{7}-*allo*-steroids with mercuric acetate, a Δ^{8}-3β,7ξ-dihydroxy-*allo*-steroid diacetate is formed simultaneously with the desired $\Delta^{7,9(11)}$-*allo*-steroid.

Analysis of the kinetic data over the primary reaction period (*i.e.*, prior to the intrusion of the side reaction of II with mercuric acetate or of the secondary decomposition of $\Delta^{8,22}$-ergostadien-3β,7ξ-diol diacetate) indicates that the reaction is first order in mercuric acetate and first order in the $\Delta^{7,22}$-diene (I). In these experiments, no attempt was made to maintain each run at the same temperature but there appears little doubt from the constants listed in Table II concerning the roles of the reactants on the rate of reaction. Based on this fact and the considerations previously discussed, a general mechanism for the reaction of mercuric acetate and Δ^{7}-*allo*-steroids is presented.

The first step involves the formation of a mercurated complex (III), similar to the intermediates

TABLE II

CALCULATIONS OF SECOND ORDER RATE CONSTANTS

$$Hg(OAc)_2 + \Delta^{7,22}\text{ Diene} \xrightarrow{\text{slow}} \text{Complex} \xrightarrow{\text{fast}} \Delta^{7,9(11)}\text{-Diene} + \text{Precursor} + Hg_2(OAc)_2$$

$$K = (2.303/t(2a - b)) \log (b(a - x)/a(b - 2x))$$

where t = time, a = initial concentration of $\Delta^{7,22}$-diene (I), b = initial concentration of $Hg(OAc)_2$, x = amount of $\Delta^{7,22}$-diene (I) reacted (equivalent to mercurous acetate formed)

Moles $Hg(OAc)_2$ / Moles sterol	t, min.	a, mole/l.	b, mole/l.	x, mole/l.	$K \times 10^{-1}$, l./mole min.
2.4/1.0	30	0.0638	0.153	0.0286	1.7
2.4/1.0	90	.0638	.153	.0480	1.8
2.4/1.0	210	.0638	.153	.0605	2.6
6.0/1.0	30	.0325	.194	.0214	2.1
6.0/1.0	60	.0325	.194	.0300	2.8
0.5/1.0	30	.129	.0657	.0265	2.5
0.5/1.0	60	.129	.0657	.0314	2.5

previously proposed for olefin-mercuric salt interactions,[5] which would undergo a relatively rapid transformation to IV.[6] The postulation of IV as an intermediate in preference to the alternative $\Delta^{8(14)}$-analog might not be evident from *a priori* considerations in view of the conformal equivalence of the C-9 and C-14 hydrogen atoms but there is little doubt that IV provides a more rational explanation for the formation of the Δ^{8}-3β,7ξ-diacetoxy-*allo*-steroids (VII).[7]

Further decomposition of IV to the carbonium intermediate (V) is not unexpected in view of the

(5) J. Chatt, *Chem. Revs.*, **48**, 7 (1951). It appears desirable to postulate frontal attack by mercuric acetate in this instance, to accommodate the "*trans*" attack of the electron pair from the C-9-H in the opening of the mercuronium ion. However, it should be noted that G. Wright has questioned the validity of the mercuronium concept in the mechanism of olefin mercuration (ref. 20).

(6) After the completion of the work presented in this paper D. H. R. Barton and W. J. Rosenfelder proposed an analogous mechanism to explain the action of mercuric acetate on isodehydrocholesterol *p*-nitrobenzoate; *J. Chem. Soc.*, 2381 (1951).

(7) It is possible that elimination of the C-14 hydrogen actually occurs to a minor extent with the formation of the $\Delta^{8(14)}$-analog of IV since a small amount of $\Delta^{7,14,22}$-ergostatriene-3β-ol acetate can actually be isolated from the mother liquor in the conversion of I to II.

similarity of the C–Hg(OAc) function to a C-halogen function.[5] The $(HgOAc)^-$ eliminated from IV in the formation of V would eventually be converted to mercurous acetate by mercuric acetate. The postulated solvolysis of IV through the carbonium ion (V) to a mixture of VI and VII is rendered more credible by further analysis of the data of Table I with respect to the ratio of the concentrations of the $\Delta^{7,9(11),22}$-triene (II) and the typical non-mercurated precursor, $\Delta^{8,22}$-ergostadiene-3β,7ξ-diol diacetate in the early phase of the reaction. Since the amount of mercurous acetate formed is equivalent to the amount of I converted to a mixture of II and the $\Delta^{8,22}$-derivative, the difference between the total amount of mercurous acetate and II must be a measure of the concentration of $\Delta^{8,22}$-ergostadiene-3β,7ξ-diol diacetate. In Table III the ratios of II to the non-mercurated precursor (II/P) have been calculated. The ratios in individual runs are fairly constant as would be expected for the simultaneous formation of II and its non-mercurated precursor (or in general, VI and VII) from a common carbonium ion intermediate such as V.

TABLE III

RATIO OF II TO $\Delta^{8,22}$-ERGOSTADIENE-3β,7ζ-DIOL DIACETATE

Time, hr.	$Hg_2(OAc)_2$, mole	$\Delta^{7,9(11),22}$-Triene (II), mole	$\Delta^{8,22}$-Diacetate (P), moles	Ratio (II/P)
		Run A		
0.5	0.0285	0.009	0.0195	0.46
1.5	.048	.017	.0310	.55
3.5	.0605	.021	.0395	.52
		Run B		
0.5	0.0215	0.007	0.0145	0.48
1.0	.0300	.010	.0200	.50
3.0	.0395	.013	.0265	.49
		Run C		
0.5	0.0265	0.010	0.0165	0.61
1.0	.0315	.012	.0195	.61
		Run D		
7.75	0.0195	0.008	0.0118	0.70
24	.0430	.017	.0260	.65
48	.0550	.021	.0340	.62

Although the conversion of Δ^{7}-*allo*-steroids was achieved in 90% yield by the reaction of excess steroid with mercuric acetate, the method was impractical in view of the difficulties of separation of Δ^{7}- and $\Delta^{7,9(11)}$-*allo*-steroids. The most practical synthesis of $\Delta^{7,9(11)}$-*allo*-steroids embodied the reaction of the Δ^{7}-*allo*-steroid with slightly more than two moles of mercuric acetate at room temperature until all of the mercuric acetate had been consumed. After removal of mercurous acetate, the reaction product was either refluxed in acetic acid–chloroform for an appropriate period of time or the steroid reaction product heated at 200° in tetralin for a short period.

Attempts were made to improve these conversions by confinement of the reaction either to the formation of a stable mercuri-derivative or the formation of Δ^{8}-3β,7ξ-diacetoxy-steroids in order to avoid the competitive reaction of the $\Delta^{7,9(11)}$-*allo*-steroid with mercuric acetate. In the experiment to obtain methoxy mercuration of I,[5] no reaction could be detected in the absence of a minimal quantity of acetic acid (two moles). With excess acetic acid present, no improvement of yield was observed. Finally attempts were made either to enhance the rate of reaction of the Δ^{7}-*allo*-steroid or to inhibit the reaction of the $\Delta^{7,9(11)}$-*allo*-steroid with mercuric acetate. It was observed that mercuric nitrate or small amounts of nitric acid catalyzed not only the formation of the $\Delta^{7,9(11),22}$-triene (II) but likewise the mercuration of II as well. Pyridine and sodium acetate inhibited the mercuration of II but likewise inhibited the conversion of I to II. The conversion of I to II at a lower temperature merely slowed up both the desired reaction as well as the side reaction without appreciable increase in selectivity.

Experimental[8]

Mercury Balance and Kinetic Studies.—The following general procedure was used to obtain the quantitative results described in Table I. Solutions of $\Delta^{7,22}$ ergostadiene-3β-ol acetate (I) in chloroform and mercuric acetate in acetic acid were prepared at the desired concentrations. Aliquots of these solutions (*ca.* 35 ml.) at room temperature were mixed in glass stoppered flasks and maintained at room temperature for the periods designated. Preliminary experiments indicated that the reaction could be "frozen" by direct filtration of the aliquot through a buchner funnel into a suction flask containing sufficient water (*ca.* 300 ml.) to cause immediate separation of the mercuric acetate–water layer from the steroid reaction product in chloroform.

The amount of mercurous acetate was determined gravimetrically after washing with *ca.* 25 ml. of chloroform and drying at room temperature *in vacuo*. The aqueous layer and the water washes of the chloroform layer were combined and unreacted mercuric acetate was determined by titration with standarized potassium thiocyanate solution with ferric sulfate indicator.[9] The amount of $\Delta^{7,9(11),22}$ ergostatrien-3β-ol acetate (II) present was determined by ultraviolet absorption spectroscopy of the solution using a Cary recording spectrophotometer. From the maximum at 242.5 mμ and the known extinction coefficient at this point, E_M 18,600 (the peak of maximum intensity), the concentration of II was readily determined. For the purpose of determining the maximum amount of $\Delta^{7,9(11),22}$-triene (II) which could be formed, the chloroform extract was either diluted with acetic acid directly or concentrated to a small volume and refluxed for periods of 2 to 24 hours. Ultraviolet absorption spectroscopy of the solutions before and after reflux demonstrated that additional $\Delta^{7,9(11),22}$-triene (II) had been formed. Thus in the case of the 3.5-hour aliquot from run A (Table I), the solution was 0.021 *M* in $\Delta^{7,9(11),22}$-triene (II) originally and after reflux the concentration of II was increased to 0.041 *M*. Likewise after 22 hours at room temperature, in the case of run C (Table I), the concentration of II was increased from 0.017 to 0.029 *M* after reflux corresponding to the formation of II in 90% yield on the basis of the mercuric acetate consumption.

At 0°, run D (Table I), it was not possible to maintain a homogeneous mixture. The mixture was stirred vigorously for the allotted period of time, poured into water, the residual mercurial salts filtered and dried. Mercuric acetate was removed from the filter cake by extraction with chloroform–acetic acid at room temperature and the amount of mercurous acetate was determined gravimetrically. The amount of unreacted mercuric acetate was determined by titration of the aqueous liquor and chloroform–acetic acid washes in the usual manner.

Reaction of $\Delta^{7,22}$-Ergostadien-3β-ol Acetate with Mercuric Acetate. (a) Preparation of $\Delta^{7,9(11),22}$-Ergostatrien-3β-ol Acetate.—To a stirred solution of 200 g. of $\Delta^{7,22}$-

(8) All melting points are corrected. All rotations measured with 1% chloroform solutions.

(9) Scott's "Standard Methods of Chemical Analysis," N. H. Furman, Editor, 5th Edition, D. Van Nostrand and Co., Inc., New York, N. Y., p. 590.

ergostadien-3β-ol acetate[10] in 1100 ml. of chloroform was added a solution of 290 g. of mercuric acetate in 1670 ml. of acetic acid. The suspension was stirred for 23 hours at 25–30° and then filtered to remove mercurous acetate; wt. 231 g. (98%). The filtrate was then concentrated at 70–80° *in vacuo*[11] to a volume of *ca.* 600 ml. Upon cooling to room temperature, the crude II was filtered off, washed with glacial acetic acid and dried *in vacuo;* yield 156 g. (78%), m.p. 163–175°, $[\alpha]_D$ +12.9°, λ_{max}^{EtOH} 235 mμ (E_M 12,900), 242.5 mμ (E_M 14,250) and shoulder at 250 mμ (E_M 9,650) equivalent to a purity of 76.5%. This material is pure enough for most purposes and contains I as the major contaminant. Further purification is extremely wasteful. Repeated crystallization yielded $\Delta^{7,9(11),22}$-ergostatrien-3β-ol acetate, m.p. 178–181°, $[\alpha]_D$ +27.3°, λ_{max}^{EtOH} 242.5 mμ (E_M 17,100), which was apparently still contaminated with some $\Delta^{7,22}$-diene (II) despite a favorable phase solubility analysis.[12] Preparations free from the $\Delta^{7,22}$-diene (I) have been prepared in this Laboratory by the action of bromine on I. These preparations possessed similar melting points; m.p. 178–180°, but significantly higher optical rotations and extinction coefficients, $[\alpha]_D$ +32°, λ_{max}^{MeOH} 242.5 mμ (E_M 18,600).[13]

(b) **Effect of Temperature.**—Two reactions similar to those described above were carried out at room temperature and the reaction mixtures freed of mercurous acetate by filtration. The one reaction mixture, A, was diluted with water, the layers separated and the chloroform layer washed with water until free of acetic acid. After concentration of the reaction mixture *in vacuo* at 30–40° the residue was crystallized from ethyl acetate to give II. The other reaction mixture, B, was concentrated directly after filtration of mercurous acetate in such a manner that the internal temperature was maintained at 80–90° for two to three hours for the removal of chloroform. The product which crystallized was filtered, dried and crystallized from ethyl acetate. The comparison of the two procedures is tabulated below.

	Temp. of work-up A low	B high
Mercuric acetate/steroid ratio	2.0	2.0
Time, hr.	24	24
Wt. yield of crude $\Delta^{7,9(11),22}$-triene (II), %	62	78
$[\alpha]_D$	+17°	+3.6°
$E^{1\%}_{1\,cm}$ at λ_{max}^{EtOH} 242.5	313	336
Actual yield of $\Delta^{7,9(11),22}$-triene (II), %	46	63

(c) **Isolation of $\Delta^{8,22}$-Ergostadien-3β,7ξ-diol.**—A solution of 21.0 g. of mercuric acetate in 500 ml. of acetic acid and a solution of 56.5 g. of $\Delta^{7,22}$-ergostadien-3β-ol acetate in 500 ml. of chloroform were mixed at room temperature and permitted to react for 2.5 hours. After filtration of the precipitated mercurous acetate (16.6 g.), the mixture was diluted with 3 l. of water and the separated chloroform layer washed several times with water to remove residual acetic acid. The major portion of the solvent was removed from the steroid fraction by spontaneous evaporation at room temperature and the remaining chloroform was evaporated at 30–40° *in vacuo*. The solid residue was digested with 100 ml. of methanol and a crop of $\Delta^{7,22}$-steroid (I) contaminated with II was filtered off. After a removal of a second crop of a mixture of I and II, the residual oil was hydrolyzed by treatment with 5.0 g. of potassium hydroxide in 50 ml. of methanol for three hours at room temperature. Upon addition of water to incipient turbidity, 7.9 g. of solid was obtained; m.p. 169–177°. Careful recrystallization of this crude solid from acetone yielded $\Delta^{8,22}$-ergostadien-3β,7ξ-diol, m.p. 193–196°, m.p. not depressed by admixture with a sample prepared from $\Delta^{8,22}$-ergostadien-3β-ol-7-one as described below.

(d) **Reduction of $\Delta^{8,22}$-Ergostadien-3β-ol-7-one.**—A solution of 2.8 g. of $\Delta^{8,22}$-ergostadien-3β-ol-7-one[14] in 100 ml. of ether was stirred with 1.5 g. of lithium aluminum hydride for 24 hours. After acidification of the reduction product with cold dilute acetic acid, the ethereal layer was washed with dilute sodium hydroxide solution and concentrated *in vacuo* whereupon 950 mg. of crude diol separated as plates, m.p. 189–193°. Recrystallization from acetone afforded pure $\Delta^{8,22}$-ergostadiene-3β,7ξ-diol, m.p. 193–196°, $[\alpha]_D$ +34.2° (0.6% $CHCl_3$), end absorption in ultraviolet above 220 mμ.

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 81.09; H, 11.18. Found: C, 81.79; H, 10.92.

(e) **Conversion of $\Delta^{8,22}$-Ergostadien-3β,7ξ-diol to $\Delta^{7,9(11),22}$-Ergostatrien-3β-ol.**—Preliminary evidence indicated that the $\Delta^{8,22}$-diol was particularly unstable since on attempted acetylation and upon chromatography of mother liquors from (c) and (d), $\Delta^{7,9(11),22}$-triene (II) was isolated in considerably greater amounts than indicated by the ultraviolet absorption spectrum of the initial products.

In another experiment, 169 mg. of the $\Delta^{8,22}$-diol (isolated according to (c)) in 25 ml. of chloroform and 5 ml. of glacial acetic acid was refluxed for 17 hours. Ultraviolet absorption spectroscopy of the residue indicated that 84% conversion to $\Delta^{7,9(11),22}$-ergostatrien-3β-ol had been effected. On recrystallization of the residue from methanol $\Delta^{7,9(11),22}$-ergostadien-3β-ol was isolated and shown to be identical with a pure sample prepared by hydrolysis of the ester II. Practically identical results were obtained from a sample of the $\Delta^{8,22}$-diol prepared according to (d). Acetylation of the 3β,7ξ-diol with pyridine–acetic anhydride resulted in at least partial conversion to II.

Reaction of Δ^7-5α,22a-spirosten-3β-ol Acetate with Mercuric Acetate. (a) Preparation of $\Delta^{7,9(11)}$-5α,22a-spirostadien-3β-ol Acetate.—A solution of 8.05 g. of Δ^7-5α,22a-spirosten-3β-ol acetate[10] in 80 ml. of chloroform was mixed with 13.5 g. of mercuric acetate in 220 ml. of acetic acid and the resultant solution stirred for 18 hours at room temperature. After this period 8.62 g. of mercurous acetate was filtered off, the filtrate diluted with 500 ml. of water and the chloroform layer was washed successively with 500 ml. of water and dilute sodium bicarbonate solution to neutrality. The residual solid, remaining after concentration to dryness *in vacuo*, was triturated with methanol whereupon 6.8 g. of crystalline solid was obtained; m.p. 170–190° (dec.), resolidified and remelted 205–215°, λ_{max}^{EtOH} 235 mμ (E_M 7,100), 243 mμ (E_M 8,000). This product, a mixture consisting principally of the desired $\Delta^{7,9(11)}$-diene and the Δ^8-3β,7ξ-diacetate precursor, was dissolved in 6 ml. of tetralin and heated under nitrogen for five minutes at 200°. The cooled reaction mixture yielded 5.69 g. (71%) of fairly pure $\Delta^{7,9(11)}$-5α,22a-spirostadien-3β-ol acetate, m.p. 215–220.5°, λ_{max}^{EtOH} (E_M 12,400), 243 mμ (E_M 13,900) and shoulder 251 mμ (E_M 9,200). Although this sample was still contaminated with the Δ^7-derivative, further purification was not possible. The preparation was sufficiently pure for further synthetic use.

The purest sample of $\Delta^{7,9(11)}$-5α,22a-spirostadien-3β-ol acetate was obtained by pyrolysis of the intermediate diacetate as described below; m.p. 213–218°, $[\alpha]_D$ −15.5°; λ_{max}^{EtOH} 242.5 mμ (E_M 17,500).

Anal. Calcd. for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.66; H, 9.46.

(b) **Isolation of By-product (Δ^8-5α,22a-spirosten-3β,7ξ-diol Diacetate).**—A reaction product similar to that obtained in (a), except the pyrolysis in tetralin was omitted, was subjected to a triangular crystallization process using ethanol. From 6.5 g. of total reaction product 1.68 g. of a

(10) W. V. Ruyle, E. M. Chamberlin, J. M. Chemerda, L. M. Aliminosa, R. E. Erickson and G. E. Sita, THIS JOURNAL, **75**, 5929 (1953).

(11) Since the concentration process requires *ca.* 3 hours, a deliberate reflux period to decompose the non-mercurated precursor is not necessary. Reflux of the liquor for the same period prior to concentration does not increase the yield of II.

(12) Although the presence of I cannot be demonstrated directly, subsequent reactions with most "pure" II preparations always resulted in the recovery of small amounts of I from the mother liquors of these reaction products.

(13) The preparation of $\Delta^{7,9(11)}$-steroids by this procedure will be the subject of a subsequent communication. After the completion of our experimental work, Anderson, Stevenson and Spring, *J. Chem. Soc.*, 2901 (1952), disclosed similar results. Their physical constants for II were similar to ours with respect to the m.p. 178–180° and the $[\alpha]_D$ +32–33° but were slightly higher with respect to the extinction coefficients λ_{max}^{EtOH} 242 mμ (E_M 19,000).

(14) E. Schoenewaldt, L. Turnbull, E. M. Chamberlin, D. Reinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda and M. Tishler, *ibid.*, **74**, 2696 (1952).

fraction, m.p. 165–172° (dec.), was obtained in addition to the above described $\Delta^{7,9(11)}$-diene. Further purification of this material proved extremely capricious in view of its tendency to solvate and in view of its thermal instability. The above sample appeared to contain *ca.* 20% $\Delta^{7,9(11)}$-5α, 22a-spirostadien-3β-ol acetate although upon occasion samples m.p. 174–178° (dec.) have been obtained which contained only 5% of the $\Delta^{7,9(11)}$-contaminant. This latter sample of Δ^{8}-5α,22a-spirostadien-3β,7ξ-diol diacetate was evidently solvated judging from its analysis even after heating at 100° for two hours at 0.1 mm.

Anal. Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 71.26; H, 9.03.

Pyrolysis of a 0.50-g. sample of the 3β,7ξ-diacetate (λ_{max}^{EtOH} 235 mμ (E_M 3,200), 242.5 mμ (E_M 3,600), inflection 251 mμ (E_M 2,300)) at 200° for 15 minutes in a nitrogen atmosphere yielded the theoretical amount of acetic acid which was determined quantitatively by titration and characterized through the *p*-bromophenacyl ester. The crystalline residue, 442 mg., proved to be $\Delta^{7,9(11)}$-5α,22a-spirostadien-3β-ol acetate, m.p. 212–218°, λ_{max}^{EtOH} 235 mμ (E_M 13,700), 243 mμ (E_M 15,500), inflection 251 mμ.

Reaction of Methyl Δ^{7}-3β-Acetoxy-bisnor*allo*cholenate with Mercuric Acetate. (a) **Preparation of Methyl $\Delta^{7,9(11)}$-3β-Acetoxybisnor*allo*choladienate.**—A solution of 16.75 g. of methyl Δ^{7}-3β-acetoxybisnor*allo*cholenate[10] in 235 ml. of chloroform was added to 31.8 g. of mercuric acetate in 525 ml. of acetic acid at room temperature and the mixture stirred for 16 hours at room temperature. At the end of this period, 22.0 g. of mercurous acetate was obtained and the filtered liquor was diluted with 1250 ml. of water. The chloroform layer was washed with water and dilute sodium bicarbonate solution to remove acetic acid and then concentrated *in vacuo* at 30–40°. The residue was dissolved in hot acetone, filtered from a small amount of metallic mercury and the crude $\Delta^{7,9(11)}$-derivative was precipitated by the addition of methanol. After two crystallizations from methanol and one crystallization from acetone 3.91 g. of the acetone solvate of methyl $\Delta^{7,9(11)}$-3β-acetoxybisnor*allo*choladienate as prisms or needles was obtained, m.p. 162–165°, $[\alpha]_D$ +54.7°, λ_{max}^{EtOH} 235 mμ (E_M 16,900), 242.5 mμ (E_M 18,000), $\lambda_{infl.}^{EtOH}$ 250 mμ (E_M 12,300).

Anal. Calcd. for $C_{25}H_{36}O_4 \cdot C_3H_6O$: C, 73.32; H, 9.23. Found: C, 73.33; H, 9.08.

Desolvation was effected by recrystallization of the acetone solvate from methanol in which case methyl $\Delta^{7,9(11)}$-3β-acetoxybisnor*allo*choladienate crystallized as platelets, m.p. 164–165.5°, $[\alpha]_D$ +31.3°, λ_{max}^{EtOH} 235 mμ (E_M 16,500), 242.5 mμ (E_M 18,100), $\lambda_{infl.}^{EtOH}$ 250 mμ (E_M 11,900).

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.82; H, 9.05.

(b) **Isolation of By-product (Methyl Δ^{8}-3β,7ξ-Diacetoxybisnor*allo*cholenate).**—The reaction liquor from 5.75 g. of mercuric acetate and 3.02 g. of Δ^{7}-derivative was worked up as described in (a) except that the $\Delta^{7,9(11)}$-derivative was isolated by trituration with methanol; 1.31 g., m.p. 150–156°, $[\alpha]_D$ +44.7°, λ_{max}^{EtOH} 242.5 mμ (E_M 15,600). Upon concentration of the mother liquor to a small volume, 280 mg. of crude methyl Δ^{8}-3β,7ξ-diacetoxybisnor*allo*cholenate was obtained (m.p. 142–147°) which was obtained pure after three recrystallizations from methanol, Skellysolve B-acetone and Skellysolve B; m.p. 169–170°, end absorption above 220 mμ.

Anal. Calcd. for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.46; H, 8.41.

A small sample, subjected to pyrolysis at 200° for five minutes yielded crude $\Delta^{7,9(11)}$-diene, λ_{max}^{EtOH} 243 mμ (E_M 9,770) corresponding to *ca.* 55% of the $\Delta^{7,9(11)}$-derivative.

Reaction of Δ^{7}-*allo*-Pregnen-3β-ol-20-one Acetate with Mercuric Acetate. (a) **Preparation of $\Delta^{7,9(11)}$-*allo*-Pregnen-3β-ol-20-one Acetate.**—A solution of 22.5 g. of Δ^{7}-*allo*-pregnen-3β-ol-20-one and 60 g. of mercuric acetate in 1000 ml. of acetic acid and 250 ml. of chloroform was stirred for 16 hours at room temperature. After filtration of mercurous acetate (34.0 g.), the reaction mixture was diluted with 800 ml. of water, the separated chloroform layer washed with two additional 800-ml. portions of water and the solution concentrated to dryness *in vacuo*. After two crystallizations of the residue from ethanol, 15.8 g. of crude $\Delta^{7,9(11)}$-derivative was obtained, m.p. 137–141°. Further purification was best effected by chromatography over alumina in which case development was carried out successively with benzine–ethyl ether (9:1), benzine–ethyl ether (4:1), benzine–ethyl ether (1:1), benzine–ethyl ether (1:2) and finally ethyl ether–benzene (1:1). From the benzine–ethyl ether (9:1) and (4:1) eluates, 5.0 g. of pure $\Delta^{7,9(11)}$-*allo*-pregnen-3β-ol-20-one acetate was obtained which melted at 165–167° after crystallization from methanol; $[\alpha]_D$ +82°, λ_{max}^{EtOH} 235 mμ (E_M 14,500), 242.5 mμ (E_M 16,000), $\lambda_{infl.}^{EtOH}$ 251 mμ (10,400).

Anal. Calcd. for $C_{23}H_{30}O_3$: C, 77.48; H, 9.05. Found: C, 77.08; H, 9.10.

(b) **Isolation of By-product (Δ^{8}-*allo*-Pregnene-3β,7ξ-diol-20-one Diacetate.**—In the course of the experiments reported above, numerous attempts were made to isolate the Δ^{8}-non-mercurated precursors by chromatography. However, these efforts proved unavailing except in the pregnenolone series. Thus the benzine–ethyl ether (1:1) and (1:2) eluates yielded 4–5 g. of Δ^{8}-derivative, m.p. 140–150°. Crystallization from ethanol yielded solvates either as plates, prisms or needles which exhibited poorly defined melting points. However, Δ^{8}-*allo*-pregnene-3β,7ξ-diol-20-one diacetate crystallized from aqueous pyridine (1:1) in diamond-shaped plates, m.p. 175–177°.

On drying at 78° for two hours, partial deacetylation was effected since the analytical sample developed an odor of acetic acid. On drying at room temperature *in vacuo*, the preparation analyzed for the hemihydrate.

Anal. Calcd. for $C_{25}H_{36}O_5 \cdot {}^1/_2H_2O$: C, 70.56; H, 8.77. Found: C, 70.98; H, 8.21.

A solution of 1.0 g. of the above diacetate was refluxed with 15 ml. of 1.0 *N* methyl alcoholic potassium hydroxide for 40 minutes. Upon the addition of water, fine needles of the diol precipitated; 782 mg., m.p. 100–125°. After two recrystallizations from acetone–Skellysolve B, Δ^{8}-*allo*-pregnene-3β,7ξ-diol-20-one was obtained as an acetone solvate, m.p. 151–155°.

Anal. Calcd. for $C_{21}H_{32}O_3 \cdot C_3H_6O$: C, 72.80; H, 9.62; active hydrogen, 2.0. Found: C, 72.26; H, 9.51; active hydrogen, 2.2.

The original diacetate was obtained by warming 100 mg. of the diol in 3 ml. of pyridine with 0.5 ml. of acetic anhydride on the steam-bath for one hour. Upon dilution with ice-water, the original diacetate hemihydrate was obtained, m.p. 175–178°. After recrystallization from 50% aqueous pyridine the diacetate crystallized in diamond-shaped plates, m.p. 175–177°, which proved to be identical with the sample of Δ^{8}-*allo*-pregnene-3β,7ξ-diol-20-one diacetate originally isolated from the reaction with mercuric acetate.

Pyrolysis of a sample of diacetate in tetralin at 200° yielded acetic acid and $\Delta^{7,9(11)}$-*allo*-pregnadiene-3β-ol-20-one acetate, identical with a sample isolated from the mercuric acetate reaction.

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