On Steroidal Sapogenins. X. Structural Influences of the A Ring on 11α-*p*-Toluenesulfonyloxy Steroidal Sapogenin Acetolyses[1,2]

KEN'ICHI TAKEDA, HIROSHI TANIDA, AND KUSUO HORIKI

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

Received July 30, 1965

Sixteen kinds of A-ring substituted A/B *trans*- and *cis*-11α-hydroxysapogenins were synthesized and the acetolysis rates and products of their *p*-toluenesulfonates were determined. The acetolyses proceed with formation of the $\Delta^{9(11)}$-olefins with one exception. In this case, the acetolysis of the cross-dienone system **19c** involves the formation of a B-secosteroid, **25a**, and a styrene derivative, **24**. The satisfactory correlation of rate data with the application of the Hammett–Taft equation suggests that a dominant factor governing the rate effects is due to the inductive origin.

Some suitable model systems for elucidation of a remote structural influence upon chemical reactivity have been provided by the steroidal compounds. During the course of synthetic study on some steroidal hormone intermediates, we have found that, when 11α-tosyloxy-25D,5β-spirostane-2β,3β-diol acetonide (**2b**) is treated with acetic acid under mild conditions, an elimination reaction takes place to give the corresponding $\Delta^{9(11)}$-olefin **7** in quantitative yield.[1] Partly because we have many kinds of11 α-hydroxylated sapogenins and intermediates easily convertible to the A-ring substituted 11α-hydroxysapogenins, and partly because the mechanism of the SN1 acetolysis of secondary alkyl toluenesulfonates and the nature of the transition state are fairly well understood,[3] we undertook a rate and product study in the acetolysis of A/B-*cis* and A/B-*trans* series of 11α-*p*-toluenesulfonyloxy steroidal sapogenins.

Results

Preparations. A. A/B-*cis* Series.—The following four compounds had been synthesized by our group: 11α-hydroxy-25D,5β-spirostane (**1**),[4] 11α-tosyloxy-25D,5β-spirostane-2β,3β-diol (**2c**),[1] 11α-hydroxy-25D,5β-spirost-2-ene (**3**),[4] and 11α-hydroxy-25D,5β-spirostan-3-one (**4a**).[5]

11α-Hydroxy-25D,5β-spirostan-2-one (**5**) was obtained by the Birch reduction of the 2-ethyleneketal of 2,11-dione **8b**[6] followed by acid hydrolysis. 11α-Acetoxy-25D,5β-spirost-1-en-3-one (**6a**) was obtained in the following way: the 11α-acetoxy-2,3-diol[7] **2d** was converted to its 2-monotoluenesulfonate **2e** and this was oxidized to the 3-keto derivative **9** by chromic acid followed by the elimination of toluenesulfonyloxy group to furnish the desired 11α-acetoxy-1-en-3-one **6b** (Chart I).

B. A/B-*trans* Series.—11α-Hydroxy-25D,5α-spirost-2-ene (**13**),[8] 11α-hydroxy-25D,5α-spirostan-3-one (**15a**),[9] 11α-acetoxy-25D-spirost-4-en-3-one (**18b**),[9] and 11α-acetoxy-25D-spirost-1,4-dien-3-one (**19b**)[10] are known compounds (Chart II). Catalytic hydrogenation of the 11α-hydroxy-2-ene **13** over palladium on charcoal gave the saturated compound **10**. 3-Methylene-11α-hydroxy-25D,5α-spirostane (**20**) was prepared from **15b** by the Wittig reaction, the introduced *exo*-methylene group was evidenced by the absorption at 873 cm^{-1} in the infrared spectrum, and this compound **20** was converted into 3-methyl-11α-hydroxy-25D,5α-spirost-2-ene (**11**) by treatment with perchloric acid according to the method of Cookson, *et al.*[11] Action of perchloric acid or thionyl chloride upon 11α-hydroxy-25D,5α-spirostane-3-benzylcarbinol (**21a**) prepared by the reaction of **15b** with benzylmagnesium chloride yielded the 11α-hydroxy-3-benzyl-2-ene **12**,[12] instead of the expected 3-benzylidene-type compound. Two isomeric 11α-hydroxy-3-methoxyimino-25D,5α-spirostanes (**14**) were obtained by the reaction of **15a** with O-methylhydroxylamine hydrochloride and sodium acetate. These two isomers were separated by preparative thin layer chromatography; however, it was found that each of them was interconvertible under the acetolysis condition used in this study. 11α-Hydroxy-25D,5α-spirostan-2-one (**16**) was obtained from 25D,5α-spirostane-2,11-dione (**22a**)[6] using a similar route to that used in the A/B-*cis* series. According to Ringold's procedure,[13] dichlorodicyanobenzoquinone (DDQ) dehydrogenation of the 11α-acetoxy-5α-3-one **15b** followed by saponification yielded the 11α-hydroxy-5α-1-en-3-one **17**. On this reaction, because the direct separation of the starting material **15a** and the desired 1-en-3-one **17** was very difficult, the former was reduced to the corresponding 3-ol by the action of sodium borohydride in isopropyl alcohol under the condition that the latter was not reduced, in order to facilitate separation of these components.

Acetolysis Rates.—Measurements of the rates of acetolyses were carried out in the usual manner.[14] The first-order kinetics were obtained in all of the acetolyses and the rate coefficients are summarized in Table I. For comparison, the relative rates at 65.4° were determined. Since the acetolyses of 11α-tosyloxy-1,4-dien-3-one **19c** were carried out at higher temperatures, its rate constant at 65.4° was calculated from the least-squares slope of the Arrhenius plots. It

(1) Part IX: K. Takeda, K. Hamamoto, K. Horiki, and E. Honda, *Chem. Pharm. Bull.* (Tokyo), in press.

(2) Presented, in part, at the 18th Annual Meeting of the Chemical Society of Japan in Osaka, April 1965.

(3) *Cf.* S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1965).

(4) K. Hamamoto, *Chem. Pharm. Bull.* (Tokyo), **9**, 32 (1961).

(5) K. Takeda, T. Okanishi, H. Osaka, A. Shimaoka, and N. Maezono, *ibid.*, **9**, 388 (1961).

(6) H. Osaka, *ibid.*, **10**, 404 (1962).

(7) K. Takeda and K. Hamamoto, *ibid.*, **8**, 1004 (1960).

(8) K. Takeda, H. Osaka, and K. Horiki, *J. Pharm. Soc. Japan*, **81**, 1662 (1961).

(9) J. Romo, *Bol. Inst. Quim. Univ. Nacl. Auton. Mex.*, **7** (2), 59 (1955).

(10) K. Igarashi, *Chem. Pharm. Bull.* (Tokyo), **9**, 722 (1961).

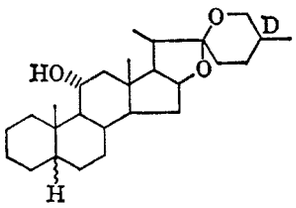
(11) R. C. Cookson, D. P. G. Houson, and R. E. Parker, *J. Chem. Soc.*, 5014 (1962).

(12) *Cf.* R. L. Shriner, *Org. Reactions*, **1**, 13 (1942).

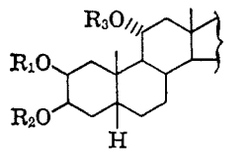
(13) H. J. Ringold and A. Turner [*Chem. Ind.* (London), 211 (1962)] reported that in the A/B-*trans* steroids the dehydrogenation with 1 mole equiv of DDQ occurred at C-1 more preferably than at C-4.

(14) S. Winstein, C. Hanson, and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 812 (1948); S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

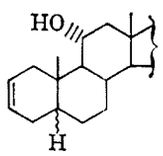
CHART I



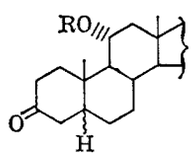
1, 5β-H
10, 5α-H



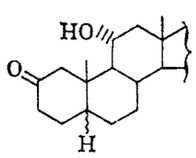
2a, $R_1=R_2=R_3=H$
b, $R_1, R_2=>C(CH_3)_2$; $R_3=Ts$
c, $R_1=R_2=H$; $R_3=Ts$
d, $R_1=R_2=H$; $R_3=Ac$
e, $R_1=Ts$; $R_2=H$; $R_3=Ac$



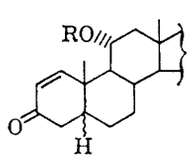
3, 5β-H
13, 5α-H



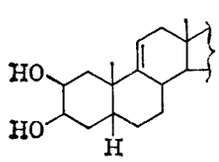
4a, R=H; 5β-H
b, R=Ac; 5β-H
15a, R=H; 5α-H
b, R=Ac; 5α-H



5, 5β-H
16, 5α-H



6a, R=H; 5β-H
b, R=Ac; 5β-H
17, R=H; 5α-H



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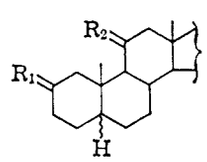
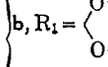
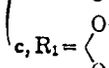
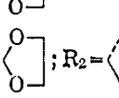
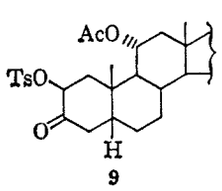


8, 5β-H
22, 5α-H
a, $R_1=R_2=O$
b, $R_1=$  ; $R_2=O$
c, $R_1=$  ; $R_2=$ 



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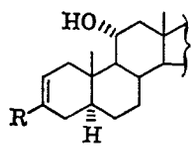
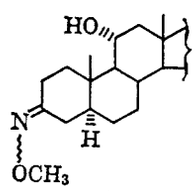
was found that the acetolysis rates of the A/B-*trans* compounds were faster than that of the corresponding A/B-*cis* compounds by a factor of about 2–4. The introduction of a double bond between C-2 and C-3 is effective in causing a decrease in rate of 0.48 in the A/B-*trans* series and 0.62 in the A/B-*cis* series below the parent compound. The carbonyl group at the C-2 or C-3 position results in a rate that is slower than the parent compound by a factor of 0.19 in the A/B-*trans* series and 0.14 in the A/B-*cis* series. The further introduction of a double bond at the C-1 position in the A/B-*trans* 3-keto compound causes a slowness in rate of 0.22 below **15**. The similar introduction of a double bond at the C-4 results in the same factor, 0.22.

CHART II



11, R=CH_3
12, R=$CH_2C_6H_5$



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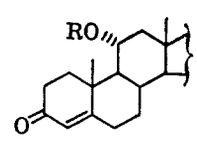
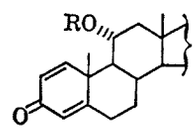
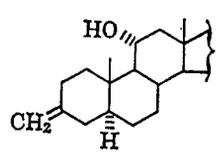


18a, R=H
b, R=Ac



19a, R=H
b, R=Ac
c, R=Ts



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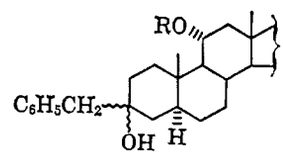


21a, R=H
b, R=Ac

Furthermore, the rate of the cross-dienone system **19** is slower than that of the 3-one **15** by a factor of 0.014. Therefore, the rate range between the parent compound **10** and the cross-dienone compound **19** covers a factor of 2.7×10^{-3}. The acetolysis rates of the A/B-*cis* and A/B-*trans* series of compounds relative to the corresponding parent compounds **1** and **10** are summarized in Table I.

TABLE I
ACETOLYSIS RATES OF 11α-*p*-TOLUENESULFONATES AT 65.40°

Compd	k_ϕ, sec^{-1}	Relative rate (relative to **1**)
1	1.77×10^{-4}	1
2	1.52×10^{-4}	0.86
3	1.10×10^{-4}	0.62
4	2.56×10^{-5}	0.15
5	2.44×10^{-5}	0.14
6	2.21×10^{-6}	1.25×10^{-2}
		(relative to **10**)
10	3.79×10^{-4}	1
11	1.95×10^{-4}	0.52
12	1.86×10^{-4}	0.49
13	1.82×10^{-4}	0.48
14	1.09×10^{-4}	0.29
15	7.17×10^{-5}	0.19
16	7.22×10^{-5}	0.19
17	1.53×10^{-5}	4.0×10^{-2}
18	1.48×10^{-5}	3.9×10^{-2}
19	1.02×10^{-6}[a]	2.7×10^{-3}

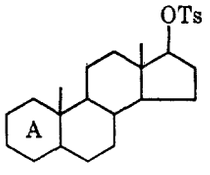
[a] Calculated from the Arrhenius plots of the rates at 90.5, 105.5, and 120.5°.

Acetolysis Products.—In order to determine the products of acetolysis, we carried out the acetolysis of each of the *p*-toluenesulfonates in glacial acetic acid containing an equivalent quantity of sodium acetate.[14] In all cases, the formation of the $\Delta^{9(11)}$-olefinic product in more than 75% yield was observed. Identity of each of the olefins was established by mixture melting point

determination and comparison of infrared spectra with the corresponding authentic samples. In the case of the cross-dienone compound **19c**, besides the expected main product $\Delta^{9(11)}$-olefin **23** (33% yield), two oily phenolic substances, **24** and **25a**, were isolated after careful separation using preparative thin layer chromatography in 12 and 6.2% yield, respectively. (For the proof of structures of **24** and **25a**, see Experimental Section.)

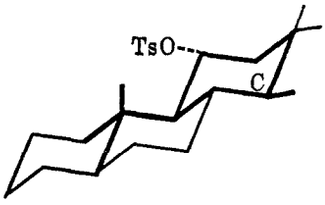
Discussion

The work of Barton, *et al.*,[15,16] has provided extensive kinetic data for the condensation of a number of triterpenoid and steroid 3-ones with benzaldehyde and has elegantly and conclusively demonstrated that the differences in rates arise principally from conformational distortion produced by unsaturated substituents rather than by the operation of polar or inductive effects. The term "conformational transmission" has been introduced for this new effect produced by substituents.[16] Since then, it appears to be customary to consider this effect for the interpretation of a subtle remote structural influence upon various reactions in the steroid system. For example, one of the works most related to ours, the rate change due to the structural variation of the A ring observed on the 17β-tosylate acetolysis, has been interpreted by Mathieu, *et al.*, in terms of the above effect.[17,18] Although this subtle



effect can not be completely excluded, at least in our solvolyses, there have been found some experimental evidences which suggest the conformational transmission is not a main contributing factor. The representative results on this line would be the small but significant difference (a factor of 1.5) observed on the rates of the 3-ketone **15** and 3-oxime ether **14**, in which both the compounds are reasonably assumed to have a similar conformational distortion; the same rate within an experimental error observed by the Δ^1-3-ketone **17** and the Δ^4-3-ketone **18**, because it is unlikely that the distortions of both ketones are similar.[19]

In order to know the influence of steric effects upon the rates, the geometry around the reaction site was considered. Since the alkyl branching at the C-10 position is regarded as a *t*-butyl group substituted at the *trans* 2-position of a cyclohexanol system, the kinetic behavior of *trans*-2-*t*-butylcyclohexyl *p*-toluenesulfonate would be the most suitable model system. Available data indicate the acetolysis rate of this compound is 13.2×10^{-4} sec^{-1} at 65.4°.[20] The solvolysis rates of our parent compounds **1** and **10** relative to this value are within a factor of 7 which



strongly demonstrates the suitableness of the model. The greater reactivity of the *trans*-2-*t*-butylcyclohexyl *p*-toluenesulfonate relative to the parent cyclohexyl *p*-toluenesulfonate (a factor of 115 at 50°) has been ascribed to steric acceleration (relief of strain[21]) due to the congested geometry and restricted rotation of the *t*-butyl and tosylate groups.[20,22,23]

Accordingly, although directly related kinetic data appear to be lacking, it is conceivable that the steric compression between a substituent at the C-11 position and the C-1 hydrogens might dominantly contribute to the solvolysis rates observed in this study.[24] In this connection, to derive a possible relationship between this steric factor and the observed rate data, as a first approximation, an estimation of the above strain in the ground state and in the transition state was made by measuring with Dreiding models the distances between the C-1 hydrogen and the C-11 tosyl oxygen and between the C-1 hydrogen and the sp^2-hybridized 11-carbon (carbonium ion model), respectively. The variation of the distance may correspond to the scale of a relief of the strain. If the rate effects observed in this study are due to a steric factor in origin, a kind of relation between the rates and the variation of the distance might be expected. Unexpectedly, no reliable relation was obtained. Therefore, the steric interaction between the C-1 hydrogen and the reaction center is unlikely to be a dominant factor governing the rates reported here.

Remote polar substituents may affect reactivity by an electronic interaction transmitted either through the connecting atoms or through the interannular space. It is said that both of these effects are correlatable by linear free energy functions.[25,26] Examples in

(15) (a) D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, 935 (1957); (b) D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *ibid.*, 1297 (1960).

(16) D. H. R. Barton, "Theoretical Organic Chemistry, The Kekule Symposium," Butterworths and Co. (Publications) Ltd., London, 1959, p 127.

(17) J. Mathieu, M. Legrand, and J. Valls, *Bull. Soc. Chim. France*, 549 (1960).

(18) We believe that this acetolysis rate should be more reasonably interpreted by our mechanism.

(19) However, it appears that this observation is better accounted for by the operation of an inductive effect of the carbonyl substituent, if one can assume that the inductive effect predominantly transmits through the bonds connecting the substituent and the reaction center (five carbon–carbon bonds for both the compounds) and its transmittance through the interannular space (field effect) is relatively unimportant. The inductive parameters, σ_t, for **17** and **18** in our treatments described later are 0.349 and 0.378, respectively.

(20) Calculated by the Arrhenius plots of the data reported by H. L. Goering and R. L. Reeves, *J. Am. Chem. Soc.*, **78**, 4931 (1956).

(21) (a) H. C. Brown and H. L. Berneis, *ibid.*, **75**, 10 (1953); (b) H. C. Brown and R. S. Fletcher, *ibid.*, **71**, 1845 (1949).

(22) The fact that the replacement of the *t*-butyl group into an isopropyl group in this system decreases the rate by a factor of 100 also supports this interpretation. See R. A. Wohl, *Chimia* (Aarau), **18**, 219 (1964).

(23) The slight rate difference among *trans*-2-*t*-butylcyclohexyl tosylate, **10**, and **1** was observed in the decreasing order 1.0, 0.29, and 0.13, respectively, which suggests more compactness of the system decreases the rate. Although we do not attempt to rationalize this observation at the present time, the idea of steric retardation (F-strain) might be the most responsible factor.

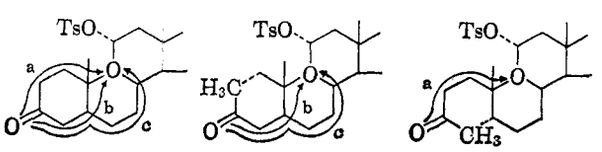
(24) There are some experimental data related to this steric interaction. J. Schreiber and A. Eshenmoser [*Helv. Chim. Acta*, **38**, 1529 (1955)] observed the extraordinarily high chromic acid oxidation rate of the C-11 hydroxyl substituent and suggested that it is due to steric acceleration. Not quite, but somewhat, related phenomena were reported in the nmr spectra of the octahydrophenanthrene systems by W. Nagata, T. Terasawa, and K. Tori [*J. Am. Chem. Soc.*, **86**, 3746 (1964)].

(25) R. W. Taft, Jr., *ibid.*, **74**, 2729, 3120 (1952); **75**, 4231, 4534, 4558 (1953).

(26) J. D. Roberts and W. T. Moreland, *ibid.*, **75**, 2167 (1953).

steroidal compounds dealing with remarkably large effects of polar substituents at long distances have been presented by Schwartz,[27] Peterson,[28] and Moriarty, *et al.*,[29] and in some cases[28] a logical estimation of the inductive effects of substituents was achieved by application of the Hammett–Taft relationship, log $k/k_0 = \rho^*\sigma^*$.[28a,30]

Therefore, a similar treatment was applied for our solvolyses, in which the effect of a remote substituent is calculated from the effect of a closer substituent by assuming that the effect falls off by a constant factor, here used as 0.500 for one methylene[32] and as 0.508 for one ethylene,[33] for each additional bond separating the remote substituent from the reaction center. For polycyclic systems such as steroids, an unambiguous calculation will be accomplished if it is assumed that all of the bond paths between the substituent and the reaction center contribute to the inductive effect. For example, the σ^* value of 1.65 for the CH_3CO substituent[34] was employed for the 3-keto compound (**4** and **15**) by assuming that the α-methylene of the 3-keto group is nearly equal to the methyl of CH_3CO substituent. The number of the intervening methylene and ethylene was summed up to C-9 through all possible carbon paths from the carbonyl, in order to make it possible to refer to the reported data in cyclohexyl *p*-bromobenzenesulfonates acetolyses.[31] Thus, the over-all σ_t^* value of **4** and **15** reacting at the C-11 position is given by the following.



$$\Sigma\sigma_t^* = 1.65\,[(0.50)^4 + (0.50)^4 + (0.50)^6] = +0.231$$
path a path b path c

general formula

$$\Sigma\sigma_t^* = \sigma^*[a^1 + b^m + c^n + \ldots\ldots\ldots\ldots]$$

The calculated over-all σ_t^* is listed in Table II. A reasonably good correlation was realized for each series of the 5α-steroids and the 5β-steroids by a plot of the logarithm of the acetolysis rates *vs.* the σ_t^* constants, as shown in Figure 1. Moreover, the calculated value for the reaction constant, ρ^*, is −3.3, a value substantially consistent with that reported in cyclohexyl *p*-bromobenzenesulfonate acetolysis. The plots of the Δ^4-3-one **18** and the $\Delta^{1,4}$-dien-3-one **19** fit on the line of the 5α series. This seems to be quite

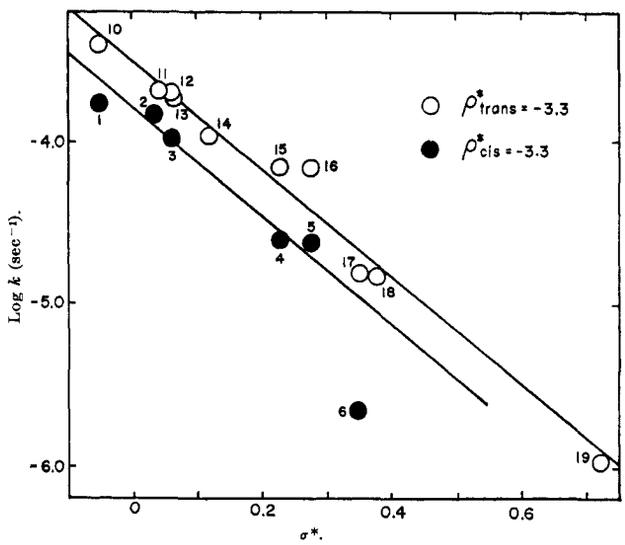


Figure 1.—The ρ–σ^* treatment of the acetolysis rates.

reasonable on the basis of the consideration of that the molecular shape of **18** and **19** do not resemble those of the 5β series, but those of the 5α series. Consequently, it may be concluded that the dominant factor governing the rate effects observed in this study is due to the inductive origin which are predicted by use of a Hammett–Taft approach. Only one significant deviation from the line was observed in the case of Δ^1-3-one **6**. It is noticed that the distance (2.3 A) between the C-1 hydrogen and the C-11 tosyl oxygen of this compound is remarkably different from the average value (1.9 A) of all other compounds. Therefore, it may be safe to assert that the Hammett–Taft relationship in our reaction is held only in the limited cases where the steric strain between the C-1 hydrogen and C-11 reacting center is in a similar degree.

TABLE II

Compd	σ^*
1 and 10	−0.0528
2	+0.0373
11	+0.0477[a]
3 and 13	+0.0634
4 and 15	+0.231
5 and 16	+0.271
6 and 17	+0.349
12	+0.063[b]
14	+0.120[c]
18	+0.378
19	+0.727

In the following cases where the directly related σ^* constants have not been reported: [a] the value of $CH_3CH{=}CH-$ instead of that of $CH_3CH{=}C(CH_3)-$ was used in the path b and c on the basis of an idea that an α-methyl branch in an allyl system is effective much less than a branch at the other positions; [b] the value of $CH_3CH{=}CH-$ instead of that of $CH_3CH{=}C(CH_2Ph)-$ was used in the path b and c; [c] the value of $CH_3\overset{|}{C}{=}NOH$ calculated from the dissociation constant of pyruvic acid oxime was used. Refer to H. C. Brown, D. H. McDaniel, and Q. Häfliger, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press Inc., New York, N. Y., 1955, Chapter 14, p 578.

The predominant formation of the $\Delta^{9(11)}$-olefin from all of our tosylates, except for the cross-dienone tosylate **19c**, can be rationalized by the Saytzeff rule,

(27) (a) V. Schwartz, S. Hermaneck, and J. Trojanek, *Chem. Ind.* (London), 1212 (1960); (b) *Collection Czech. Chem. Commun.*, **26**, 1483 (1960); (c) *Tetrahedron Letters*, **No. 18**, 809 (1962); (d) V. Schwarz and S. Hermanek, *Tetrahedron*, **29**, 2360 (1964).

(28) (a) P. E. Peterson, *Tetrahedron Letters*, **No. 4**, 181 (1963); (b) P. E. Peterson and G. Allen, *J. Am. Chem. Soc.*, **85**, 3608 (1963).

(29) R. M. Moriarty and T. D. J. D'Silva, *Tetrahedron*, **21**, 547 (1965).

(30) The substantially same idea had been used by Streitwieser[31] for the substituent effects in cyclohexyl *p*-bromobenzenesulfonate acetolyses, yielding the value of $\rho^* = -3.49$ at 70–75°.

(31) A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **78**, 4935 (1956).

(32) J. C. McGowan, *J. Appl. Chem.*, **10**, 312 (1960).

(33) This value is available by comparison of the substituent effects upon the dissociation constants in a series of benzoic acids and cinnamic acids: H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

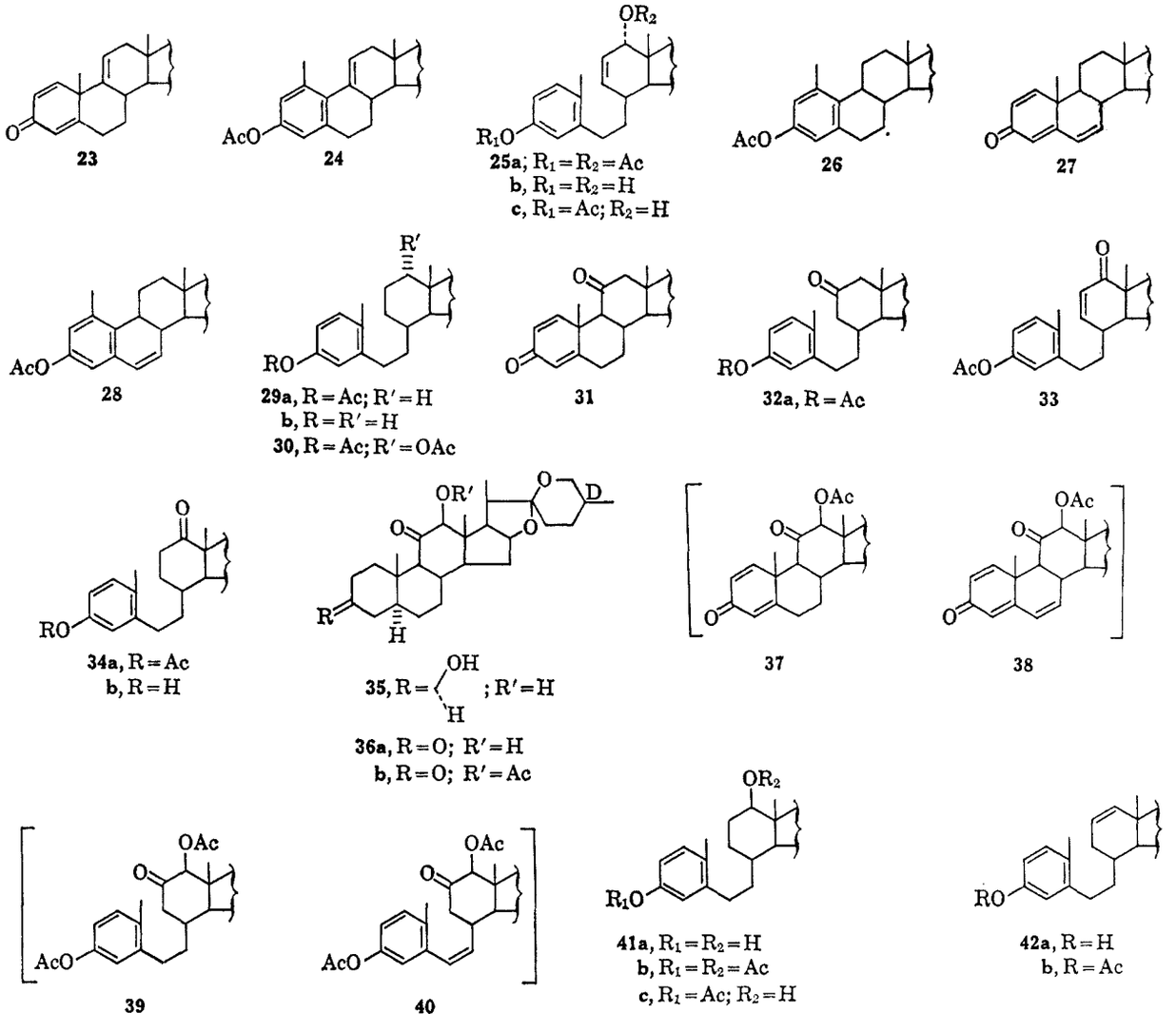
(34) The σ^* values used in this study were cited from the literatures.[35,36]

(35) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 556.

(36) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).

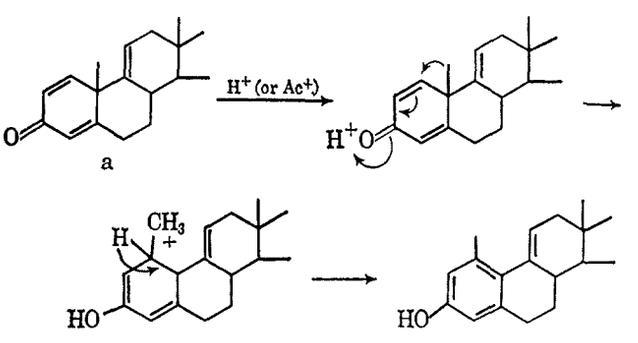
CHART III

ACETOLYSIS PRODUCTS OF 19c AND THEIR STRUCTURAL ELUCIDATION

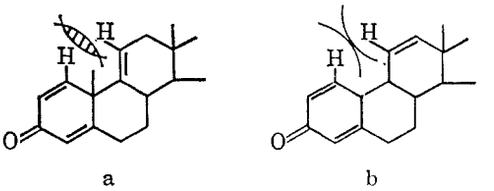


which is generally applied for the E1 solvolytic elimination.[37]

The most significant and striking result in this acetolysis study is the formation of the B-secosteroid **25a** and the styrene compound **24** from **19c**, along with the major amount of the Saytzeff olefinic product **23** (Chart III). Other possible products predicted by the mechanism of the acetolysis of this kind will be the Hofmann olefin, the C-11 acetate, and the other kinds of rearranged products. Careful investigation did not indicate any evidences of the formation of the acetate[38] and the rearranged products. It was proved that, although treatment of **23** with the acetolysis solvent used in this study did not afford a detectable amount of phenolic products, a similar treatment with glacial acetic acid containing a high concentration of lithium perchlorate gave **24** (a salt acceleration effect). Therefore, it appears that the formation of **24** can be rationalized by the acid-catalyzed isomerization of **23** as shown in the following diagram. Inspection of the Dreiding models of the Saytzeff and the Hofmann



olefins suggests that the former, a, would have increased steric hinderance between the C-1 hydrogen and the C-11 hydrogen much more than the latter, b, does.

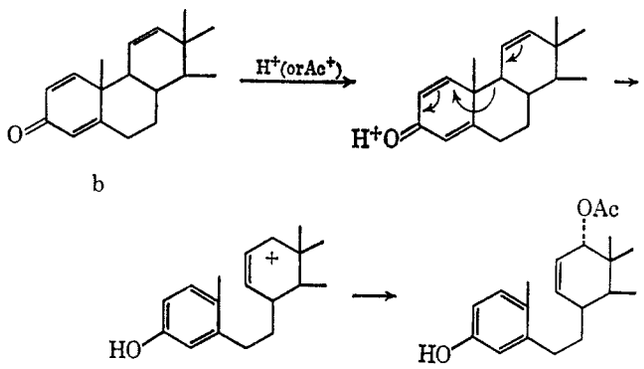


(37) For example, refer to D. V. Banthorpe, "Reaction Mechanisms in Organic Chemistry," Vol. II, E. D. Hughes, Ed., Elsevier Publishing Co., New York, N. Y., 1963.

(38) The formation of this kind of substituted product is usually unexpected in the steroid reaction.[39]

(39) *Cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 681.

This kind of circumstance is not the case for the olefins having other kinds of the A-ring structure. Therefore, the formation of b in the solvolysis of the cross-dienone compound in a considerable yield might be anticipated by the consideration of the well-known steric orientation effects in the E1 reactions.[40] If we assume the formation of the Hofmann olefin b, the formation of the products **25a** may be reasonably illustrated on the basis of acid-catalyzed isomerization as follows.



The acid-catalyzed cleavage of the allylic 9,10-bond appears not to be unlikely. We have had some positive evidences which indicate that the $\Delta^{11(12)}$-steroidal olefin does transform into a phenolic olefin under a condition such as used in this study. However, the complete elucidation of the mechanism and the further development of the facile dienone–phenol rearrangements observed in the above kinds of steroidal olefins will be the subject of the future research.

Experimental Section[41]

11α-Hydroxy-25D,5β-spirostan-2-one (5) (synthesized by A. Murabayashi).—To a suspension of 1.3 g of **8a** in 30 ml of ethylene glycol was added 430 mg of *p*-toluenesulfonic acid and the ethylene glycol was distilled off under the reduced pressure of 4 mm during 4 hr. Working up as usual gave 1.37 g of the 2-monoketal-11-one **8b**, mp 170–173°, ν_{max}^{Nujol} 1700 and 1115 cm^{-1} (*Anal.* Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.34; H, 8.88.). To a solution of 2.0 g of lithium metal in 200 ml of liquid ammonia was added a solution of 1.17 g of **8b** in 40 ml of ether and 10 ml of methanol. Excess of lithium was decomposed by addition of methanol, and liquid ammonia was evaporated at room temperature. Working up in the usual way yielded 1.15 g of the 2-ethyleneketal-11α-ol **8c**, mp 157–159°, ν_{max}^{Nujol} 3440 and 1115 cm^{-1} (*Anal.* Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.05; H, 9.46.). To a solution of 1.15 g of **8c** in 15 ml of acetone and 1 ml of water was added 100 mg of *p*-toluenesulfonic acid and the solution was refluxed for 1 hr on a steam bath. The reaction mixture was treated with 5% aqueous sodium carbonate, and the acetone was distilled over *in vacuo*. Crystallization of 1.14 g of the residue afforded 700 mg of **5**, mp 183–186°. An analytical sample showed mp 184–187° (from *n*-hexane–methylene dichloride), $[\alpha]_D$ −78.5° (*c* 0.348), ν_{max}^{Nujol} 3506 and 1714 cm^{-1} (*Anal.* Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 74.66; H, 9.77.).

11α-Hydroxy-25D,5β-spirost-1-en-3-one (6a).—The 11α-acetoxy-2β,3β-diol **2d** (250 mg) was dissolved in 16 ml of dry pyridine and tosylated with 400 mg of *p*-toluenesulfonyl chloride, and working up in the usual manner furnished 200 mg of the tosylate **2e**: mp 170–170.5° dec (from *n*-hexane–methylene dichloride); $[\alpha]_D$ −63.5° (*c* 1.112); ν_{max}^{Nujol} 3409, 1725, 1600, 1359, and 1169 cm^{-1} (*Anal.* Calcd for $C_{36}H_{52}O_8S$: C, 67.05; H, 8.13. Found: C, 67.09; H, 8.22.). (The monotosylate **2e** was converted to the known 3-keto derivative **4b**, mp 218–220°, in order to confirm the structure, by treatment with boiling collidine.) A solution of 8 *N* chromic acid in aqueous sulfuric acid was added dropwise to a solution of 9.0 g of **2e** in 150 ml of acetone until the orange color persisted. After being shaken at room temperature for 5 min, the mixture was diluted with water and extracted with chloroform–ether. An amorphous tosyloxy ketone **9** was obtained whose infrared band showed no hydroxyl absorption. To a solution of 9 g of **9** in 130 ml of dimethylformamide were added 5 g each of lithium chloride and lithium carbonate and the mixture was refluxed for 4 hr under nitrogen atmosphere. The reaction mixture was treated in the usual manner and the resulting product was chromatographed on alumina (Woelm II). Elution with petroleum ether (bp 35–55°)–benzene followed by benzene yielded 1.8 g of crystals of **6b**. Crystallization from *n*-hexane–methylene dichloride gave compound of mp 225–227°, $[\alpha]_D$ +22.4° (*c* 1.012), $\nu_{max}^{CCl_4}$ 1732 and 1685 cm^{-1} (*Anal.* Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 74.27; H, 9.10.). This material, **6b** (2.0 g), was saponified with 5% potassium hydroxide in methanol to afford about 2 g of the crude **6a**. Pure **6a** (from *n*-hexane–methylene dichloride) showed mp 270–271°: $[\alpha]_D$ −13.6° (*c* 1.057); $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (ε 9800); ν_{max}^{Nujol} 3370, 1655, and 1610 cm^{-1} (*Anal.* Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.39; H, 9.47.).

11α-Hydroxy-25D,5α-spirostane (10).—A solution of 3 g of **13** in 50 ml of ethyl acetate was shaken with 500 mg of platinum oxide under hydrogen, the catalyst was filtered off, and the filtrate was evaporated in a reduced pressure. The residue was recrystallized from methanol–chloroform to give 2.43 g of **10**, mp 178–181°, $[\alpha]_D$ −74.2° (*c* 0.780), ν_{max}^{Nujol} 3428 cm^{-1} (*Anal.* Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.80; H, 10.77.).

3-Methyl-11α-hydroxy-25D,5α-spirost-2-ene (11).—To a suspension of 30 g of triphenylmethylphosphonium bromide in 100 ml of anhydrous ether was added an ether solution of butyllithium under nitrogen atmosphere and the color of the solution was gradually changed into red. To this mixture 9 g of **15b** in 300 ml of anhydrous ether was added and the reaction mixture was allowed to stand overnight at room temperature. Then the ether was displaced with 250 ml of anhydrous tetrahydrofuran by slow distillation and the reaction mixture was refluxed for 7 hr with stirring. A large amount of water was added and the organic layer that separated was extracted with ether. After evaporation of the solvent, 15 g of the obtained residue was saponified with 10% methanolic potassium hydroxide. After treatment in the usual manner, the product was chromatographed on 200 g of alumina. Petroleum ether–benzene and benzene eluates gave 7.0 g of crystals, mp 210–217°, which on crystallization from *n*-hexane–methylene dichloride afforded 6.0 g of **20**: mp 215–217°; $[\alpha]_D$ −83.7 (*c* 0.919); ν_{max}^{Nujol} 3464, 3084, 1652, and 873 cm^{-1} (*Anal.* Calcd for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35. Found: C, 78.32; H, 10.36.). The 11-benzoate had mp 212–213°, $[\alpha]_D$ −78.8 (*c* 0.734) (*Anal.* Calcd for $C_{35}H_{48}O_4$: C, 78.90; H, 9.08. Found: C, 79.14; H, 9.18.). Isomerization of 1.0 g of **20** in 10 ml of dioxane and 1 ml of 70% perchloric acid at room temperature for 17 hr, followed by crystallization from methanol–chloroform, yielded 800 mg of the 3-methyl-2-en-11α-ol **11**, mp 204–207°, $[\alpha]_D$ −36.0° (*c* 1.141), ν_{max}^{Nujol} 3520 cm^{-1} (*Anal.* Calcd for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35. Found: C, 78.69; H, 10.35.).

3-Benzyl-11α-hydroxy-25D,5α-spirost-2-ene (12).—To a mixture of a few crystals of iodine and 3 g of magnesium turnings in 100 ml of anhydrous ether was added 20 g of benzyl chloride in 40 ml of anhydrous ether and, after the magnesium was completely dissolved, a solution of 3 g of **15b** in 50 ml of anhydrous benzene was added during 30 min. The reaction mixture was refluxed for 4 hr, cooled, and poured into dilute hydrochloric acid. The organic layer was separated and water phase was extracted with ether. The combined ethereal solution was washed with water, dried, and evaporated. The crude product was washed with petroleum ether to remove amorphous by-products. The crystals obtained (2.5 g) were further purified by alumina chromatography to yield 1.7 g of the 11α-hydroxy-3-benzylcarbinol **21a**: mp 234–235°; $[\alpha]_D$ −66.1° (*c* 1.001); ν_{max}^{Nujol} 3408, 1600, 1583, and 1495 cm^{-1} (*Anal.* Calcd for C_{34}-

(40) (a) H. C. Brown, and I. Moritani, *J. Am. Chem. Soc.*, **77**, 3607 (1955); (b) ref 37.

(41) Melting points were determined on a Yanagimoto micro melting point apparatus and are corrected. Ultraviolet spectra were recorded on a Hitachi recording spectrophotometer, Model DS301; infrared spectra were determined with a Nippon Bunko DS201B spectrometer; nmr spectra were determined at 60 Mc with a Varian A-60 spectrometer using tetramethylsilane as internal standard. Specific rotations were recorded in chloroform containing 1% ethanol with a Rudolf polarimeter.

TABLE III

Tosylate	Mp, °C[a]	[α]D, deg[b]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
1	156–157	−43.7	$C_{34}H_{50}O_6S$	71.54	71.53	8.83	8.75
2	156–157[c]	−54.6	$C_{34}H_{50}O_7S$	67.74	67.85	8.36	8.49
3	164–166.5	−26.2	$C_{34}H_{48}O_5S$	71.79	71.55	8.51	8.32
4	174–176	−33.9	$C_{34}H_{48}O_6S$	69.83	69.93	8.27	8.54
5	117–119	−15.3	$C_{34}H_{48}O_6S$	69.83	69.93	8.27	8.30
6	187–188.5	+53.2	$C_{34}H_{46}O_6S$	70.07	69.82	7.96	8.09
10	135–136	−55.2	$C_{34}H_{50}O_5S$	71.54	71.80	8.83	8.96
11	150–151	−30.4	$C_{35}H_{50}O_5S$	72.12	71.94	8.65	8.68
12	146–147	−28.7	$C_{41}H_{54}O_5S$	74.73	74.84	8.26	8.33
13	143–144	−33.7	$C_{34}H_{48}O_5S$	71.79	71.77	8.51	8.58
14	166–168	−36.2	$C_{35}H_{51}O_6NS$	68.48	68.44	8.38	8.28
15	150–152	−42.4	$C_{34}H_{48}O_6S$	69.83	69.97	8.27	8.39
16	159–160	−54.3	$C_{34}H_{48}O_6S$	69.83	69.74	8.27	8.37
17	176–177	−52.3	$C_{34}H_{48}O_6S$	70.07	70.34	7.96	7.91
18	174–176	−8.8	$C_{34}H_{46}O_6S$	70.07	70.02	7.96	7.91
19	197–198	+2.9	$C_{34}H_{44}O_6S$	70.31	70.09	7.64	7.65

[a] All the tosylates decompose at the melting point. [b] Measured in chloroform solution containing 1% ethanol. [c] Reference 1.

$H_{50}O_4$: C, 78.12; H, 9.64. Found: C, 78.25; H, 9.81.). The 11-monoacetate **21b** had mp 219–220°; [α]D −70.2 (*c* 1.112); ν_{max}^{Nujol} 3436, 1704, 1605, and 1495 cm^{-1} (*Anal.* Calcd for $C_{36}H_{52}O_5$: C, 76.55; H, 9.28. Found: C, 76.53; H, 9.28.).

Dehydration of 21a. A.—A solution of 1.7 g of **22a** in 30 ml of dioxane and 1 ml of 70% perchloric acid was refluxed for 1.5 hr on a water bath and then allowed to stand overnight at room temperature. Work-up in the usual manner gave 1.52 g of **13** as plates: mp 220–221°; [α]D 27.4° (*c* 0.813); ν_{max}^{Nujol} 3486, 3060 3020, 1600, 1495, and 710 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 260–262 mμ (ε 272) and 265–269 mμ (ε 215) (*Anal.* Calcd for $C_{34}H_{48}O_3$: C, 80.90; H, 9.59. Found: C, 80.94; H, 9.58.).

B.—To a solution of **21b** in 3 ml of anhydrous pyridine was added 0.2 ml of thionyl chloride at 0° with stirring. After a reaction time of 15 min, the reaction mixture was poured into water and the resulting precipitate was isolated. This precipitate (200 mg) was saponified with 20 ml of 5% methanolic potassium hydroxide to yield 150 mg of crystals. Recrystallization from *n*-hexane–chloroform afforded 80 mg of **12**, mp 221–223°, which was identical with that obtained in A.

11α-Hydroxy-3-methoxyimino-25D,5α-spirostane (14).—To a solution of 1 g of **15a** in 55 ml of ethanol was added 1 g each of O-methylhydroxylamine hydrochloride and sodium acetate, and the mixture was refluxed for 3 hr on a water bath. Water was added; the precipitate was filtered and recrystallized from aqueous ethanol to afford 600 mg of **14** as needles, mp 233–234°, [α]D −71.8° (*c* 1.051). Examination of the above crude precipitate by thin layer chromatography showed two kinds of isomeric products. By preparative thin layer chromatography, the two isomers were separated in nearly the same ratio and had the same melting point, 232–233°.

11α-Hydroxy-25D,5α-spirostan-2-one (16).—The 2,11-dione **22a** (4 g) was converted into 4.0 g of the 2-monoethyleneketal-11-one **22b** in the usual way: mp 223–228°, [α]D −42.0° (*c* 1.116) (*Anal.* Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.90; H, 9.52.). Reduction of **22b** as in the case of **8b** afforded 4.0 g of **22c**, mp 215–222°. Pure sample showed mp 223–225°: [α]D −73.3° (*c* 1.013); ν_{max}^{Nujol} 3463, 1071, and 1098 cm^{-1} (*Anal.* Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.42; H, 9.86.). **22c** (4.0 g) was converted to the crude **16** (2.89 g), mp 229–235°, by treatment with *p*-toluenesulfonic acid. An analytical sample exhibited mp 237–238°, [α]D −60.1° (*c* 1.038), ν_{max}^{Nujol} 3426 and 1694 cm^{-1} (*Anal.* Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.14; H, 9.90.).

11α-Hydroxy-25D,5α-spirost-1-en-3-one (18a).—A solution of 9.0 g, of **15b** and 5.4 g (1.2 mole equiv) of DDQ in dry dioxane was refluxed for 22.3 hr, avoiding moisture, and the usual work-up procedure afforded 9.0 g of brown crystals. Examination of the product by thin layer chromatography indicated contamination by the starting material **15a** and the dienone **19b**, besides the desired **17**. Chromatography on alumina afforded 3.5 g of crystals, mp 196–198°, but their further purification failed. Saponification of the crystals, mp 196–198°, with 50 ml of 5% methanolic potassium hydroxide followed by the reduction with 50 mg of sodium borohydride in 100 ml of 2-propanol for 10 min at room temperature yielded 3.2 g of an amorphous product. The product was purified by alumina chromatography, and the eluate from a mixed solvent of benzene and ether (4:1) was recrystallized from methanol–methylene dichloride to afford 600 mg of crystals of **17**: mp 240–242°; [α]D −70.9° (*c* 1.170); $\lambda_{max}^{95\%\ EtOH}$ 232 mμ (ε 11,600); ν_{max}^{Nujol} 3430, 1665, and 1600 cm^{-1} (*Anal.* Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.93; H, 9.46.).

General Procedure of Tosylation.—Tosylation was carried out by the following procedure except for **2c**. To a solution of 11α-hydroxy compound in pyridine was added about 2 or 3 mole equiv of *p*-toluenesulfonyl chloride under ice cooling and the mixture was allowed to stand at room temperature for 2 days. Cracked ice and water were added to the reaction mixture; the resulting precipitate was extracted with a mixed solvent of chloroform and ether, washed, dried over anhydrous sodium sulfate, evaporated, and recrystallized from *n*-hexane–acetone. The physical properties and elementary analyses of these tosylates are listed in Table III.

Structure of Acetolysis Products.—The acetolysis solution was allowed to remain in a constant-temperature bath for more than 10 half-lives of each of the *p*-toluenesulfonates, concentrated by distilling the acetic acid under a reduced pressure, diluted with ether–methylene dichloride, and treated with water and solid sodium carbonate to remove acetic acid. Most of all the products were separated with thin layer chromatography and in some cases with alumina chromatography. The results are listed in Table IV.

Structural Elucidation of the Phenolic Products Formed in the Acetolysis of 19c. A. Isolation.—The 11α-tosyloxy-1,4-dien-3-one **19c** (4.0 g) in acetic acid containing 0.035 *N* sodium acetate was heated at 90° avoiding moisture for 120 hr. Evaporation of the acetic acid, followed by isolation with ether–methylene dichloride, afforded 3.0 g of oily products, whose infrared spectrum showed bands at 1765 and 1735 cm^{-1}. Repeated extraction of a portion (2.5 g) of the products with petroleum ether, followed by preparative thin layer chromatography of the extracts, gave the three main compounds. One of them, a crystalline component, mp 210–212°, 0.825 g (33%), was identical with **23**.[1] The second was identified as **24**, 0.291 g (12%) of an oily material: [α]D −15.4° (*c* 1.064); $\nu_{max}^{CCl_4}$ 1772 (phenolic ester), 1208 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 247.5 mμ (ε 10,400) (styrene-type chromophore); nmr, singlet at τ 7.61 (methyl on aromatic ring), AB-type quartet (J = 3 cps) at τ 3.23 and 3.37 (two aromatic protons), multiplet at τ 4.32 (one vinyl proton), singlet at τ 7.73 (acetyl methyl). The third was **25a**, 0.156 g (6.2%) of an oily material: [α]D −18.3° (*c* 0.389); $\nu_{max}^{CCl_4}$ 1768 (phenolic ester), 1738 (ester), 1613, 1588, 1240, and 1210 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 266 mμ (ε 990) and 273 mμ (ε 910) (B-secosteroid type); nmr, τ ~2.8 (one aromatic proton),[17] ~3.1 (two aromatic protons),[42] 7.95 (singlet, methyl on aromatic ring), 4.15 (two vinyl protons), 5.03 (C*H*–OCOCH$_3$), and 7.75 (two methyls of acetoxyl group).

(42) These signals are characteristic of B-secosteroids. Refer to E. Kondo and K. Tori, *J. Am. Chem. Soc.*, **86**, 736 (1964).

TABLE IV

Δ⁹(¹¹)-Olefin produced from the tosylate of	Mp, °C	[α]D, deg[a]	Yield, %	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
1	109–110	−50.0	~100	$C_{27}H_{42}O_2$	81.35	81.21	10.62	10.54
2	197–200[b]		>90					
3	143–144	−101.6	~88	$C_{27}H_{40}O_2$	81.76	81.86	10.71	10.41
4	184–185[c]		~100					
5	163–165	−84.8	~100	$C_{27}H_{40}O_3$	78.59	78.61	9.77	9.73
6	186–188[c]		>80					
10	142–144	−62.9	~100	$C_{27}H_{42}O_2$	81.35	81.65	10.62	10.78
11	194–196	−22.8	~100	$C_{28}H_{42}O_2$	81.90	82.16	10.31	10.36
12	219–222	−15.2	~100	$C_{34}H_{46}O_2$	83.90	84.20	9.53	9.77
13	176–177	−38.4	>90	$C_{27}H_{40}O_2$	81.76	81.51	10.17	10.09
14	177–179	−37.6	~75	$C_{28}H_{43}NO_3$	76.15	75.97	9.81	9.68
15	185–187	−42.3	>90	$C_{27}H_{40}O_3$	78.59	78.48	9.77	9.54
16	194–197	−58.6	>90	$C_{27}H_{40}O_3$	78.59	78.33	9.77	9.59
17	194–196	−71.0	88	$C_{27}H_{38}O_3$	78.98	78.87	9.33	9.36
18	179–181	−14.9	>90	$C_{27}H_{38}O_3$	78.98	78.93	9.33	9.20

[a] Measured in chloroform containing 1% ethanol. [b] Its acetate was identified with an authentic sample.[1] [c] Identified with an authentic sample[1] by mixture melting point and infrared spectrum.

B. Hydrogenation of 24.—A solution of 15 mg of **24** in 10 ml of ethyl acetate was shaken with 50 mg of 10% palladium on charcoal under hydrogen. Filtration of the catalyst, evaporation, and recrystallization from *n*-hexane–ethyl acetate gave the dihydro compound **26**, mp 218.5–220°, [α]D +39.5° (*c* 0.301), $\nu_{max}^{CCl_4}$ 1765 and 1210 cm^{-1}, $\lambda_{max}^{95\%\ EtOH}$ 269 mμ (ε 374) and 277 mμ (ε 312) (*Anal.* Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 77.18; H, 8.98.). The structure of **26** was confirmed as 1-methyl-19-nor-25D-spirosta-1,3,5(10)-trien-3-ol acetate by comparison of infrared spectra and mixture melting point determination with an authentic sample prepared from **27** *via* the styrene derivative **28**, mp 170–172.5°, according to the method of Sondheimer.[43] Since the compound **24** showed the unidentical infrared spectrum with **28** and the nmr spectrum suggesting one vinyl proton, the position of the double bond of **24** was deduced to be at C-9(11).

C. Hydrogenation of 25a.—A mixture of 40 mg of **25a** in 10 ml of ethyl acetate containing 50 mg of 20% palladium on charcoal was shaken under hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was evaporated to dryness. Thin layer chromatography exhibited two spots. Separation of the mixture on thin layer chromatography afforded 12 mg of crystals of **29a** and 14 mg of an oily substance (**30**): $\nu_{max}^{CCl_4}$ 1765, 1210, 1735, and 1244 cm^{-1}. **29a** was recrystallized from methanol–ether to give an analytical sample, mp 121–123° (from methanol–ether), [α]D −84.5° (*c* 0.148), $\nu_{max}^{CCl_4}$ 1765 and 1210 cm^{-1}, $\lambda_{max}^{95\%\ EtOH}$ 266.5 mμ (ε 780) and 273.2 mμ (ε 760) (*Anal.* Calcd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.30. Found: C, 76.99; H, 9.30.). Infrared and nmr spectra of **29** indicated the saturation of double bond, the loss of allylic acetoxyl group, and the presence of phenolic acetoxyl group.

D. Preparation of 1-Methyl-3-acetoxy-Δ$^{1,3,5(10)}$-9,10-seco-25D-spirostatriene (29a).[44]—To a solution of 1.2 g of the 1,4-diene-3,11-dione **31**[1] in 45 ml of pyridine was added 23 g of freshly activated zinc dust, and the reaction mixture was heated under reflux for 2.5 hr with stirring. Work-up as described by Tsuda, *et al.*,[44] followed by acetylation and chromatography on alumina, afforded 916 mg of crystals, which were recrystallized from methanol–methylene dichloride to give 580 mg of the pure phenol acetate **32**, mp 144–146°, [α]D −58.6° (*c* 0.917) (*Anal.* Calcd for $C_{29}H_{40}O_5$: C, 74.32; H, 8.60. Found: C, 74.56; H, 8.78.). A mixture of 150 mg of **32** in 2 ml of triethylene glycol, 1 g of potassium hydroxide, and 10 ml of 80% hydrazine hydrate was boiled for 1 hr at 130°. Excess hydrazine hydrate was evaporated and the solution was heated for 2 hr, maintaining the inner temperature at 195°. Water was added to the reaction mixture and the product was extracted with chloroform to yield the crude phenol **29b**. Acetylation with acetic anhydride in pyridine and chromatography on silica gel yielded 110 mg of **29a**, mp 121–123° (from methanol–methylene dichloride), undepressed with the hydrogenolysis product of **25a** (*Anal.* Calcd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.24; H, 9.49.).

E. Saponification of 25a with Lithium Aluminum Hydride.—In order to establish the position of the acetoxyl group of **25a**, 24 mg of lithium aluminum hydride was added to a solution of 300 mg of **25a** in a mixed solvent of 5 ml each of anhydrous ether and tetrahydrofuran, and the mixture was kept for 1.5 hr at room temperature. Excess lithium aluminum hydride was decomposed with ethyl acetate and the solution was poured into cold water. Separation and concentration of the organic layer afforded 240 mg of an oily substance **25b**, which was purified by preparative thin layer chromatography. Since **25b** decomposed when kept at room temperature, it was used at once for the next step.

F. Partial Acetylation of 25b.—A solution of the above diol **25b** (330 mg) in a mixture of 13 ml each of chloroform and pyridine and 3.3 ml of acetic anhydride was allowed to stand at 0° for 3.5 hr. Work-up in the usual manner and purification by thin layer chromatography afforded 98 mg of the oily diacetate **25a** and 227 mg of the phenolic monoacetate **25c** as needles, mp 87–89° (from *n*-hexane–ether), [α]D −64.7° (*c* 0.300), $\nu_{max}^{CCl_4}$ 3300–3600 cm^{-1} (*Anal.* Calcd for $C_{29}H_{40}O_5 \cdot 0.5H_2O$: C, 72.92; H, 8.65. Found: C, 73.26; H, 8.69.).

G. Oxidation of the Phenolic Monoacetate 25c with Chromium Trioxide.—To a stirred solution of 140 mg of **25c** in 7 ml of pyridine was added 175 mg of chromium trioxide with cooling, and the mixture was kept for 23.5 hr at room temperature and then diluted with water. An oily oxidation product **33** (140 mg) was purified with thin layer chromatography: $\lambda_{max}^{95\%\ EtOH}$ 235 mμ (ε 16,600) (α,β-unsaturated ketone); $\nu_{max}^{CCl_4}$ 1768, 1210, and 1688 cm^{-1}.

H. Hydrogenation of the Conjugate Ketone 33.—A mixture of 45 mg of the conjugate ketone **33** in 10 ml of acetone containing 50 mg of 20% palladium on charcoal was shaken under a hydrogen current. Removal of the catalyst and evaporation of the acetone yielded 38 mg of an oily material, **34a**. A solution of 85 mg of this oil was allowed to stand on 5 g of basic alumina in benzene for 7 hr at room temperature. Washing the column with ether afforded 80 mg of an oily material, which was crystallized from *n*-hexane–acetone, giving 54 mg of long needles of **34b**, mp 88–90°, [α]D −27.6° (*c* 0.950), $\nu_{max}^{CCl_4}$ 3624–3400 and 1711 cm^{-1}, $\lambda_{max}^{95\%\ EtOH}$ 279.5 mμ (ε 21,000) (*Anal.* Calcd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 76.04; H, 8.87.). Since the nmr signal of the C-18 methyl proton[45] of **34b** is shifted to a lower field by 0.295 ppm when compared with that of the β-secosteroid **29** having no substituent in the C ring, the location of the carbonyl group of **34** was suggested to be at C-12. Complete structure proof of **34** was achieved by mixture melting point and comparison of infrared spectra with an authentic sample prepared as described below.

(43) F. Sondheimer, F. Neumann, H. J. Ringold, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 2230 (1954).

(44) The substantially identical procedure was used by Tsuda, *et al.*, for the preparation of 3-acetoxy-Δ$^{1,3,5(10)}$-9,10-secoandrostatriene-11,17-dione from androsta-1,4-diene-3,11,17-trione. See K. Tsuda, E. Ohki, and S. Nazoe, *J. Org. Chem.*, **26**, 2614 (1961); **28**, 783 (1963).

(45) *Cf.* K. Tori and K. Aono, *Ann. Rept. Shionogi Res. Lab.*, **14**, 136 (1964); R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

I. Preparation of an Authentic Sample of 34. 1. 3,12β-Diacetoxy-9,10-seco-25D-spirosta-1,3,5(10)-triene-3,11-dione (39).—A solution of the ketol **35**[46] (2.0 g) in 50 ml of toluene containing 20 ml of cyclohexanone was a little concentrated to remove moisture. Aluminum isopropoxide (1.0 g) was added and the mixture was refluxed for 1 hr. Water was added to the mixture, the organic layer was separated, and the aqueous phase was extracted with ether. The combined organic solutions were concentrated, leaving crude product of **36a**. Acetylation, followed by chromatography on alumina, yielded needles of **36b**, mp 251–253°, $[\alpha]_D$ −65.2° (*c* 1.004) (*Anal.* Calcd for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.54; H, 8.62.). Saponification of **36b** with methanolic potassium hydroxide afforded **36a**, mp 266.5–269.5°, $[\alpha]_D$ −24.8° (*c* 1.129), ν_{max}^{Nujol} 3446 and 1713 cm^{-1} (*Anal.* Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.99; H, 9.18.). To a solution of 14.0 g of **36b** in 250 ml of anhydrous dioxane was added 21 g of DDQ (2 mole equiv) and the solution was heated under reflux for 20 hr. The usual work-up procedure gave 10 g of brown crystals [mixture of **37** and **38** as suggested by ultraviolet spectrum: $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (ε *ca.* 7400) and 295 mμ (ε *ca.* 3800)], which were used for the next step without separation. The aromatization of 1.0 g of the crystals with 19 g of zinc in 38 ml of pyridine was carried out as described before,[47] and the oil so obtained was reduced catalytically with 20% palladium on charcoal in acetone. Purification by chromatography on silica gel gave 460 mg of a pure oil. Acetylation of this oil with acetic anhydride in pyridine followed by purification with thin layer chromatography yielded 318 mg of oily **39**: $\nu_{max}^{CCl_4}$ 1756, 1210, 1736, and 1235 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 266 mμ (ε 690) and 273 mμ (ε 650) (B-secosteroid type).

2. The 3-Monoacetate 41c and 3,12β-Diacetate of 41b.—The above-obtained **39** (200 mg) was treated with Huang-Minlon's procedure as described above and the product was separated into two oily components, **41a** (100 mg) and **42a** (38 mg), by thin layer chromatography. Acetylation of **42a** with acetic anhydride in pyridine yielded **42b** as needles, mp 113–114° (from methanol–ether), $[\alpha]_D$ −99.0° (*c* 0.789), $\nu_{max}^{CCl_4}$ 1765 and 1210 cm^{-1} (*Anal.* Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 76.99; H, 9.26.). Catalytic reduction of **42b** with palladium carbon in acetone gave **29a** as needles, mp 120–122°. The 9,10-seco-3,12β-diol **41a** (20 mg) was acetylated in the usual manner to yield the 3,12-diacetate **41b**: mp 162–163° (*n*-hexane–ether); $[\alpha]_D$ −79.1° (*c* 0.981); $\nu_{max}^{CCl_4}$ 1765, 1733, 1245, and 1210 cm^{-1} (*Anal.* Calcd for $C_{31}H_{44}O_6$: C, 72.62; H, 8.65. Found: C, 72.54; H, 8.64.). Acetylation of **41a** under mild conditions (with acetic anhydride in a mixture of pyridine and chloroform (1:1) at room temperature), followed by separation with preparative thin layer chromatography, yielded the monoacetate **41c**: mp 142–143° (*n*-hexane–ether); $[\alpha]_D$ −89.3° (*c* 0.664); $\nu_{max}^{CCl_4}$ 3600, 1768, and 1210 cm^{-1} (*Anal.* Calcd for $C_{29}H_{42}O_5 \cdot 0.5H_2O$: C, 72.62; H, 9.04. Found: C, 72.99; H, 9.00.).

3. 3-Hydroxy-9,10-seco-25D-spirosta-1,3,5(10)-trien-12-one (34b).—To a solution of 22.5 mg of **41c** in 1 ml of acetone was added 34 mg of chromic acid in aqueous sulfuric acid and the mixture was shaken for 4 min at room temperature. Work-up in the usual manner gave 21 mg of the oily substance: $\nu_{max}^{CCl_4}$ 1768, 1210, and 1713 cm^{-1}. Saponification with basic alumina as in the case of **34a** afforded long needles of **34b**, mp 88–90° (*n*-hexane–acetone), $\nu_{max}^{CCl_4}$ 3630–3400 and 1711 cm^{-1}, which was identified on admixture with the above degradation product **34b**. Consequently, **25a** was defined as 3-hydroxy-$\Delta^{1,3,5(10)}$-9,10-seco-25D-spirostatetraen-12ξ-ol 3,12-diacetate and there remains only the determination of configuration of the acetoxyl group at the C-12.

J. Orientation of the C-12 Acetoxy Group of 25a.—Since the infrared and nmr spectra of the saturated diacetoxyphenol **30** obtained from **25a** and those of the synthesized 3,12-dihydroxy-diacetate **41b**, even though the former could not be obtained in a crystalline form, are not identical with each other, and since the C-12 hydroxyl group of **41b** is to be β oriented, the configuration of the 12-hydroxyl group of **30** was assigned to be α. The C-12 proton signal of **30** was observed around τ 4.99 as a triplet (J = 2.5 cps), supporting the above assignment.[48]

Kinetic Measurements.—The chosen acetolysis conditions and procedures were similar to those of Winstein, *et al.*[14] Reagent grade acetic acid was heated under reflux with about 5% potassium permanganate for 10 hr, distilled dried over phosphorus pentoxide, and then redistilled. The distilled acid was further purified by collecting the fraction boiling at 117–118° after refluxing with 3% of acetic anhydride, and stored for use with addition of 0.5% acetic anhydride. Sodium acetate standard solution was made by dissolving anhydrous sodium carbonate in acetic acid and by refluxing for 5 hr with sufficient acetic anhydride to remove the water of neutralization, and its concentration was adjusted to 0.036 N at room temperature. Perchloric acid standard solution was prepared by adding reagent grade 70% perchloric acid to the solution of the above acetic acid and sufficient acetic anhydride to remove the water; the concentration was approximately 0.01 M. Samples of sulfonate ester were weighed into 40-ml volumetric flasks so that solutions approximately 0.035 M in ester would be obtained, then filled to 40 ml with sodium acetate–acetic acid solution. Rate constants were determined by the infinity titer method; zero time meant that the complete solution and thermal equilibrium had been reached. Aliquots, usually eight 4-ml portions of a reaction solution at reaction temperature, were pipetted directly from the volumetric flask into 20 ml of purified dioxane[49] in a constant-temperature bath at recorded times. In necesssary cases, aliquots were pipetted from the flask at a constant temperature into ampoules. The sealed ampoules were placed in the constant-temperature bath at once and individual ampoules were removed at recorded times and plunged into ice-cold water. "Infinity" ampoules were removed after at least ten half-lives and usually two were taken for each run. The contents of each ampoule were diluted with 20 ml of dioxane. Two drops of saturated solution of bromophenol blue in acetic acid was added, and the residual sodium acetate was titrated with the perchloric acid solution. Plots of log $(A_t - A_\infty)$ *vs.* time, where A_t and A_∞ are titers at any time and "infinity," respectively, were uniformly linear. The slopes multiplied by −2.303 gave the pseudo-first-order rate coefficients. Data from a representative run are presented in Table V. The plot of log $(A_t - A_\infty)$ *vs.* time was linear with slope 6.720 × 10^{-4}; multiplied by −2.303/60, this gave the rate coefficient, 2.58 × 10^{-5} sec^{-1}.

TABLE V

ACETOLYSIS OF 4. A TYPICAL RUN AT 65.40 ± 0.02°

Time, min	Ml of $HClO_4$ required	$A_t - A_\infty$	log $(A_t - A_\infty)$
15	13.75	11.78	1.0712
75	12.68	10.71	1.0298
200	10.80	8.83	0.9460
275	9.75	7.78	0.8910
395	8.55	6.58	0.8182
515	7.65	5.68	0.7543
755	5.80	3.83	0.5832
975	4.70	2.73	0.4362
∞	1.97 (an average value of two aliquots)		

(46) J. Elks, G. H. Philips, T. Walker, and K. J. Wymann, *J. Chem. Soc.*, 4330 (1956).

(47) It has been known that the 11-keto-12-ols are not subjected to a reductive elimination of the hydroxyl group under the condition used here: refer to F. J. Mcquillin, "Technique of Organic Chemistry," Vol. 11, Part 1, A. Weissberger, Ed., Chapter 9, p 543.

(48) *Cf.* Y. Kawazoe, Y. Sato, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963).

(49) Refer to L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 285.