(26) J. W. Wilt and W. J. Wagner, *J. Org. Chem.*, **29**, 2788 (1964).
(27) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **86**, 485 (1964).
(28) J. F. Sawage, R. H. Baker, and A. S. Hussey, *J. Am. Chem. Soc.*, **82**, 6090 (1960).
(29) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).
(30) H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *J. Am. Chem. Soc.*, **91**, 2150 (1969).
(31) H. C. Brown and K. Murray, *J. Am. Chem. Soc.*, **81**, 4108 (1959).

Mass Spectrometry in Structural and Stereochemical Problems. 248.[1] Stereochemical Effects in Electron Impact Induced Retro-Diels–Alder Fragmentations[2]

J. Scott Dixon, I. Midgley, and Carl Djerassi*

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received October 26, 1976*

Abstract: A series of Δ^7-steroidal olefins has been synthesized in order to study the effect of stereochemistry on the electron impact induced retro-Diels–Alder (RDA) fragmentation. The mass spectra show a marked dependence upon the stereochemistry of the A/B ring juncture, in accord with orbital symmetry rules for a thermal concerted process. These results represent the first example of such apparent symmetry control in olefinic hydrocarbons. It is proposed that electron impact results in an ion in which the stereochemistry of the ring juncture is preserved and that this ion undergoes RDA fragmentation via a concerted mechanism.

Electron impact induced fragmentations which formally correspond to a retro-Diels–Alder (RDA) reaction are frequently observed in the mass spectra of six membered ring olefins and their utility in the structure elucidation of organic compounds is well established.[3] However, the mechanism of this fragmentation is still unclear and has been the subject of several recent studies. The two mechanisms which have been proposed are a stepwise cleavage initiated by electron impact or a concerted "quasi-thermal" or "quasi-photochemical" process.

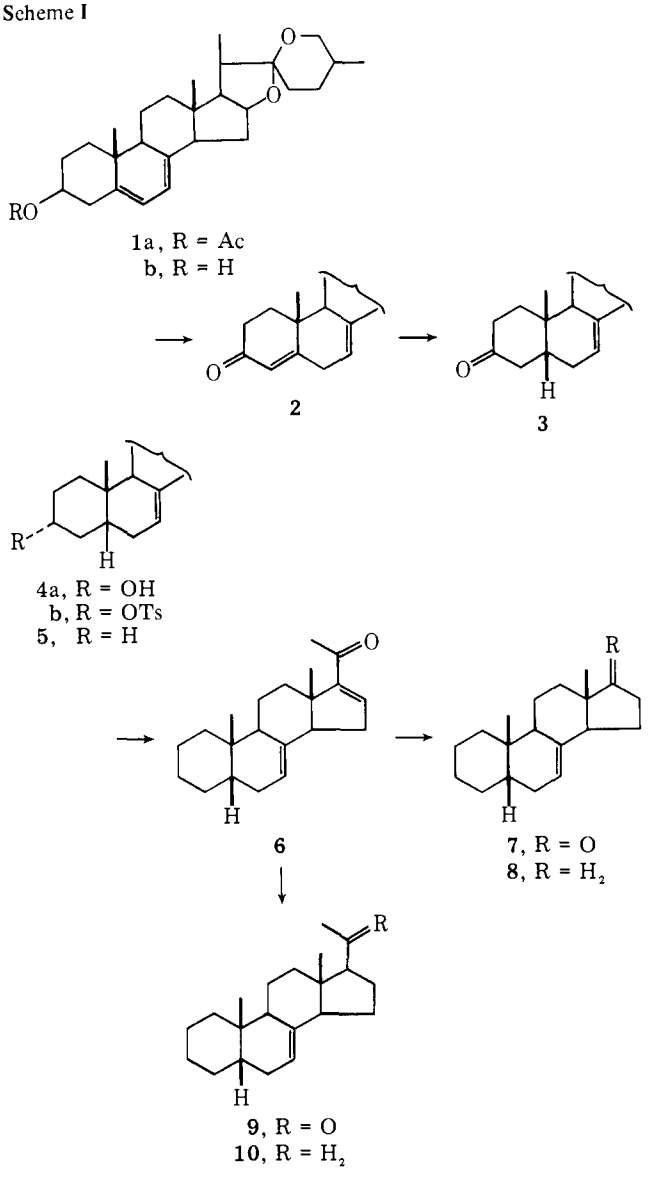
Evidence for the stepwise process comes from studies of the charge distribution in the RDA fragmentation products of numerous organic compounds.[4,5] The fact that these distributions can be rationalized by consideration of the stabilities of the various possible radical and carbonium ion intermediates is taken as support for the stepwise pathway.

Dougherty[6] supports the concerted process based on theoretical considerations. The work of Elwood and Beynon[7] also would seem to support the concerted mechanism. They suggest that a correlation exists between the energy released in the metastable transitions of the RDA reaction of some gaseous bicyclic hydrocarbon ions and the ground state activation energy for the Diels–Alder reaction for formation of similar neutral molecules in solution.

If the electron impact induced RDA is concerted then it should follow the same orbital symmetry rules[8] as a thermal or photochemical RDA reaction. Mandelbaum and co-workers[9] have reported that the RDA of some cis- and trans-fused polycyclic ketones shows a dependence on the stereochemistry of the ring juncture which is in accord with the rules for a thermal concerted process. However, other studies of polycyclic compounds[10] and simple bicyclic olefins[11] have not consistently shown similar dependencies. A fortuitous observation in our laboratory[11] that the RDA of some Δ^7-steroidal olefins shows a remarkable dependence on the stereochemistry (5β series strongly favored) of the A/B ring juncture has prompted us to prepare and study a series of 5α- and 5β-Δ^7 steroids in order to gain further insight into the mechanistic aspects of these results, which imply the occurrence of a concerted, symmetry controlled process.

Synthesis of Δ^7 Steroids. The hitherto undescribed 5β isomers of androst-7-ene (**8**) and pregn-7-ene (**10**) were synthe-

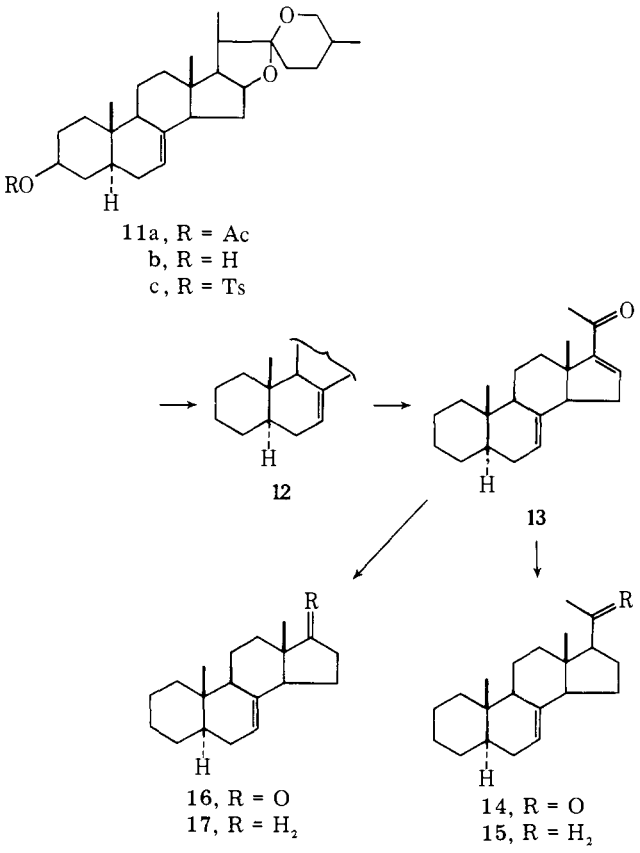
Scheme I



sized beginning with 22α-$\Delta^{5,7}$-spirostadien-3β-ol acetate (**1a**) (Scheme I). Hydrolysis of the acetate and Oppenauer oxidation gave **2**[12] which was catalytically reduced to produce the cis ring juncture in **3**.[13] The ketone was converted to the hydrocarbon **5** by lithium aluminum hydride reduction, formation of the tosylate **4b**, and treatment with lithium aluminum hydride. The side chain degradation was performed by the method of Wall[14] to give 5β-pregna-7,16-dien-20-one (**6**). Beckmann rearrangement[15] led to 5β-androst-7-en-17-one (**7**) which was reduced by the Wolff-Kishner method to 5β-androst-7-ene (**8**). Catalytic reduction[13] of **6** gave 5β-pregn-7-en-20-one (**9**) whose keto function was similarly reduced to give 5β-pregn-7-ene (**10**).

The isomeric A/B trans-fused hydrocarbons **15** and **17** were prepared as shown in Scheme II. 5α,22α-Δ^7-Spirosten-3β-ol

Scheme II

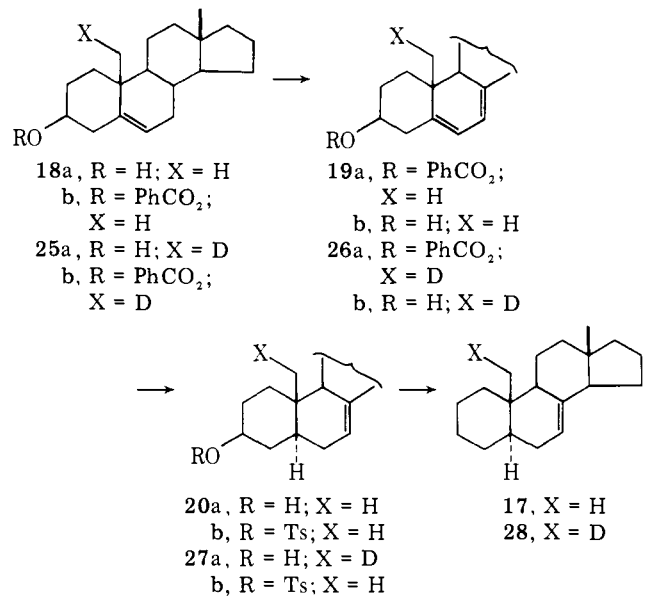


acetate (**11a**) (which can be prepared by hydrogenation[16] of **1a**) was hydrolyzed and the alcohol function removed by reduction of the derived tosylate **11c**. The degradation of the side chain gave 5α-pregna-7,16-dien-2-one (**13**) which was transformed in the same manner as the 5β isomer (**6**) to give 5α-androst-7-en-17-one (**16**), 5α-androst-7-ene (**17**), and 5α-pregn-7-ene (**15**).

5α-Androst-7-ene (**17**) was also prepared by the method shown in Scheme III as a model for the preparation of the C-19 deuterated compound **28** which was also needed. The known benzoate ester **18b** was allylically brominated[17] with 1,3-dibromo-5,5-dimethylhydantoin and dehydrobrominated[17] with trimethyl phosphite to give the 5,7-diene **19a** which was hydrolyzed to alcohol **19b**. Platinum oxide reduction of this diene was unsuccessful owing to double bond migration even though a neutral medium was employed. However, reduction with W-5 Raney nickel[18] afforded 5α-androst-7-en-3β-ol (**20a**) which was converted to the tosylate and reduced with lithium aluminum hydride to the desired hydrocarbon **17**.

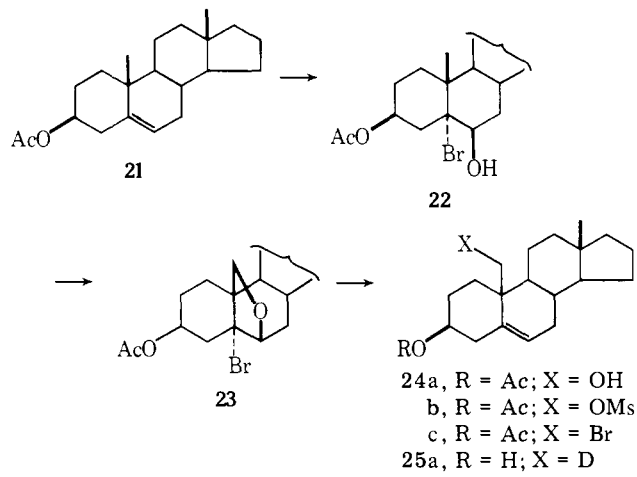
The key intermediate for the synthesis of 5α-androst-5-en-3β-ol-*19-d* (**25a**) was 5α-androst-5-ene-3β,19-diol 3-acetate

Scheme III



(**24a**), which was prepared (Scheme IV) from androst-5-en-3β-ol acetate (**21**) via the bromohydrin **22** and the ether **23**

Scheme IV



followed by reductive cleavage with zinc.[19] Deuterium was introduced, as peviously described,[20] via the mesylate **24b** and bromide **24c** to yield 5α-androst-5-en-3β-ol-*19-d* (**25a**) whose further transformation to 5α-androst-7-ene-*19-d* (**28**) was effected according to Scheme III.

In order to study the possible effect of the stereochemistry of the C/D ring juncture, cis-fused 14β steroids were generated by reduction of the corresponding $\Delta^{8(14)}$-7 ketones (Scheme V), a method developed earlier[21] for the preparation of 5α,14β-cholest-7-ene (**41**). 5α,14β-Pregn-7-ene (**31**) and 5α,14β-androst-7-ene (**34**) were synthesized in a similar manner except that reduction of the α,β-unsaturated ketones (**30** and **33**) was performed with zinc and 1 N methanolic sulfuric acid[22] to yield directly the 14β-Δ^7 steroids. This latter procedure gave compound **31** cleanly but resulted in some isomerization (presumably to the $\Delta^{8(14)}$ isomer) in the case of the androstene **34**, which had to be purified by preparative gas chromatography.

5β-Chol-7-ene (**40**) was prepared from 7-ketocholic acid (**35**) as shown in Scheme VI. The Δ^7 double bond was introduced by a Bamford-Stevens[23] reaction followed by formation of the tosylate **37** and reduction to **38a**. This compound was transformed to the alcohol **38c** by way of the tosylate **38b** and lithium aluminum hydride reduction. The C-12 alcohol was removed by oxidation to the ketone followed by Wolff-Kishner

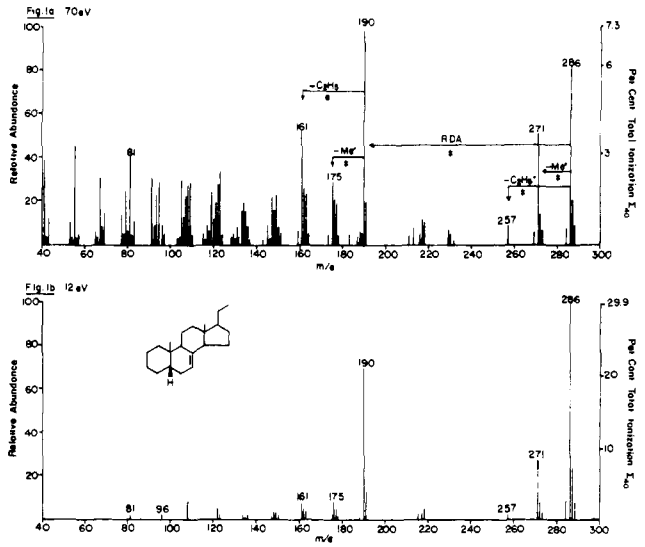


Figure 1. Mass spectra of 5β-pregn-7-ene (**10**): (a) 70 eV; (b) 12 eV.

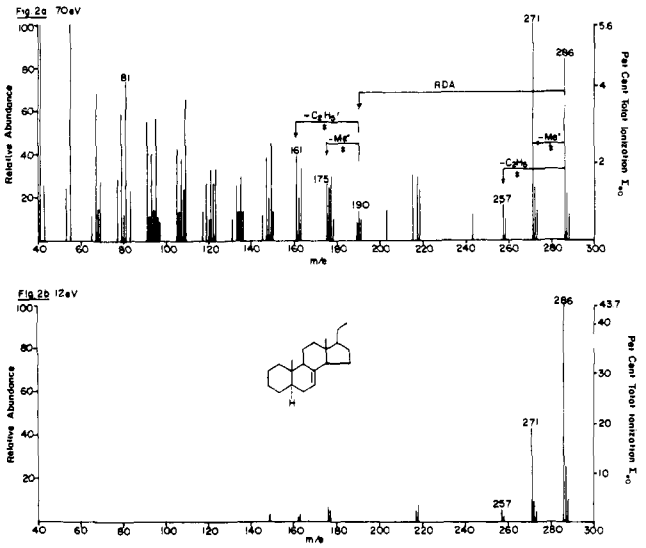
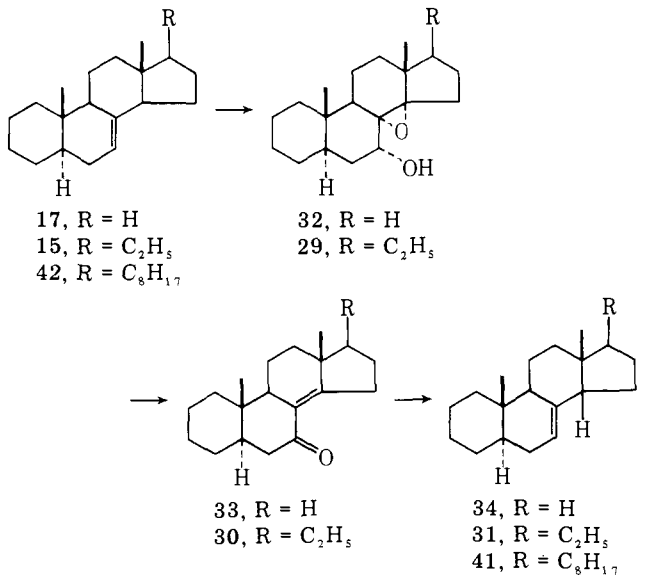


Figure 2. Mass spectra of 5α-pregn-7-ene (**25**): (a) 70 eV; (b) 12 eV.

Scheme V

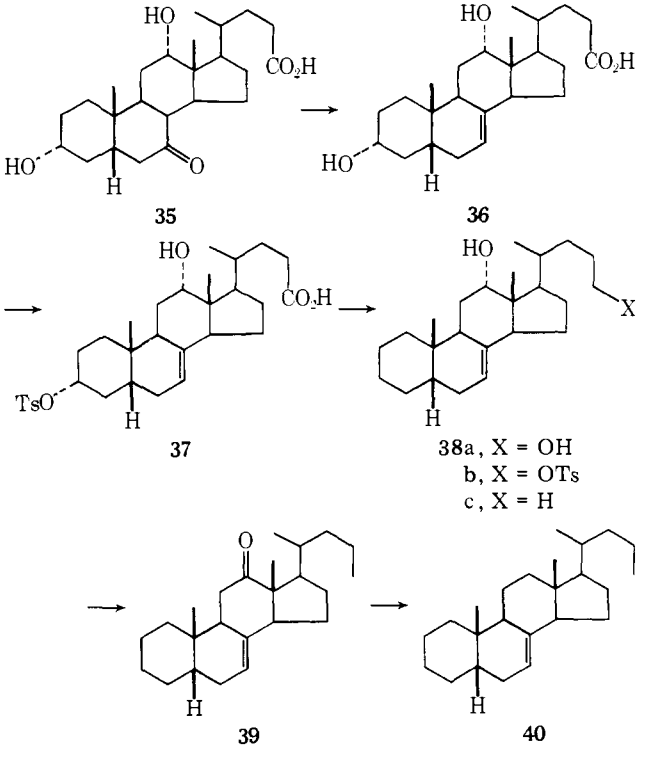


reduction to 5β-chol-7-ene (**40**). An appropriate 5α counterpart, 5α-cholest-7-ene (**42**), has already been described.[24]

Results and Discussion

Although the mass spectra of 5α-Δ^7 steroids have been described previously, the corresponding 5β-Δ^7 isomers have not been investigated. Figures 1 and 2 show the mass spectra of 5β-pregn-7-ene (**10**) and 5α-pregn-7-ene (**15**), respectively. The most striking difference between the two spectra is the intensity of the peak at *m/e* 190 which corresponds to the diene fragment from the RDA. While the *m/e* 190 peak is the base peak in the spectrum of **10** it is one of the minor peaks in the spectrum of **15**. It can be seen from the data in Table I that, in all the Δ^7-steroidal olefins studied, the isomers with cis-fused A/B ring junctures show more intense peaks for the RDA fragmentation than the corresponding trans-fused ring isomers. Since this difference is in accord with orbital symmetry predictions[8] for concerted thermal processes, it suggests that the electron impact induced RDA in these compounds is "quasi-thermal". The greatly increased contributions from the RDA fragmentation at 12 eV in the 5β isomers (Figure 1b) suggests that the RDA in these compounds is a low energy process as compared to the 5α isomers (Figure 2b) in which the RDA

Scheme VI



contributes little at 12 eV. More significantly, the 12-eV spectra effectively rule out extensive secondary fragmentation of the RDA ion in the 5α series. Such secondary fragmentations, if they had occurred preferentially in the 5α series, could have accounted for some of the spectral differences.

A priori, these results are somewhat surprising, since data from the mass spectra of other steroidal olefins favor a stepwise mechanism for the RDA. For example, in the mass spectrum of 5α-androst-2-ene,[25] in which the thermal RDA is not allowed, the base peak is the RDA diene fragment. Even stronger evidence for the stepwise cleavage mechanism is found in comparison of the mass spectra of 5α-cholest-2-ene (**43**) and 5α-lanost-2-ene (**44**).[4] In the former, the major RDA fragment ion is the ene b whereas in the latter the major RDA fragment ion is dimethylbutadiene d. This reflects the difference in stability of the stepwise intermediates a and c which lead to the ionized ene or ionized diene, respectively.[4]

Table 1. Mass Spectral Data[a]

	M^+		$M^+ - Me$		$M^+ -$ side chain		RDA		RDA − Me		RDA − side chain	
	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV	70 eV	12 eV
5α-Androst-7-ene **(17)**	6.3 (67)	27.9 (100)	9.4 (100)	19.3 (69)			2.6 (28)	4.7 (17)	3.6 (38)	1.4 (5)		
5α,14β-Androst-7-ene **(34)**	7.2 (37)	48.5 (100)	19.5 (100)	21.8 (45)			4.1 (21)	3.9 (8)	2.9 (15)	0 (0)		
5β-Androst-7-ene **(8)**	2.0 (26)	24.3 (100)	3.7 (35)	9.7 (40)			7.6 (100)	24.3 (100)	5.0 (66)	1.7 (7)		
5α-Pregn-7-ene **(15)**	4.7 (84)	43.7 (100)	5.5 (99)	18.8 (43)	0.9 (16)	2.2 (5)	0.7 (13)	0 (0)	1.5 (26)	0 (0)	2.2 (39)	0 (0)
5α,14β-Pregn-7-ene **(31)**	3.4 (37)	34.8 (100)	9.2 (100)	14.3 (41)	0.9 (10)	1.4 (4)	0.4 (4)	0.7 (2)	1.6 (17)	0 (0)	4.6 (50)	0.7 (2)
5β-Pregn-7-ene **(10)**	6.0 (82)	29.9 (100)	3.6 (50)	8.4 (28)	0.6 (8)	0.9 (3)	7.3 (100)	21.0 (70)	2.0 (28)	0.9 (3)	3.8 (52)	2.1 (7)
5α-Cholest-7-ene **(42)**[24]	8.5 (100)	42.2 (100)	3.0 (35)	7.2 (17)	4.8 (57)	10.1 (24)	0.3 (3)	0.6 (2)	0.3 (3)	0.6 (2)	1.7 (20)	1.2 (4)
5α,14β-Cholest-7-ene **(41)**[b]	5.5 (100)	37.4 (100)[c]	4.9 (89)	17.5 (47)	2.2 (41)	6.7 (18)	0 (0)	0 (0)	0.2 (3)	1.5 (4)	2.5 (47)	0 (0)
5β-Chol-7-ene **(40)**	11.0 (100)	44.3 (100)	2.6 (24)	4.4 (10)	3.0 (28)	5.3 (12)	6.4 (58)	16 (36)	0.8 (7)	0.7 (2)	4.2 (38)	1.8 (4)
5α-Androst-7-en-17-one **(16)**	5.6 (95)	58.1 (100)	1.8 (31)	5.8 (10)			2.6 (44)	6.4 (11)	0.7 (12)	0 (0)		
5β-Androst-7-en-17-one (7)	6.3 (48)	35.4 (100)	1.7 (13)	3.5 (10)			13.2 (100)	31.8 (90)	0 (0)	0 (0)		

[a] Mass spectra obtained with a MS9 unless otherwise noted. The numbers in parentheses are percent relative abundance. The other numbers are percent total ionization (% $\Sigma_{4\,0}$). [b] Mass spectrum obtained with an Atlas CH4. [c] Spectrum taken at 15 eV.

Allylic cleavage of the 5-6 or 9-10 bonds in the Δ^7 steroids would lead to intermediates similar to a or c and these would not be expected to show stereochemical dependence. However, allylic cleavage of the 13-14 bond leads to intermediates such as e in which the stereochemistry of the A/B ring juncture is preserved. Cleavage of the 13-14 bond (Scheme VII) should be a favorable process since it relieves the strain of the trans-fused hydrindan (C/D) system and also relieves the steric crowding between the C-18 methyl group and the C-17 side chain (in those cases where R ≠ H).

It is ion e which we postulate undergoes symmetry controlled RDA decomposition (Scheme VII). This would explain why

Scheme VII

Table II.[a] Metastable Defocusing Data

Compd	Daughter ion	Parent ion
5β-Chol-7-ene (**40**)	232 RDA	328 M^+
	161	232 (l) RDA
		257 (s)
5β-Pregn-7-ene (**10**)	190 RDA	286 M^+
	175	190 (l) RDA
		271 (m)
	161	190 (l) RDA
		271 (s)
		257 (s)
5α-Pregn-7-ene (**15**)	190 RDA	286 (l) M^+
		272 (m)
	161	190 (m) RDA
		271 (m)
		176 (s)
		257 (s)
		286 (s) M^+
5α-Androst-7-ene (**17**)	162 RDA	258 (l) M^+
		244 (s)
	149	258 (l) M^+
		243 (m)
		164 (s)
	148	258 (l) M^+
		244 (s)
		163 (s)
	147	162 (m) RDA
		243 (m)
		258 (s) M^+
		176 (s)

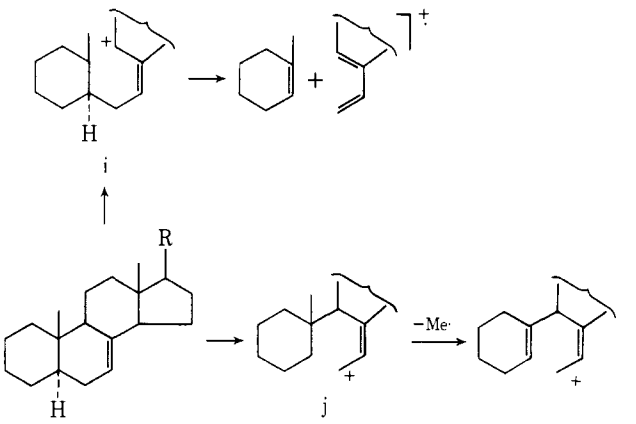
[a] The letters l, m, and s indicate the approximate relative intensities of the metastable peaks for each daughter ion; l = 60-100%, m = 30-60%, s = 0-30%. These results are indicative only of processes occurring in the first field-free region of the mass spectrometer.

the 5β compounds show more intense RDA peaks since, in ion e, the thermal concerted RDA is a symmetry allowed [$_\pi 2_s + {}_\pi 4_s$][8] process whereas the 5α steroids lead to ions such as f in which the RDA is not thermally allowed. It is also reasonable that the Δ^2 steroids fragment by a stepwise RDA process since, in the Δ^2 steroids, no allylic cleavages (see a and c) are possible in which the stereochemistry of the ring juncture remains intact.

Metastable defocusing[26] measurements (Table II) show that the RDA ion in 5β-chol-7-ene (**40**) and 5β-pregn-7-ene (**10**) arises only from the molecular ion, whereas the ion corresponding to loss of the steroid side chain from the RDA ion (h, Scheme VII) arises primarily from the RDA ion (g) and only to a small extent from the ion corresponding to loss of the side chain from the molecular ion. Conventional metastable ions (from the second field-free region) are observed for the fragmentations shown in Scheme VII for compounds **40** (R = C_5H_{11}) and **11** (R = C_2H_5) (Table III). For 5β-androst-7-ene (**8**) conventional metastable ions are observed for all fragmentations except the RDA. It should be noted that this compound (**8**) also shows the lowest degree of stereochemical dependence in the RDA fragmentation as judged by the RDA ion intensities. In addition, in the octalin series,[11] metastable peaks were not observed for the RDA cleavage, and no stereochemical dependence was evident.

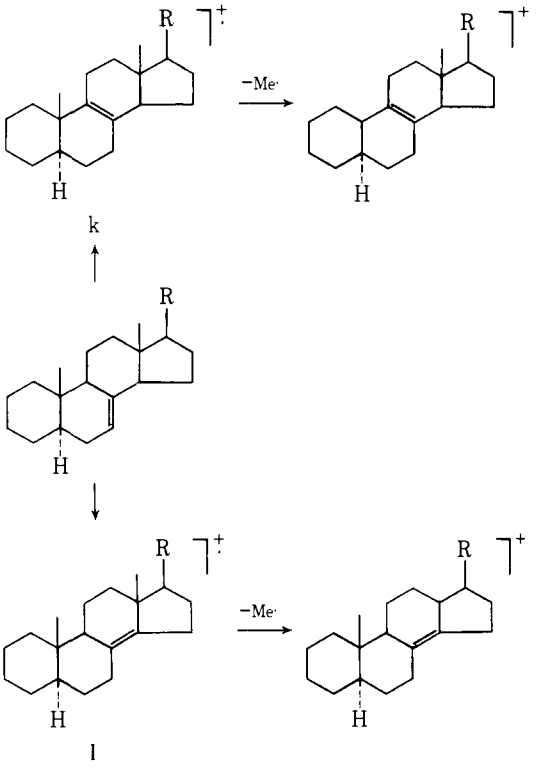
Another important difference between the mass spectra of the 5α and 5β compounds is in the intensity of the $M^+ - Me$ peaks. The 5α-steroidal hydrocarbons display consistently more intense $M^+ - Me$ peaks than the 5β isomers. Although the loss of 15 mass units can arise from many sources if hydrogen rearrangements should intervene, one attractive mechanism is allylic cleavage of the 5-6 bond to give ion j which would then favor expulsion of the C-19 methyl group (Scheme VIII). In order to ascertain the amount of loss of the

Scheme VIII



C-19 methyl group, 5α-androst-7-ene-*19-d* (**28**) was synthesized. Examination of the mass spectrum of this compound shows that loss of the C-19 methyl group accounts for 37% (after correction for isotopic purity and ^{13}C natural abundance) of the $M^+ - Me$ ion intensity. Since the loss of the C-19 methyl group also accounts for 37% of the $M^+ - Me$ ion intensity in androstane,[27] the presence of a Δ^7 double bond apparently does not facilitate loss of the C-19 methyl. The 12-eV spectrum of the C-19 labeled compound **28** shows that secondary fragmentations cannot result in preferential destruction of M − (C-18) or M − (C-19) ions, since the amount of C-19 loss is the same in the low-voltage spectrum. Therefore, contributions from ion j (which would be expected to be less stable than i in any case) are negligible. The methyl loss could also occur by migration of the double bond to the tetrasubstituted 8-9 or 8-14 positions (Scheme IX), which would facilitate loss of the C-19 or C-18 methyl groups, respectively.

Scheme IX



Increased loss of the C-19 methyl group (through ion k) can be ruled out by the results presented above for the deuterated compound **28**. Increased loss of the C-18 methyl group (through **1**) is unlikely since 5α-cholest-8(14)-ene ($M^+ = \Sigma_{40}$ 14.1%; $M^+ - Me = \Sigma_{40}$ 3.7%) shows only slightly more methyl

Table III. Metastable Ions

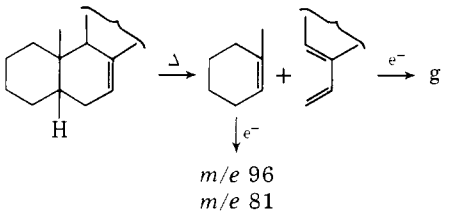
Fragmentation compd	$M^+ \rightarrow M^+ - Me$	$M^+ \rightarrow M^+ -$ side chain	$M^+ \rightarrow RDA$	$M^+ - Me \rightarrow RDA - Me$	$RDA \rightarrow RDA - Me$	$RDA \rightarrow RDA -$ side chain
5α-Androst-7-ene (**17**)	229.0			89.0	133.3	
5α,14β-Androst-7-ene (**34**)				89.2		
5β-Androst-7-ene (**8**)	229.0			89.2	133.5	
5α-Pregn-7-ene (**15**)	257.0	231.0			161.5	136.5
5α,14β-Pregn-7-ene (**31**)	257.0				161.2	
5β-Pregn-7-ene (**10**)	257.0	231.0	126.2		161.5	136.4
5α-Cholest-7-ene (**42**)	340.5	178.5			340.6	94.6
5β-Chol-7-ene (**40**)	298.5	201.5	164.0		203.0	111.6

loss[28] than 5α-cholest-7-ene ($M^+ = \Sigma_{40}$ 8.5%; $M^+ - Me = \Sigma_{40}$ 3.0%). Thus it seems that the increased methyl group loss in the 5α steroids is not due to participation of the double bond but instead reflects the absence of the low-energy concerted RDA fragmentation as a competing pathway.

According to the hypothesis presented here, compounds in which cleavage of the 13–14 bond (ion e) is less favorable should show more stepwise RDA fragmentation and hence less dependency on the stereochemistry of the A/B ring juncture. Removal of or reduction of the size of the side chain should result in less 13–14 bond cleavage since the steric interactions with the C-18 methyl group are relieved. The data in Table I show an increase in the RDA fragmentation in both the 5α, 14α (**17** > **15** > **42**) and 5α, 14β (**34** > **31** > **41**) series as the size of C-17 side chain decreases. In the cholestene series, loss of the side chain becomes more important; this is a process previously noted to be diagnostic in Δ^7-steroidal hydrocarbons.[29] Another factor which might influence the amount of 13–14 bond cleavage is the stereochemistry of the C/D ring juncture. However, comparison between the 14α (trans) and 14β (cis) compounds shows little difference in the amount of RDA fragmentation, indicating that 13–14 bond cleavage is favorable in either case.

Our data appear consistent with the view that formation of ion e is the factor which determines whether the electron impact induced RDA fragmentation goes through a symmetry controlled "quasi-thermal" mechanism or a stepwise mechanism. In the cases where formation of ion e is most favorable, the greatest amount of symmetry control is observed. In the cases where formation of ion e is less favorable, products from higher energy stepwise processes (Scheme VIII) become more prevalent. However, an alternative mechanism involving thermally induced RDA prior to electron impact induced ionization (Scheme X) should also be considered. Contributions from such a mechanism are probably minor since ions of mass 96 and 81 are of low intensity in the spectra (particularly at 12 eV) of the 5β compounds (for example, Figure 1b).

Scheme X



m/e 96
m/e 81

Budzikiewicz and Linscheid[5] have concluded that the site of electron impact induced ionization determines the course of the RDA fragmentation. In their study of Δ^2 steroids they found that in cases where ionization involves the double bond, stepwise RDA fragmentation results, whereas when ionization occurs away from the double bond, the RDA fragmentation is repressed. However, they examined only 5α steroids in which the concerted RDA fragmentation is not symmetry allowed. In light of the results with 5β steroids where the concerted RDA is allowed, it is possible to extend the conclusions of Budzikiewicz and Linscheid[5] by stating that the course of initial ionization determines whether a stepwise or a "quasi-thermal" RDA fragmentation can occur. When ionization proceeds with retention of the stereochemistry of the cyclohexene ring fusion (by formation of ions of type e or else by ionization at a site removed from the double bond) then a concerted RDA will occur (when symmetry allowed). When the initial ionization involves destruction of the ring stereochemistry (such as in ions a and g), then stepwise RDA fragmentation will intervene.

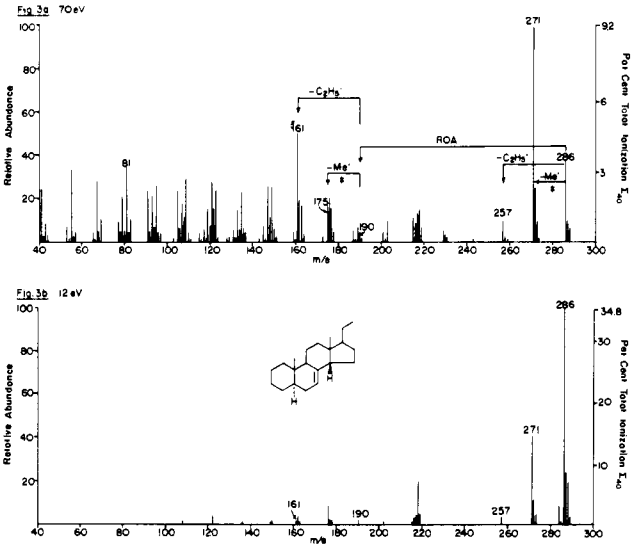


Figure 3. Mass spectra of 5α,14β-pregn-7-ene (**31**): (a) 70 eV; (b) 12 eV.

Experimental Section

General. Melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on Varian T-60 or XL-100 spectrometers using deuteriochloroform as solvent and tetramethylsilane as an internal standard. Infrared spectra were obtained on Perkin-Elmer 41 or 700 spectrophotometers. Low-resolution mass spectra were obtained by Mr. R. G. Ross on an AEI MS-9 instrument using a direct inlet system. Elemental analyses were determined by the Microanalytical Laboratory, Stanford University. Optical rotations were measured for solutions in chloroform using a Perkin-Elmer Model 141 spectropolarimeter. UV spectra were recorded on a Cary 14 spectrometer. Exact masses were determined on a Varian-MAT 711 high-resolution mass spectrometer.

Gas chromatography was done on a Hewlett-Packard 402 high-efficiency gas chromatograph using a 6-ft column packed with 3% OV-25 on Gas-Chrom Q (100–200 mesh). Preparative gas chromatography was done with a column of 3% OV-17 on Gas Chrom Q.

Column chromatography was done on Merck neutral activity 1 alumina or silica gel 60 as noted. TLC was done with silica gel HF 254 + 356 plates visualized by spraying with ceric sulfate solution (2% in 1 M sulfuric acid) followed by heating.

Chemical shifts for the C-18 and C-19 methyl signals were calculated by the method of Zürcher.[30]

5β,22α-Spirost-7-ene (5). 5β,22α-Spirost-7-en-3α-ol[13] (**4a**, 9.5 g) and 10.5 g of tosyl chloride were dissolved in 100 mL of dry pyridine and allowed to stand at room temperature in the dark for 4 days. The reaction mixture was poured into ice water (500 mL), collected by suction filtration, washed with water, and dried at room temperature under vacuum, yield 12.8 g, mp 186–187 °C dec. This tosylate (**4b**) was not further purified but dissolved directly in 175 mL of dry THF and added to a stirred suspension of 3.5 g of $LiAlH_4$ in 50 mL of dry THF under nitrogen over a 0.5-h period. The solution was refluxed for 24 h at which time TLC analysis (5% ether/benzene) showed the reaction to be complete. The following workup was used for all workups of lithium aluminum hydride reductions. The excess hydride was destroyed by cautious addition of ethyl acetate. When the mixture became too thick to stir magnetically, ether was added and then saturated aqueous Rochelle salt was added dropwise. The mixture turned milky white and thinned enough so that stirring was resumed. Careful addition of the Rochelle salt was continued until a granular white precipitate separated from the organic layer. The precipitate was removed by filtration and washed with ether, and the combined ether phases were washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent gave a thick, yellow oil which was recrystallized from acetone to give 5.6 g of white crystals, mp 122–124 °C, $[\alpha]^{20}_D$ −33.7°.

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.17; H, 10.84.

5β-Pregna-7,16-dien-20-one (6). 5β,22α-Spirost-7-ene (**5**, 5.6 g) was treated by the method of Wall[14] by heating with 1.8 g of pyridine hydrochloride under reflux in 35 mL of acetic anhydride for 5 h. After cooling, the reaction mixture was oxidized with 2.6 g of CrO_3, neutralized with aqueous KOH, and hydrolyzed with 6.5 g of KOH in 100 mL of *tert*-butyl alcohol. Workup by extraction with ether and purification by column chromatography yielded 3.0 g of white, crystalline material (after recrystallization from methanol): mp 116–118 °C; IR 1670 cm^{-1}; $[\alpha]^{20}_D$ 136.5°; UV (EtOH) 238 nm (ε 13 800); NMR δ 6.7 (m, 1 H, C-16), 5.1 (m, 1 H, vinyl), 2.2 (s, 3 H, C-21), 0.92 (s, 3 H, C-19, calcd 0.93), 0.77 (s, 3 H, C-18, calcd 0.75).

Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.47; H, 10.17.

5β-Androst-7-en-17-one (7). 5β-Pregna-7,16-dien-20-one (**6**, 2.5 g) and 1 g of hydroxylamine hydrochloride were dissolved in 3.6 mL of pyridine and 15 mL of 95% ethanol and refluxed for 0.5 h. The reaction mixture was partitioned between ether and water. The ether layer was evaporated to a very thick oil which had a different R_f in TLC and did not show a carbonyl absorption in the IR. This product was dissolved in 10 mL of dry pyridine and 3.6 g of *p*-acetamidobenzenesulfonyl chloride was added in 10 mL of dry pyridine at 0 °C. The mixture was stirred for 2 h at 0 °C and 2 h at room temperature. Then 60 g of ice and 20 mL of concentrated H_2SO_4 were added and the reaction mixture was left in the refrigerator overnight. A yellow solid precipitated and was collected by filtration, taken up in methanol, and coated on a silica gel column which was eluted with hexane, then 5% ether/hexane. The product was recrystallized from methanol: yield 1.0 g; mp 85–88 °C; IR 1742 cm^{-1}; NMR δ 5.18 (m, 1 H, vinyl), 0.83 (s, 3 H, C-19, calcd 0.92), 0.68 (s, 3 H, C-18, calcd 0.74). The analytical sample was recrystallized from methanol: mp 93–94 °C; $[\alpha]^{20}_D$ 106.7°; IR 1743 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.55; H, 10.52.

5β-Androst-7-ene (8). 5β-Androst-7-en-17-one (**7**, 58 mg) was dissolved in 10 mL of diethylene glycol, 2 mL of 97% hydrazine, and 3 mL of 1-butanol. The mixture was heated to 90 °C and 0.6 g of KOH was added. The heating was continued under reflux for 1 h. The condenser was arranged for distillation and the solvent was distilled until the pot temperature reached 215 °C and then heating was continued under reflux for 5 h. The mixture was cooled, poured into water, and extracted with ether. The ether extracts were washed, dried, and evaporated to give a colorless liquid. Preparative TLC (silica gel, hexane) gave 30 mg of a colorless liquid which contained less than 1% impurities (by GC analysis) but would not crystallize. The sample for mass spectroscopy was purified by preparative gas chromatography: NMR δ 5.0 (m, 1 H, vinyl), 0.87 (s, 3 H, C-19, calcd 0.917), 0.87 (s, 3 H, C-18, calcd 0.575).

Calcd for $C_{19}H_{30}$: 258.2348. Found: 258.2322.

5β-Pregn-7-en-20-one (9). 5β-Pregna-7,16-dien-20-one (**6**, 150 mg) was dissolved in ethyl acetate and 1 drop of piperidine. The solution was hydrogenated over 10% Pd/C at atmospheric pressure for 3.5 h and then the catalyst was removed by filtration and the solvent evaporated to give 120 mg of white, crystalline material: mp 99–100 °C; IR 1706 cm^{-1}; $[\alpha]^{20}_D$ 106.8°; NMR δ 5.1 (m, 1 H, vinyl), 2.1 (s, 3 H, C-21), 0.88 (s, 3 H, C-19, calcd 0.91), 0.50 (s, 3 H, C-18, calcd 0.49).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.73; H, 10.85.

5β-Pregn-7-ene (10). The Wolff-Kishner procedure used for compound **8** was carried out using the same quantities of reagents on 120 mg of 5β-pregn-7-en-20-one (**9**). The product was purified by column chromatography (eluted with hexane) to provide 93 mg of crystalline product: mp 69–71 °C (after recrystallization from methanol); $[\alpha]^{20}_D$ 41.0°; NMR δ 5.02 (m, 1 H, vinyl), 0.85 (s, 1 H, C-18, calcd 0.92), 0.57 (s, 1 H, C-19, calcd 0.58).

Anal. Calcd for $C_{21}H_{34}$: C, 88.04; H, 11.96. Found: C, 87.73; H, 11.72.

5α,22α-Spirost-7-ene (12). 5α,22α-Spirost-7-en-3-ol[16] (**11b**, 9.8 g) and 11.8 g of tosyl chloride were dissolved in 200 mL of pyridine and allowed to stand in the dark at room temperature for 3 days. The mixture was poured onto ice and the product was collected by suction filtration and air dried overnight. The yield of crude product was 15 g, mp 190–193 °C dec.

The crude tosylate was dissolved in 200 mL of dry THF and added to 4.25 g of $LiAlH_4$ in 50 mL of dry THF. The mixture was heated under reflux for 24 h and then worked up by the procedure used for compound **5**, yield 7.2 g after recrystallization from acetone, mp 174–176 °C, $[\alpha]^{20}_D$ −76.3°.

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.55; H, 10.66

5α-Pregna-7,16-dien-20-one (13). 5α,22α-Spirost-7-ene (**12**, 9 g) was reacted with proportional amounts of reagent by the procedure used for compound **6**: yield 3.5 g of white, crystalline material; mp 93–94 °C (after recrystallization from methanol); IR 1670 cm^{-1}; $[\alpha]^{20}_D$ 77.50°; NMR δ 6.73 (m, 1 H, C-16), 5.25 (m, 1 H, vinyl), 2.27 (s, 3 H, C-21), 0.82 (s, 3 H, C-19, calcd 0.80), 0.77 (s, 3 H, C-18, calcd 0.75); UV (ethanol) 237 nm (ε 8300).

Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.31; H, 10.19.

5α-Pregn-7-en-20-one (14). 5α-Pregna-7,16-dien-20-one (**13**, 1.4 g) was reduced with 10% Pd/C in the same manner as compound **9**: yield 1.4 g of white, crystalline material; mp 120–122 °C; IR 1710 cm^{-1}; $[\alpha]^{20}_D$ 35.0°; NMR δ 5.18 (m, 1 H, vinyl), 2.03 (s, 3 H, C-21), 0.77 (s, 3 H, C-19, calcd 0.78), 0.49 (s, 3 H, C-18, calcd 0.49).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 84.08; H, 10.86.

5α-Pregn-7-ene (15). 5α-Pregn-7-en-20-one (**14**, 1.3 g) was reduced by the standard Wolff-Kishner procedure: yield 1.0 g after recrystallization from acetone; mp 68–69 °C; NMR δ 5.15 (m, 1 H, vinyl), 0.78 (s, 3 H, C-19, calcd 0.78), 0.43 (s, 3 H, C-18, calcd 0.43); mass spectrum M^+ *m/e* 286; $[\alpha]^{20}_D$ −4.5°.

Anal. Calcd for $C_{21}H_{34}$: C, 88.04; H, 11.96. Found: C, 87.65; H, 11.98.

5α-Androst-7-en-17-one (16). 5α-Pregna-7,16-dien-20-one (**13**, 3.4 g) was treated with proportional amounts of reagents in the procedure used for compound **7**. The yield after chromatography was 1.45 g, mp 71–75 °C. After recrystallization from acetone/methanol the yield was 1.2 g of white crystals: mp 101.5–103.5 °C; IR 1740 cm^{-1}; $[\alpha]^{20}_D$ 70°; NMR δ 5.23 (m, 1 H, vinyl), 0.80 (s, 3 H, C-19, calcd 0.80), 0.70 (s, 3 H, C-18, calcd 0.74).

Calcd for $C_{19}H_{28}O$: 272.2140. Found: 272.2156.

5α-Androst-7-ene (17). A. From 5α-Androst-7-en-17-one (16). 5α-Androst-7-en-17-one (**16**, 500 mg) was heated under reflux for 2 h in 25 mL of absolute ethanol with 500 mg of *p*-toluenesulfonyl hydrazide. The ethanol was evaporated and the residue reduced with 800 mg of $NaBH_3CN$ (by the method of Hutchins)[31] in 20 mL of 1:1 DMF/sulfolane and 5 drops of concentrated HCl at 105 °C for 5 h. After cooling the mixture was poured into water, extracted with ether, washed, dried, and evaporated. The product was obtained by column chromatography on silica gel eluted with hexane, yield 220 mg, mp 41–45 °C. An analytical sample was recrystallized from ether/

methanol: mp 51-52 °C; $[\alpha]^{20}_D$ −13.2°; NMR δ 5.13 (m, 1 H, vinyl), 0.7 (s, 3 H, C-19, calcd 0.78), 0.60 (s, 3 H, C-18, calcd 0.58).

Calcd for $C_{19}H_{30}$: 258.2348. Found: 258.2338.

B. From 5α-Androst-7-en-3β-ol (20a). 5α-Androst-7-en-3β-ol (**20a,** 1.1 g) and 1 g of tosyl chloride were dissolved in 20 mL of dry pyridine, left at room temperature in the dark for 36 h, then poured into water. The product was extracted with ether, the ether extract washed (three times) with 10% aqueous HCl and dried, and the ether evaporated to give 1.45 g of crude product (mp 118-120 °C). The crude product (**20b,** 1.45 g) was dissolved in 80 mL of dry THF and added to 0.7 g of $LiAlH_4$ in 20 mL of dry THF. The reaction was carried out in the usual manner (see the procedure of **5**) to give 0.91 g of a colorless oil which crystallized on standing. Column chromatography (hexane) yielded 0.82 g of 5α-androst-7-ene which was identical with that prepared above.

5α-Androst-5-en-3β-ol Benzoate (18b). Eight grams of 5α-androst-5-en-3β-ol (**18a**) was dissolved in 40 mL of pyridine and 5 mL of benzoyl chloride and the mixture left overnight and then poured into water. The product was collected by filtration, triturated with boiling acetone, cooled, and filtered to give 10 g of product, mp 173-174 °C (lit.[32] 173-174 °C).

5α-Androsta-5,7-dien-3β-ol (19b). The benzoate **18b** (10 g) was dissolved in 200 mL of 1:1 benzene/petroleum ether (bp 30-60 °C) and heated under reflux. Then 4.1 g of 1,3-dibromo-5,5-dimethylhydantoin was added and the heating under reflux continued for 15 min.

The mixture was cooled and filtered and the solvent was evaporated. The resulting solid was dissolved in 10 mL of mixed xylenes and added to 9 mL of trimethyl phosphite in 70 mL of refluxing xylenes. The heating under reflux was continued for 1 h and then the solution was evaporated under vacuum (bath temperature 80 °C). The product was recrystallized from 700 mL of 2:1 acetone/methanol, yield 3.5 g of white crystals.

The resulting 5,7-diene (**19a**) was very insoluble in organic solvents and so it was hydrolyzed to the known alcohol **19b**[33] by heating under reflux in methanolic KOH for 1 h. The standard workup yielded 1.9 g of 5α-androsta-5,7-dien-3β-ol (**19b**), mp 157-158 °C (lit.[33] mp 157-158 °C). The UV spectrum was also in agreement with the reported data.[33]

5α-Androst-7-en-3β-ol (20a). Androsta-5,7-dien-3β-ol (**19b,** 700 mg) was dissolved in 20 mL of ethyl acetate and 5 mL of W-5 Raney nickel suspension[18] in ethanol was added. The mixture was stirred under hydrogen at atmospheric pressure for 3.5 h, then the catalyst was filtered, the solvent evaporated, and the product purified by recrystallization from acetone to give 600 mg of white crystals, mp 173-175 °C, $[\alpha]^{20}_D$ −46.95°.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.95; H, 11.08.

5α-Bromoandrosta-3β,6β-diol 3-Acetate (22). To 10 g of androst-5-en-3β-ol acetate (**21**) dissolved in 130 mL of dioxane was added 11.5 mL of $HClO_4$ and 7 mL of water. The mixture was stirred in the dark for 15 min and cooled below 20 °C. Then 10 g of NBS was added and the mixture was stirred in the dark for 45 min, then cooled to 5 °C and 50 mL of saturated aqueous $Na_2S_2O_3$ was added, followed by 50 mL of water. The product was extracted with ether and the ether extracts evaporated at room temperature until the volume was about 100 mL. Hexane was added and the product collected by suction filtration, yielding 8 g of white crystals: mp 177-178 °C dec; $[\alpha]^{20}_D$ −60.97°; NMR δ 5.4 (m, 1 H, C-3), 4.10 (m, 1 H, C-6), 1.93 (s, 3 H, C-21), 1.32 (s, 3 H, C-19, calcd 1.38), 0.73 (s, 3 H, C-18, calcd 0.74).

Anal. Calcd for $C_{21}H_{33}O_3Br$: C, 61.01; H, 8.05; Br, 19.33. Found: C, 61.31; H, 8.39; Br, 18.78.

Androst-5-ene-3β,19-diol 3-Acetate (24a). 5α-Bromoandrosta-3β,6β-diol 3-acetate (**22,** 6 g) was dissolved in 500 mL of benzene and 9.8 g of iodine was added followed by 33.4 g of lead tetraacetate. The mixture was heated under reflux overnight. Workup by ether extraction in the usual manner gave a yellow oil which was used directly by dissolving it in 250 mL of 95% ethanol. To this solution was added 15 g of zinc powder (which was activated by washing with 5% HCl (twice), then ethanol). The mixture was stirred and heated under reflux for 6 h and the product purified by column chromatography to yield 2.4 g of a white solid, mp 170-172 °C (lit.[20] 170-172 °C).

Androst-5-en-3β,19-diol 3-Acetate 19-Mesylate-*19-d* (24b). Androst-5-en-3β,19-diol-*19-d* 3-acetate (**24a,** 2.3 g) was dissolved in 20 mL of pyridine and 2.5 mL of methanesulfonyl chloride was added. After 2 h at room temperature the mixture was poured into water and extracted with ether. The ether extracts were washed with 10% HCl (three times), then water, and then dried, and the solvent was evaporated. After recrystallization from methanol the product (1.4 g) melted at 123.5-124 °C (lit.[20] 120-121 °C).

Androst-5-en-3β-ol Benzoate-*19-d* (25b). Androst-5-ene-3β,19-diol 3-acetate 19-mesylate (**24b,** 1.4 g) was dissolved in 100 mL of 2-propanol and treated with 1.5 g of freshly dried LiBr. The mixture was heated under reflux for 2 h and worked up by ether extraction and evaporation to yield 1.28 g of thick, slightly yellow oil which was homogeneous by TLC (10% ether/hexane), R_f of mesylate 0.2, R_f of bromide (**24c**) 0.6.

The bromide (**24c**) was dissolved in 100 mL of dry diglyme (dried by vacuum distillation from sodium) and added to 0.2 g of lithium aluminum deuteride in 25 mL of dry diglyme under N_2. The mixture was heated under reflux for 2 h and then worked up as usual (see **5**) to give white, crystalline material. This was dissolved in 15 mL of pyridine and 0.7 mL of benzoyl chloride. After standing for 24 h the mixture was worked up by pouring onto ice and filtration. The product was recrystallized from acetone to give 620 mg of white crystals, mp 171-173 °C, undepressed with unlabeled material **18b.**

Androsta-5,7-dien-3β-ol Benzoate-*19-d* (26a). Androst-7-en-3β-ol benzoate-*19-d* (**25b,** 60 mg) was treated with 257 mg of 1,3-dibromo-5,5-dimethylhydantoin in 15 mL of 1:1 benzene/petroleum ether by the procedure used for compound **9a.** The bromide was dehydrobrominated with 1 mL of trimethyl phosphite and recrystallized from acetone/methanol to give 130 mg of white, crystalline material which was shown by NMR spectroscopy to contain 5-10% impurities (starting material and 4,6-diene). A second crop was obtained but it proved to be mainly the 4,6-diene and only the first crop was used.

Androst-7-en-3β-ol-*19-d* (27a). The benzoate (**26a,** 130 mg) was hydrolyzed in methanolic KOH in the usual manner and the product (without purification) was dissolved in 10 mL of ethyl acetate and 2 mL of W-5 Raney nickel[18] suspension in ethanol. The mixture was hydrogenated at atmospheric pressure for 3 h. Filtration and evaporation of the solvent provided the crude material which was recrystallized from acetone, mp 172-174 °C, undepressed upon mixture with undeuterated material **20a.** The yield was 83 mg.

5α-Androst-7-ene-*19-d* (28). 5α-Androst-7-en-3β-ol-*19-d* (**27a,** 80 mg) was converted into the tosylate **27b** in the usual way (crude yield 103 mg). The crude product (50 mg) was dissolved in dry ether, added to 0.2 g of $LiAlH_4$ in dry ether, and heated under reflux overnight. The usual workup (see compound **5**) gave 40 mg of crude, crystalline product which was purified by preparative TLC (10% ether/hexane) resulting in 30 mg of crystalline product, mp 51-52 °C, undepressed with compound **17.** Mass spectrum (70 eV) *m/e* 258/259 = 15/94. After correction for ^{13}C natural abundance and isotopic purity (86%) the ratio of *m/e* 243:244 (M^+ − Me peaks) was 50:87 showing that 37% of the C-19 methyl group was expelled.

5α-Pregn-8(14)-en-7-one (30). To 500 mg of 5α-pregn-7-ene (**15**) in 20 mL of $CHCl_3$ was added 800 mg of *m*-chloroperoxybenzoic acid (85%) and the mixture was allowed to stand in the refrigerator for 8 days. It was then filtered, washed with 5% aqueous $NaHSO_3$ and 10% aqueous $NaHCO_3$, dried, and evaporated. Analysis by TLC (10% ether/benzene) showed one major product (R_f 0.4), some starting material, and several minor products. Column chromatography on alumina eluted with hexane gave a small amount of starting material. Elution with 20% ether/hexane gave the major component as an oil. The NMR spectrum was in good agreement with the presumed structure (8α,14α-epoxy-5α-pregnan-7α-ol): δ 4.6 (t, J = 3 Hz, 1 H, C-7), 0.83 (s, 3 H, C-18, calcd 0.86), 0.79 (s, 3 H, C-19, calcd 0.85). However, this product contained ~10% impurities and it was used directly in the next reaction where purification was easier. The entire product was dissolved in 10 mL of 95% ethanol containing 0.6 mL of concentrated HCl and heated under reflux for 2 h. The reaction mixture was diluted with water and extracted with ether. The ether extracted was washed with water, dried, and evaporated, and the UV active product was isolated by column chromatography (silica gel, 10% ether/hexane) to yield 93 mg of a yellowish solid. Recrystallization twice from methanol resulted in 85 mg of colorless needles (mp 90-92 °C). The UV maximum is in excellent agreement with the value reported[21,34] for other $\Delta^{8(14)}$-7-ones: IR 1675, 1600 cm^{-1}; $[\alpha]^{20}_D$ −61.3°; UV 262 nm (ε11 000).

Calcd for $C_{21}H_{32}O$: 300.2453. Found: 300.2448.

5α,14β-Pregn-7-ene (31). The enone **30** (80 mg) was dissolved in 100 mL of methanol and 19.2 g of zinc powder was added. Then 3 mL

of concentrated sulfuric acid was added dropwise with stirring and cooling to keep the temperature at 20 °C (according to the procedure of Anatasia et al.).[22] After the addition was complete the mixture was stirred for 2 min, then the zinc was removed by filtration and washed with ether. The ether and methanol phases were combined and washed with water (three times), 10% $NaHCO_3$ (three times), and saturated brine, and then the solvent was evaporated. After preparative TLC and recrystallization from methanol the yield was 40 mg of white crystals melting at 81.5–82.5 °C (depressed to 40–60 °C upon admixture with the 14α isomer **25**). The mass spectrum was similar to that of the 14α isomer **25** and showed the RDA and loss of side chain reported to be diagnostic of the Δ^7 olefins.[29] The NMR spectrum was also in good agreement with the assigned structure: $[\alpha]^{20}_D$ 26.7°; NMR δ 5.33 (m, 1 H, vinyl), 0.83 (s, 3 H, C-19, calcd 0.88), 0.73 (s, 3 H, C-18, calcd 0.73).

Calcd for $C_{21}H_{34}$: 286.2661. Found: 282.2658.

5α-Androst-8(14)-en-7-one (33). To 800 mg of 5α-androst-7-ene (**27**) in 30 mL of $CHCl_3$ was added 1.3 g of *m*-chloroperoxybenzoic acid (85%) and the mixture was allowed to stand for 8 days in the refrigerator. After workup in the manner of compound **30** followed by chromatography a crude product was obtained. This was dissolved in 20 mL of 95% ethanol containing 2.5 mL of concentrated HCl. After heating under reflux for 2 h the reaction mixture was worked up in the manner of **30**. After chromatography and recrystallization from methanol (three times), 160 mg of colorless needles was obtained (mp 88–89 °C): IR 1670, 1598 cm^{-1}; UV (ethanol) 262 nm (ε 7700); $[\alpha]^{20}_D$ −75.8°.

Calcd for $C_{19}H_{28}O$: 272.2140. Found: 272.2136.

5α,14β-Androst-7-ene (34). Androst-8(14)-en-7-one (**33**, 100 mg) was dissolved in 100 mL of methanol and reduced with 19.4 g of zinc powder and 3 mL of sulfuric acid by the procedure given for compound **31**. After workup the resulting oil showed one major spot on TLC analysis; this spot was collected by preparative TLC (hexane, R_f 0.9). The NMR spectrum indicated that this was a mixture of two compounds. This was confirmed by GC which showed a ratio of about 2/1. The two compounds were separated by preparative GC and the major component (which had a lower retention time) was identified by its NMR and mass spectra to be 5α,14β-androst-7-ene. The mass spectrum was very similar to that of the 14α isomer **17**; the NMR spectrum showed a vinyl resonance at the usual place for the Δ^7 olefins and the methyl group resonances were in reasonable agreement with the calculated values. The other component was assumed to be the $\Delta^{8(14)}$ isomer since it lacked a vinyl proton signal in its NMR spectrum. Compound **34** was obtained as an oil even after preparative GC: NMR (100 MHz) δ 5.19 (m, 1 H, vinyl), 0.740 (s, 3 H, C-19, calcd 0.759), 0.930 (s, 3 H, C-18, calcd 0.875).

Calcd for $C_{19}H_{30}$: 258.2348. Found: 258.2352.

3α,12α-Dihydroxy-5β-chol-7-en-24-oic Acid (36). A solution of 7-ketocholic acid[35] (30 g), *p*-toluenesulfonyl hydrazide (25 g), and concentrated hydrochloric acid (10 mL) in methanol (3.5 L) was refluxed for 2 h under nitrogen, then evaporated to low volume in vacuo and diluted with water (2 L). The ether extract was washed, dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized from methanol to give 32 g (74%), mp 157–159 °C dec.

Sodium (40 g) was added in small pieces to a stirring, refluxing solution of the tosylhydrazone (30 g) in ethylene glycol (2.5 L) under nitrogen. After a further heating period of 1.5 h, the brown solution was cooled and poured onto a 1:5 mixture of concentrated HCl and ice (5 L). The precipitate (12 g) was filtered, washed excessively with water, and dried. Recrystallization from acetone/hexane afforded the analytical sample (mp 207 °C), $[\alpha]^{20}_D$ +89°, M^+ (mass spectrum) *m/e* 390 ($C_{24}H_{38}O_4$) (lit.[36] mp 210 °C, $[\alpha]_D$ +93°), but the crude product was sufficiently pure to be used in the next stage.

12α,24-Dihydroxy-5β-chol-7-ene (38a). 3α,12α-Dihydroxy-5β-chol-7-en-24-oic acid (**3**, 10 g, crude) was dissolved in pyridine (100 mL) and treated with *p*-toluenesulfonyl chloride (12 g). The resulting solution was allowed to stand for 48 h at room temperature, then poured onto ice and extracted three times with ether. The combined ether extracts were washed successively with 50% HCl (three times) and water, then dried ($MgSO_4$) and evaporated to dryness. The crude residue (**37**, 9.7 g, IR 3650, 3450, 1705, 1635, 1600, 1193, 1180 cm^{-1}) was dissolved in anhydrous ether (750 mL) and treated with lithium aluminum hydride (4.0 g). The mixture was refluxed overnight, then cooled. Excess hydride was decomposed by the addition of ethyl acetate, then dilute sulfuric acid was added and the product isolated by conventional extraction techniques. This was chromatographed on alumina (400 g, activity II) in benzene. Ether benzene (3:1) eluted the product (**38a**, 3.5 g), which was recrystallized from ethyl acetate/hexane: mp 125–126 °C; $[\alpha]^{20}_D$ +58°; NMR δ 0.58 (3 H, s), 0.84 (3 H, s), 3.52 (2 H, t, J = 7 Hz), 4.07 (1 H, t, J = 3 Hz), and 5.12 (1 H, m); M^+ (mass spectrum) *m/e* 360.

Anal. Calcd for $C_{24}H_{40}O_2$: C, 80.00; H, 11.11. Found: C, 79.78; H, 11.00.

5β-Chol-7-en-12α-ol (38c). A solution of 12α,24-dihydroxy-5β-chol-7-ene (3.5 g) in pyridine (40 mL) was treated with *p*-toluenesulfonyl chloride (3.5 g) and allowed to stand for 4 h at 5 °C, then poured onto ice and worked up as described above. The residue (**38b**, 5.1 g, IR 3450, 1635, 1600, 1193, and 1180 cm^{-1}) was dissolved in ether (400 mL), treated with lithium aluminum hydride (3 g), and refluxed overnight. The product (isolated in the standard fashion) consisted of a colorless oil (3.2 g), chromatographically homogeneous (by GLC and TLC) but which resisted all efforts to crystallize: IR 3450, 1635 cm^{-1}; NMR δ 0.57 (3 H, s), 0.83 (3 H, s), 4.07 (1 H, t, J = 3 Hz), and 5.10 (1 H, m); M^+ (mass spectrum) *m/e* 344 ($C_{24}H_{40}O$).

5β-Chol-7-en-12-one (39). A stirring solution of 5β-chol-7-en-12α-ol (0.4 g) in acetic acid (10 mL) was cooled to 10 °C and treated slowly with a solution of CrO_3 (0.2 g) in dilute acetic acid (16 mL, 15:1). After stirring for a further 1 h, the mixture was poured onto water and extracted thrice with ether. The combined organic phases were washed with water, then 5% $NaHCO_3$ solution until neutral, dried ($MgSO_4$), and evaporated. The pale yellow residue (0.36 g) was recrystallized from methanol as colorless plates: mp 117–118 °C; $[\alpha]^{20}_D$ +127°; IR 1705, 1635 cm^{-1}; NMR δ 0.92 (3 H, s), 5.12 (1 H, m); M^+ (mass spectrum) *m/e* 342.

Anal. Calcd for $C_{24}H_{38}O$: C, 84.21; H, 11.11. Found: C, 83.99; H, 10.97.

5β-Chol-7-ene (40). A mixture of 5β-chol-7-en-12-one (300 mg), diethylene glycol (60 mL), 1-butanol (24 mL), and hydrazine (12 mL) was stirred under reflux for 1 h, then cooled below 100 °C. Potassium hydroxide (3.6 g) was added, and the resulting solution heated at 200–210 °C for 3 h. It was then cooled and poured onto ice, and the product isolated by extraction with ether. The crude residue was dissolved in hexane and passed down a short column of alumina (30 g, activity II). Elution with a further 50 mL of hexane afforded the pure product (240 mg, 85%) recrystallized from ether/methanol as colorless plates: mp 104–105 °C; $[\alpha]^{20}_D$ +63°; NMR δ 0.55 (3 H, s), 0.85 (3 H, s), and 5.07 (1 H, m).

Calcd for $C_{24}H_{30}$: 328.2120. Found: 328.2129.

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References and Notes

(1) For part 247 see J. R. Wiersig, A. N. H. Yeo, and C. Djerassi, *J. Am. Chem. Soc.*, in press.
(2) Taken in part from the Ph.D. Dissertation of J. Scott Dixon, 1976.
(3) (a) K. Biemann, "Mass Spectrometry", McGraw-Hill, New York, N.Y., 1962, pp 102–107; (b) H. Budzikiewicz, D. H. Williams, and C. Djerassi, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, pp 67–71; (c) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry", Vol. 1 and 2, Holden-Day, San Francisco, Calif., 1964.
(4) H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, **21**, 1855 (1965).
(5) H. Budzikiewicz and M. Linscheid, *Org. Mass Spectrom.*, **9**, 88 (1974).
(6) R. C. Dougherty, *J. Am. Chem. Soc.*, **90**, 5788 (1968).
(7) Th. A. Elwood and J. H. Beynon, 19th Annual Conference on Mass Spectrometry and Allied Topics, Atlanta, Ga., May 1971, p 173.
(8) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim/Bergstr., W. Germany, 1970.
(9) A. Karpati, A. Rave, J. Deutsch, and A. Mandelbaum, *J. Am. Chem. Soc.*, **95**, 4244 (1973).
(10) F. Bohlmann, C. H. Fischer, J. Förster, W. Mathar, and H. Schwarz, *Org. Mass Spectrom.*, **10**, 1141 (1975).
(11) S. Hammerum and C. Djerassi, *J. Am. Chem. Soc.*, **95**, 5806 (1973).
(12) R. Yashin, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 4654 (1951).
(13) M. Velasco, J. Rivera, G. Rosenkranz, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **18**, 92 (1953).
(14) M. Wall, H. E. Kenney, and E. S. Rothman, *J. Am. Chem. Soc.*, **77**, 5665 (1955).
(15) G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).
(16) G. Rosenkranz, J. Romo, E. Batres, and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951).

(17) F. Hunziker and F. X. Müllner, *Helv. Chim. Acta*, **41**, 70 (1958).
(18) H. R. Billica and H. Adkins, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 176.
(19) J. F. Bagli, P. F. Mor, and R. Gaudry, *J. Org. Chem.*, **28**, 1207 (1963).
(20) C. Djerassi and M. A. Kielczewski, *Steroids*, **2**, 125 (1963).
(21) I. Midgley and C. Djerassi, *J. Chem. Soc., Perkin Trans. 1*, 155 (1973).
(22) M. Anastasia, A. Fiecchi, and A. Scala, *J. Chem. Soc., Perkin Trans. 1*, 378 (1976).
(23) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).
(24) I. Midgley and C. Djerassi, *J. Chem. Soc., Perkin Trans. 1*, 2771 (1972).
(25) H. Audier, M. Fetizon, and W. Vetter, *Bull. Soc. Chim. Fr.*, 1971 (1964).
(26) (a) J. H. Beynón, R. A. Saunders, and A. E. Williams, *Nature (London)*, **204**, 67 (1964); (b) K. R. Jennings, *J. Chem. Phys.*, **43**, 4176 (1965).
(27) L. Tökés and C. Djerassi, *J. Am. Chem. Soc.*, **91**, 5017 (1969).
(28) C. Djerassi and I. Midgley, unpublished results.
(29) C. Djerassi, *Pure Appl. Chem.*, **21**, 205 (1970).
(30) (a) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963); (b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964.
(31) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).
(32) N. A. Milas and C. R. Cilone, *J. Am. Chem. Soc.*, **68**, 738 (1946).
(33) H. DeVries and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **71**, 719 (1952).
(34) L. Dorfmann, *Chem. Rev.*, **53**, 47 (1953).
(35) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3935 (1949).
(36) E. Berner, A. Lardon, and T. Reichstein, *Helv. Chim. Acta*, **30**, 1542 (1947).

The Occurrence of Permutational Isomerism in the Mechanism of the Thermal Thiaallylic Rearrangement

H. Kwart* and N. A. Johnson

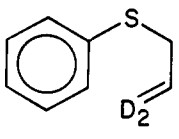
Contribution from the Department of Chemistry, University of Delaware, Newark, Delaware 19711. *Received July 6, 1976*

Abstract: The thermal 1,3 rearrangement of allyl phenyl sulfides has been found to proceed by both unimolecular and bimolecular pathways. Kinetic and product composition studies have yielded the following results: (1) the effect of solvent polarity on rate and molecularity of reaction, (2) comparison of oxyallylic, silaallylic, and thiaallylic rearrangements under thermal and photo conditions, (3) aryl substituent effects on the activation parameters correlated with the charge characteristics of the reaction transition state, (4) substituent effects in the allyl side chain and their significance in assessing the locus of charge development in the course of rearrangement, (5) evidence bearing on a possible ion-pair structure of the reaction intermediate, and other alternatives such as a radical dissociation-recombination process, (6) evidence supporting a cyclic structure of the reaction transition state, (7) a comparison of thermal allylic migration aptitudes of various heteroatoms and its significance for the thiaallylic isomerization, (8) application of the heavy atom isotope effect criterion to distinguish the mechanistic alternatives, and related considerations bearing upon the question of whether a definite reaction intermediate is formed in the course of reaction, (9) the stereochemical factors involved in the structure of the thiaallylic intermediate. These studies suggest that thermal 1,3 rearrangements involving sulfur occur via a transition state of permutational isomerism developing from an intermediate possessing a trigonal-bipyramid structure.

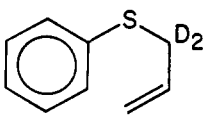
In the course of studies[1] of the thia-Claisen rearrangement, a 1,3 migration of sulfur in α-methylallyl phenyl sulfide (**1**) was observed. The products of thia-Claisen rearrangement could only be understood in terms of the occurrence of a mobile equilibrium with the more stable crotyl phenyl sulfide (**2**) established at lower temperatures. The thiaallylic rearrangement was unsuccessfully sought by Cope and co-workers[2] utilizing refractive index to detect the α-methylallyl to crotyl transformation. In a preliminary communication[3] it has been pointed out that both NMR and GLC can be applied in following the kinetic course of rearrangement. Others[4] have confirmed this reaction pattern in the course of thermolysis of α-methylallylic 2-quinolyl sulfides. This paper presents a full account of the results bearing on the mechanism of this unusual thermal isomerization reaction.

Results and Discussion

The Order of Rearrangement. The isomerization of allyl phenyl sulfide represents a degenerate rearrangement which is detectable by labeling an end of the allyl grouping. Allyl-3,3-d_2 phenyl sulfide (**3**) was used for this purpose. The rearrangement **3** $\rightleftarrows$ **3a** was kinetically monitored by means of NMR techniques. The rate was found to be independent of the initial concentration of **3** (in the range 0.70–2.50 M) in a thoroughly degassed solution of nitrobenzene. The first-order relation of the logarithm of the concentration change, $(A - A_e)$, was linear with time to more than 80% reaction completion. However, in the less polar solvents such as decalin and *o*-dichlorobenzene, the isomerization of **3** $\rightleftarrows$ **3a** was directly dependent on the initial concentration of substrate even though the apparent first-order plot was linear.



3



3a

Thus it may be assumed that rearrangement could occur by way of competing unimolecular and bimolecular processes. The rate equation for such cases can be shown to reduce to a first-order expression when the attained equilibrium constant K_e is unity, as follows.

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \qquad \text{unimolecular rearrangement}$$

$$2A \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 2B \qquad \text{bimolecular rearrangement}$$

$$\frac{k_1}{k_{-1}} = \frac{k_2}{k_{-2}} = 1 = K_e$$

The overall rate is given by

$$-dA/dt = k_1(A) - k_{-1}(A_0 - A) + 2k_2(A)^2 - 2k_2(A_0 - A)^2 \quad (1)$$

where A_0 = the initial concentration of A.
Simplification of 1 produces