stanoic acid (I) to the corresponding 17β-acetoxy-3,5-enol lactone (II) in essentially quantitative yield without formation of other side products.[4] However, with increase in reaction time or concentration of perchloric acid, or both, a second reaction product was obtained as the major product in addition to the enol lactone II. Accordingly, when the keto acid (I) was treated with a reagent consisting of 2 *M* acetic anhydride and 0.15 *M* perchloric acid in ethyl acetate for one hour at room temperature, a second product of mp 190.5–191.5° was obtained. This reaction product was identified as 17β-acetoxy-6-acetyl-5-hydroxy-3,5-seco-4-norandrost-5-en-3-oic acid 3,5-lactone (III) on the basis of analytical and other spectral data. Compound III analyzed for $C_{22}H_{30}O_5$ and had a molecular weight of 374 as determined by mass spectrum[5] (molecular ion peak at *m/e* 374). The infrared spectrum demonstrated enol lactone (1755 cm^{-1}), 17β-acetate (1725 and 1265 cm^{-1}) and conjugated carbonyl (1677 cm^{-1}) bands. The ultraviolet absorption spectrum showed an absorption maximum at 252 mμ (ε 9874) and is in good agreement with the calculated value[6] of 254 mμ. The nmr spectrum of compound III ($CDCl_3$, TMS) showed peaks at δ 0.85 (C-18 methyl), 1.22 (C-19 methyl), 2.06 (17β-acetate), and 2.51 (conjugated C-6 acetyl) ppm.

The possibility of the acetyl group being in the A ring was ruled out by mass spectral data. The major fragmentation pattern of both III and the enol lactone II showed the loss of C_3H_4O (56 mass units) as the first fragmentation product. If the acetyl group had been located in ring A, the fragmentation pattern would have been different since the C_3H_4O fragment was due to the loss of carbons 1, 2, and 3 of the lactone.

That the lactone II was the intermediate in the formation of III was shown by treatment of the lactone II with the perchloric acid reagent and isolation of the 6-acetyl product III in excellent yield.

Recently, Liston and Toft[7] have also observed a similar carbon acylation of enol acetates with perchloric acid and acetic anhydride.

(5) The mass spectrum was recorded on Model MS9 instrument of Associated Electrical Industries, Manchester, England.

(6) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 19.

(7) A. J. Liston and P. Toft, *J. Org. Chem.*, **33**, 3109 (1968).

Experimental Section[8]

Perchloric Acid Reagent.—To absolute ethyl acetate (30 ml) was added 72% perchloric acid (0.75 ml) and acetic anhydride (9.6 ml), and the solution was made up to 50 ml with ethyl acetate.

17β-Acetoxy-6-acetyl-5-hydroxy-3,5-seco-4-norandrost-5-en-3-oic acid 3,5-Lactone (III).—A sample of the keto acid (I, 200 mg) was treated with perchloric acid reagent (20 ml) for 1 hr at room temperature. The reaction mixture was then washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The total crude material was then chromatographed on silica gel to give compound III (114 mg). The analytical sample was crystallized from acetone–hexane: mp 190.5–191.5°, ν_{max}^{KBr} 1755, 1725, 1677 and 1265 cm^{-1}, $\delta_{TMS}^{CDCl_3}$ 0.85, 1.22, 2.06 and 2.51 ppm, λ_{max}^{MeOH} 252 mμ (ε 9,874).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.47; H, 8.08.

17β-Acetoxy-6-acetyl-5-hydroxy-3,5-seco-4-norandrost-5-en-3-oic acid 3,5-Lactone (III) from II.—A sample of the lactone II (31 mg) was treated with perchloric acid reagent (3 ml) for 40 min at room temperature. The crude product obtained after the usual work-up was chromatographed on silica gel to give compound III (27 mg), mp 190.5–191.5°, which was found to be identical in all respects with the authentic sample obtained earlier.

Registry No.—Perchloric acid, 7601-90-3; III, 20104-38-5.

Acknowledgment.—We wish to thank Dr. Walter J. McMurray of Yale University, School of Medicine, for determining the mass spectrum, and Dr. David Buss of our department for stimulating discussions.

(8) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60A spectrometer using TMS as internal standard. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer. Ultraviolet absorption spectra were determined with a Cary recording spectrophotometer (Model 11 MS). Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

The Acetolyses of Certain 3,5-Disubstituted 6-Oxo-5β-cholestanes[1a]

ALEX T. ROWLAND, ARTHUR F. KRINER, JR.,[1b] AND KAREN P. LONG[1c]

Department of Chemistry, Gettysburg College, Gettysburg, Pennsylvania 17325

Received February 13, 1969

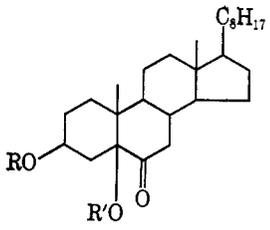
When 3β-tosyloxy-5-hydroxy-5β-cholestan-6-one (**1d**) was solvolyzed in anhydrous ethanol, methanol, or dimethyl sulfoxide, the major product was 3β,5-epoxy-5β-cholestan-6-one (**3**).[2] The formation of the oxetane ring from *cis* functional groups is unusual. Furthermore, we have found that the C-3 epimer (**2d**) of **1d** is recovered unchanged when heated under reflux for 19.5 hr in ethanol.[3] The usual stereochemical considerations lead to the conclusion that **2d** and *not* **1d** would be more likely to undergo oxetane ring formation. We have attempted to determine if some type of participation by hydroxyl occurs in the conversion **1d** → **3** by

(1) (a) This work was supported by National Science Foundation Undergraduate Research Participation Grants GE-2760 and GE-9534; (b) NSF-URP, 1964-1965; (c) NSF-URP, Summer, 1965.

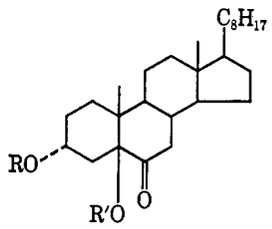
(2) A. T. Rowland, *Steroids*, **7**, 527 (1966).

(3) Unpublished observation in this laboratory.

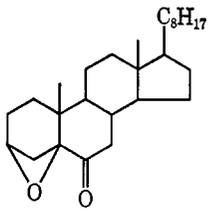
studying the kinetics and product compositions of the acetolyses of **1d**, **2d**, and their C-5 acetates **1e** and **2e**.



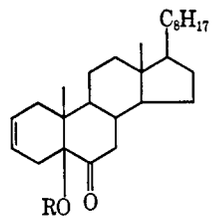
1a, R = R′ = H
b, R = Ac; R′ = H
c, R = R′ = Ac
d, R = Ts; R′ = H
e, R = Ts; R′ = Ac



2a, R = R′ = H
b, R = Ac; R′ = H
c, R = R′ = Ac
d, R = Ts; R′ = H
e, R = Ts; R′ = Ac

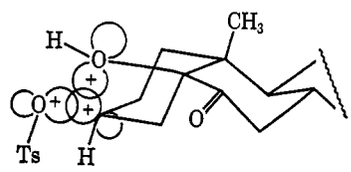


3



4a, R = H
b, R = Ac

The first-order rate constants for the acetolyses are listed in Table I. Since neighboring group participation reactions are often reflected in rate enhancements,[4] the rate ratio of 19:1 of **1d**:**2d** in buffered solution at 70° is instructive. Since the ratios for epimeric axial and equatorial tosylates are normally 2–6:1 in saturated cyclohexanes,[5] the larger ratio found here is probably due in part to the size of the C-5 axial hydroxy group, which provides some steric acceleration in the solvolysis of **1d**. Nishida has shown that an axial tosylate subjected to 1,3 diaxial interactions with a hydrogen atom and a methyl group undergoes acetolysis ten times faster than its equatorial isomer.[6] On the basis of the comparative sizes of the methyl and hydroxy groups, the rate ratio for **1d**:**2d** is probably due to a modest amount of steric acceleration in **1d** by the C-5 hydroxyl accompanied by partial bond formation in the transition state by the free p electrons on the oxygen atom



Partial bonding from the oxygen to C-3 before significant carbonium ion character at C-3 is developed is necessary to explain the facile formation of **3** in lieu of products of inversion in unbuffered acetic acid (see Table II). In solutions containing acetate ion or water the amount of **3** decreases while products of inversion and elimination increase. These results are in accord with partial bonding to C-3 of the C-5 oxygen during ionization of **1d**. Acetolysis of **2d** in buffered solution yielded products typical of those from equatorial steroid tosylates, and therefore shows no participation by the *trans* C-5 hydroxy group. In unbuffered acetic acid, **2d** gave the 3,5-diacetates **1c** and **2c** in poor yield (see Table II). In this case, **2c** (a product of retention) was probably produced by acetolysis of **2e** which was formed *in situ* from the acetylation of **2d** under *p*-toluenesulfonic acid catalysis.

TABLE I
RATE DATA FROM ACETOLYSES OF THE TOSYLATES

Tosylate	Temp, °C[a]	Equiv of added solute	$k_1 \times 10^3$, min^{-1}
1d	60	...	0.73 ± 0.02
	70	...	2.40 ± 0.08
	70	1 NaOAc	2.70 ± 0.04
	70	2 NaOAc	2.80 ± 0.13
	70	1 *p*-TsOH	2.49 ± 0.03
	70	1 $LiClO_4$	*b*
	70	1 Ac_2O	2.52
	70	3 Ac_2O	2.52
	70	1 $HClO_4$	*b*
	80	...	7.10 ± 0.03
1e	70	1 NaOAc	6.06 ± 0.19
	80	...	*b*
	80	1 NaOAc	18.1 ± 0.5
	80	2 NaOAc	18.8
2d	70	1 NaOAc	0.14 ± 0.01
	80	...	*b*
	80	1 NaOAc	0.48 ± 0.03
	80	2 NaOAc	0.49 ± 0.02
2e	60	...	5.43 ± 0.07
	70	...	16.9 ± 0.3
	70	1 NaOAc	17.5 ± 0.3
	70	2 NaOAc	17.3 ± 0.3
	80	...	48.8 ± 0.6

[a] ±0.05°. [b] Darkening of reaction mixture precluded accurate rate measurement.

The activation parameters for the acetolyses of **1d**, **2d**, and the corresponding acetates (**1e** and **2e**) are given in Table III. The values obtained are typical of saturated steroid tosylate acetolyses[6] and are consistent with rate-determining ionization reactions.

In contrast to the rates found for the acetolyses of the hydroxy tosylates **1d** and **2d**, the acetate derivative (**2e**) of the equatorial tosylate **2d** undergoes acetolysis 125 times faster than **2d** and *ca.* 3 times faster than its axial epimer **1e** at 70°. Tosylate **2e** therefore undergoes solvolysis with participation of the C-5 acetoxy group, probably through an acetoxonium ion.[7] As seen in Table II, the major product produced from the acetolysis of **1e** is 3β,5-diacetoxy-5β-cholestan-6-one (**1c**) resulting from retention of configuration at C-3 while the equatorial tosylate **2e** gives a significant amount of diacetate **1c** (product of inversion) along with the diacetate **2c** (product of retention of configuration at C-3). The difference in product composition from the acetoxy tosylate **1e** and **2e** rules out the possibility of a common intermediate and renders a firm explanation for the observed behaviors difficult. A possible rationale may lie in the formation of an acetoxonium ion during the solvolysis of **2e** followed by reaction with acetic acid by a pathway similar to that proposed for the acetolysis of *cis*-2-tosyloxymethylcyclohexyl acetate.[7] In the latter case, a mixture of *cis* and *trans* diacetates was formed with 80% retention. On the other hand, the acetoxy

(4) H. W. Heine, A. D. Miller, W. H. Barton, and R. W. Greiner, *J. Amer. Chem. Soc.*, **75**, 4778 (1953).
(5) C. W. Shoppee and G. A. R. Johnston, *J. Chem. Soc.*, 3261 (1961).
(6) S. Nishida, *J. Amer. Chem. Soc.*, **82**, 4290 (1960).
(7) Ö. K. J. Kovács, Gy. Schneider, L. K. Láng, and J. Apjok, *Tetrahedron Lett.*, **33**, 4181 (1967).

TABLE II

PRODUCT DISTRIBUTION FROM ACETOLYSES OF THE TOSYLATES[a]

Tosylate	Solvent	Added NaOAc, equiv	Reaction time, hr	% product 3	4a	2b	1b	2a	2c	1c
1d	HOAc	...	7	54	7	...	...	...	16	11
	HOAc	1.06	7	40	13	28	...	...	...	...
	HOAc	11.3	7	37.5	15	18	...	16	...	...
	HOAc–H_2O (5/1, v/v)	...	6	2.7	14	48	...	26	...	...
1e	HOAc[b]	...	4	...	10[c]	...	...	...	~4	~64
	HOAc	1.03	15	3.8	2.6[c]	...	...	...	7.3	70.5
2d	HOAc[b]	...	6.2	...	...	...	...	...	16.5	13.5
	HOAc	1.06	42.5	...	40	...	44.5	...	...	...
2e	HOAc[b]	...	2.1	...	18.5[c]	...	...	...	48	19.5
	HOAc	1.02	2.25	...	3.8[c]	...	...	...	51	34

[a] Acetolyses carried out at 92 ± 4° for indicated times. [b] All yields from the unbuffered reaction low because of side reactions of products. [c] As its acetate **4b**.

TABLE III

ACTIVATION PARAMETERS OF THE TOSYLATE ACETOLYSES

Tosylate	E_a, kcal/mole	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, eu
1d	26.8	26.1	−2.9
1e	26.3	25.6	−2.6
2d	29.6	28.9	−0.3
2e	25.6	24.9	−2.5

group in tosylate **1e** may serve only to hold the configuration of the incipient carbonium ion at C-3 without formation of a true acetoxonium ion, thus permitting attack from the β side of the molecule by a molecule of acetic acid, resulting in the production of mainly the *cis* diacetate **1c**.

Experimental Section[8]

Kinetic Procedures.—Reaction rates in anhydrous acetic acid were determined titrimetrically according to a reported procedure.[9]

Steroids.—With the exception of the three compounds discussed below, all steroids have been previously reported from this laboratory.[10]

3α,5-Diacetoxy-5β-cholestan-6-one (2c).—A solution of 562 mg (1.34 mmol) of the 3α,5β-diol-6-one **2a** and 129 mg of *p*-toluenesulfonic acid monohydrate in 5 ml of glacial acetic acid and 5 ml of acetic anhydride was allowed to remain at room temperature for 21.5 hr. The customary work-up[11] gave a crystalline precipitate which was dissolved in methanol and filtered. Partial removal of the solvent by an air steam caused the deposition of needles, one of which was used to seed the further concentrated solution (crystallization did not occur without seeding), resulting in the precipitation of 555 mg (82%) of diacetate **2c** as white needles with mp 108–110°; $[\alpha]_D$ −41° (*c* 1.095); ir (CCl_4) 1748 (s, with strong shoulders at higher frequency and at 1730), 1229 (s, br absorption with strong shoulder at higher frequency) cm^{-1}; uv max (absolute EtOH) 292 mμ (ε 53).

Anal. Calcd for $C_{31}H_{50}O_5$ (502.71): C, 74.06; H, 10.02. Found: C, 74.05, 74.10; H, 9.80, 10.00.

5-Hydroxy-5β-cholest-2-en-6-one (4a).—This material was tentatively, but incorrectly, identified previously as the isomeric 3-ene.[2] Nmr analysis (60 MHz, CCl_4) of **4a** exhibited vinyl hydrogens absorptions at C-2 and C-3 as a two-proton doublet centered at 337.5 Hz ($W_{1/2}$ = 4.5 Hz). Under increased amplification, two small satellite peaks were observed at 325 and 351 Hz. The nature and frequency of the vinyl hydrogen absorptions are strikingly similar to those of 5α-cholest-2-ene but much different from those in 5α-cholest-3-ene.[12] Also, the spectrum of 5-hydroxy-5β-cholest-3-ene[13] showed a two-proton absorption of the C-3 and C-4 hydrogens as four small peaks at 314.5, 325, 334, and 344.5 Hz in marked contrast to the vinyl hydrogens in **4a**. On the basis of these nmr data, compound **4a** must be the 2-ene.

The acetate **4b** was prepared as follows. A suspension of 471 mg (1.18 mmol) of **4a** and 44 mg of *p*-toluenesulfonic acid monohydrate in 15 ml of acetic anhydride was heated on the steam bath for 35 min. The resulting solution was cooled and diluted with ice and a little 2 *N* hydrochloric acid. The white needles that separated were collected and recrystallized from aqueous methanol, yielding 400 mg (77%) of 5-acetoxy-5β-cholest-2-en-6-one (**4b**) with mp 116–118.5°. A further recrystallization from methanol gave mp 119.5–121°; $[\alpha]_D$ −18° (*c* 1.01), −20° (*c* 1.00); ir (CCl_4) 1754 (s), 1730 (s), 1233 (s, with strong shoulder at lower frequency) cm^{-1}.

Anal. Calcd for $C_{29}H_{46}O_3$ (442.66): C, 78.68; H, 10.47. Found: C, 78.95; H, 10.31.

Solvolyses.—Acetolysis reactions were conducted with *ca.* 2×10^{-2} *M* tosylate solutions at 92 ± 4°. Standard isolation techniques were employed. Separation of products was accomplished by column chromatography and identification was made by tlc and/or ir analysis and by comparison of the crystallized materials with authentic samples. In those cases where similar adsorptivity on the column precluded separation, the entire mixture was subjected to a derivative forming reaction. Two representative solvolyses are as follows.

Acetolysis of 3β-Tosyloxy-5-hydroxy-5β-cholestan-6-one (1d) in Buffered Solution.—A solution of 660 mg (1.15 mmol) of **1d** in 59 ml of 0.0208 *N* sodium acetate–acetic acid was heated at 90–92° for 7 hr. The colorless solution was cooled, diluted with water, saturated with sodium chloride, and extracted three times with ether. The ether extracts were washed twice with water and dried. The colorless oil thus obtained was chromatographed on 24 g of alumina. Elution with 40% benzene in petroleum ether gave 184 mg (40%) of the oxide **3**. Recrystallization from acetone–methanol yielded 172 mg of **3** with mp 112–115°.[2]

The material (229 mg, a mixture of **4a** and **2b**) eluted from the column with ether–benzene mixtures was subjected to hydrogenation with a palladium-on-carbon catalyst in ethyl acetate solution. The product was chromatographed on 7 g of alumina. Elution with 50–80% benzene in petroleum ether yielded 61 mg (13%) of 5-hydroxy-5β-cholestan-6-one (reduction product of **4a**). Recrystallization from acetone–methanol gave 46 mg of the hydroxy ketone with mp 101–103°. Elution with 20% ether–benzene produced 149 mg (28%) of the 3α-acetate **2b**. Recrystallization from methanol gave, in two crops, a total of 130 mg of **2b**, mp 126–128°.

Acetolysis of 3α-Tosyloxy-5-hydroxy-5β-cholestan-6-one (2d) in Buffered Solution.—A solution of 588 mg (1.03 mmol) of

(8) Experimental details have been reported elsewhere: A. T. Rowland, P. J. Bennett, and T. S. Shoupe, *J. Org. Chem.*, **33**, 2426 (1968).

(9) S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948).

(10) See ref 8 and references cited therein.

(11) A. T. Rowland, *J. Org. Chem.*, **29**, 222 (1964).

(12) G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, E. E. Richards, and T. L. Whateley, *J. Chem. Soc., C*, 1266 (1966).

(13) (a) E. Glotter, S. Greenfield, and D. Lavie, *Tetrahedron Lett.*, 5261 (1967); (b) We thank Professor Peter S. Wharton, Wesleyan University, for the sample used in the nmr analysis.

2d in 55 ml of 0.0198 *N* sodium acetate–acetic acid was heated at 90–95° for 42.5 hr. The colorless solution was worked up as in the preceding example. A preliminary attempt to separate the products by chromatography was unsuccessful, hence the entire mixture (indicated by ir to be **4a** and **1b**) was subjected to catalytic hydrogenation. The resulting oil was chromatographed on 20 g of alumina. Elution with 80% benzene–petroleum ether gave 165 mg (40%) of 5-hydroxy-5β-cholestan-6-one which had mp 103–105° after crystallization from methanol. Elution with 15% ether–benzene yielded 210 mg (44.5%) of **1b** which melted at 141–143° when crystallized from methanol.

Registry No.—**1b**, 14956-13-9; **1d**, 6770-44-1; **1e**, 20352-32-3; **2b**, 6580-09-2; **2c**, 20352-49-2; **2d**, 20352-33-4; **2e**, 20398-53-2; **4a**, 20352-34-5; **4b**, 20352-50-5; 5-Hydroxy-5β-cholestan-6-one, 16526-09-3.

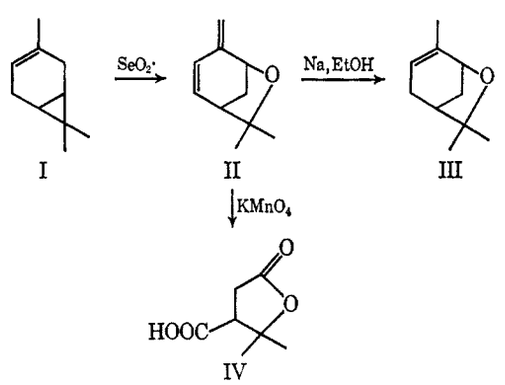
The Acid-Catalyzed Rearrangements of *endo,endo*-6,7-Dihydroxy- and *endo,endo*-6,7-Diacetoxycineole

ROBERT O. HUTCHINS AND DAVID KOHARSKI[1]

Department of Chemistry, Drexel Institute of Technology, Philadelphia, Pennsylvania 19104

Received December 30, 1968

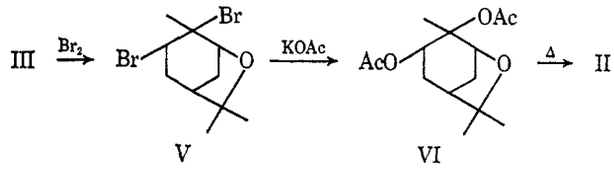
Recently, Arbuzov, Isaeva, and Ratner[2] reported the isolation of the interesting oxabicyclic diene II as one of the products arising from the oxidation of Δ^3-carene (I) with selenium dioxide. The structure assignment was substantiated by the infrared and ultraviolet spectra, the formation of pinol (III) upon reduction with sodium in ethanol, and the production of terebic acid (IV) by permanganate oxidation. Further evidence offered in support of structure II included an independent synthesis from pinol (III) using the steps outlined



I II III IV

in Scheme I based upon the early work of Wallach[3,4] in which "pinol dibromide" and "pinol diacetate" were assigned structures V and VI, respectively. Normal acetate pyrolysis of VI would be expected to afford II. Indeed, one of the pyrolysis products of VI, isolated by column chromatography, had an infrared spectrum "identical" with II (although the ir sample contained a carbonyl impurity) and gave IV upon oxidation with permanganate. Noteworthy was the finding that the pyrolysis was successful only in the presence of a small

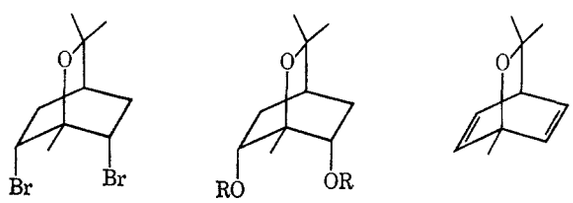
SCHEME I



V VI

amount of acid; attempts to pyrolyze VI alone gave only tar. The Russian workers also reported the presence of a ketone and a hydrocarbon in the reaction mixture, but these were not identified.

Our interest in the above series of reactions stemmed from the recently reported findings[5,6] that, contrary to the early literature,[3,4] pinol reacts with bromine to afford the rearranged dibromide VII (*endo,endo*-6,7-dibromocineole) instead of the reported structure V and that "pinol diacetate" is actually VIII (*endo,endo*-6,7-diacetoxycineole). In view of these revised assignments, regular acetate elimination reactions would be expected to give diene IX, while the conversion of VIII to II, if correct, represents a rather unusual and inter-



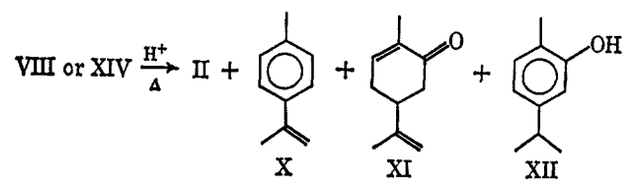
VII VIII, R = Ac XIV, R = H IX

esting rearrangement, certainly not proceeding by a normal acetate pyrolysis mechanism. In order to clear up the above anomalies and to determine the composition of the unidentified hydrocarbon and ketone, we have reinvestigated the acid-pyrolysis reaction of VIII.

Under the same conditions employed by Arbuzov and coworkers, an oily mixture was obtained which was successfully separated by gas–liquid partition chromatography and the four major components (>90% of mixture) identified as the diene II (42.2%), *p*-isopropenyltoluene (X, 36%), carvone (XI, 13.9%), and carvacrol (XII, 7.9%). The data are tabulated in Table I.

TABLE I

ACID PYROLYSIS OF *endo,endo*-6,7-DIACETOXY- AND DIHYDROXYCINEOLE



X XI XII

Compd	% II[a]	% X	% XI	% XII
VIII	42.2	36.0	13.9	7.9
XIV	8.2	8.5	65.0	18.3

[a] The percentages reflect only the relative amounts of the four major products (*ca.* 90% of the total volatile material) and are approximate, since differences in glpc detector responses were not measured.

(1) Undergraduate research participant, 1968–1969.
(2) B. A. Arbuzov, Z. G. Isaeva, and V. V. Ratner, *Zh. Org. Khim.*, **2**, 1401 (1966); *J. Org. Chem. USSR*, 1391 (1966).
(3) O. Wallach and A. Otto, *Ann.*, **253**, 249 (1889).
(4) O. Wallach, *ibid.*, **259**, 309 (1890).
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