Acetolysis of Δ^5-19-Methanesulfonoxy Steroids

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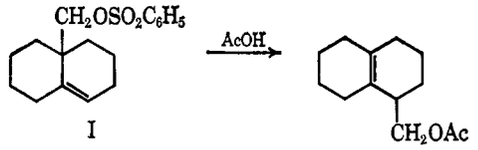
The results of kinetically and thermodynamically controlled acetolysis of Δ^5-19-methanesulfonoxy steroids are described and contrasted with the results of hydrolysis previously reported.

The recent report by Hikino and de Mayo[1] of the rearrangement of I to II under unbuffered acetolysis conditions was of particular interest to us in view of



I II

our current studies of the solvolysis reactions of Δ^5-19-methanesulfonoxy steroids.[2] Although the conditions employed for the rearrangement of I to II were those expected to result in thermodynamic control, our studies have indicated that thermodynamically controlled hydrolysis of the related Δ^5-19-methanesulfonoxy steroids III should lead to 7β-hydroxy-B-homoestr-5(10)-enes Va (Scheme I).[2]

The object of our present work was to determine whether thermodynamically controlled acetolysis of III might lead to 6β-acetoxymethylestr-5(10)-enes VIb, and if so to find the reason for the contrasting modes of rearrangement effected by hydrolysis and acetolysis.

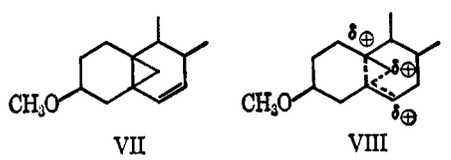
Acetolysis of III at 100° for 16 hr in the absence of a buffer, followed by basic hydrolysis of the crude acetate, led to the isolation of 3β-methoxy-6β-hydroxymethylestr-5(10)-en-17-one (VIa) in 34% yield. Nmr spectra of VIa and its acetate VIb provided the following criteria for structural assignment: (1) the absence of vinyl proton absorption; (2) two-proton absorptions due to the methylene protons of the 6β-hydroxymethyl group of the alcohol VIa (218 cps) and the 6β-acetoxymethyl group of the derived acetate VIb (247 cps); (3) the magnitude of the paramagnetic shift (29 cps) of the methylene protons of the 6β-hydroxymethyl group of VIa resulting from acetylation to form the acetate VIb, which is characteristic of primary alcohols;[3] (4) the triplet absorption of the hydroxyl proton of VIa (268 cps, J = 5.5 cps) in hexadeuteriodimethyl sulfoxide which results from coupling with the two neighboring methylene protons.[4] This latter absorption disappears after addition of deuterium oxide with the appearance of a sharp water peak at 210 cps.

The absorption of the methylene protons of the 6β-acetoxymethyl group of VIb in deuteriochloroform solution appears as a multiplet composed of a singlet at 250 cps and a doublet of equal area with peaks at 242 and 245 cps. Although an exact analysis of this absorption is not possible, the pattern is that which might be expected for the AB portion of an ABX system[5] which in this case is comprised of the methylene protons and the 6α proton.

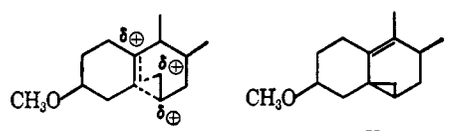
The stereochemistry of VIa and VIb at C_6 is assigned from the assumed mode of formation of the acetolysis product by attack of the nucleophile on the C_{19} methylene carbon of the homoallylic cation IX, as previously described in the case of the 6β-chloromethylestr-5-(10)-ene VIc.[2c] This corresponds to the stereochemistry assumed by Dugan and de Mayo for the analogous presenegenin–senegenin rearrangement.[6]

Since our previous work had indicated that 7β-chloro-B-homoestr-5(10)-enes Vc readily rearrange to the more stable 6β-chloromethylestr-5(10)-enes VIc,[2c] it seemed likely that formation of VIb in the acetolysis reaction simply reflected the instability of the 7β-acetoxy-B-homoestr-5(10)-enes Vb under the thermodynamically controlled acetolysis conditions. To investigate this point, 3β-methoxy-7β-acetoxy-B-homoestr-5(10)-en-17-one (Vb)[2] was subjected to the acetolysis conditions (100°, 3 hr) in the presence of 1 equiv of methanesulfonic acid. After the basic hydrolysis of the crude product, 3β-methoxy-6β-hydroxymethylestr-5(10)-en-17-one (VIa) was isolated in 34% yield.

In contrast to the results in the absence of a buffer, acetolysis of the methanesulfonate III in the presence of 4 equiv of potassium acetate (100°, 16 hr) followed by basic hydrolysis of the crude acetate gave 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (Va) in 77% yield, together with 3β-methoxy-5β,19-cycloandrost-6-en-17-one (VII) in 8% yield. Isolation of the B-homo steroid Va from the buffered acetolysis, rather than the isomeric 5β,19-cyclo-6β-ol IVa, which is formed under conditions of buffered hydrolysis,[2] is due to the instability of the acetate IVb which was found to rearrange to the B-homo steroid Vb in 63% yield under the buffered acetolysis conditions. In addition, the buffered acetolysis of IVb yielded 14% of the vinylcyclopropane VII.



VII VIII



IX X

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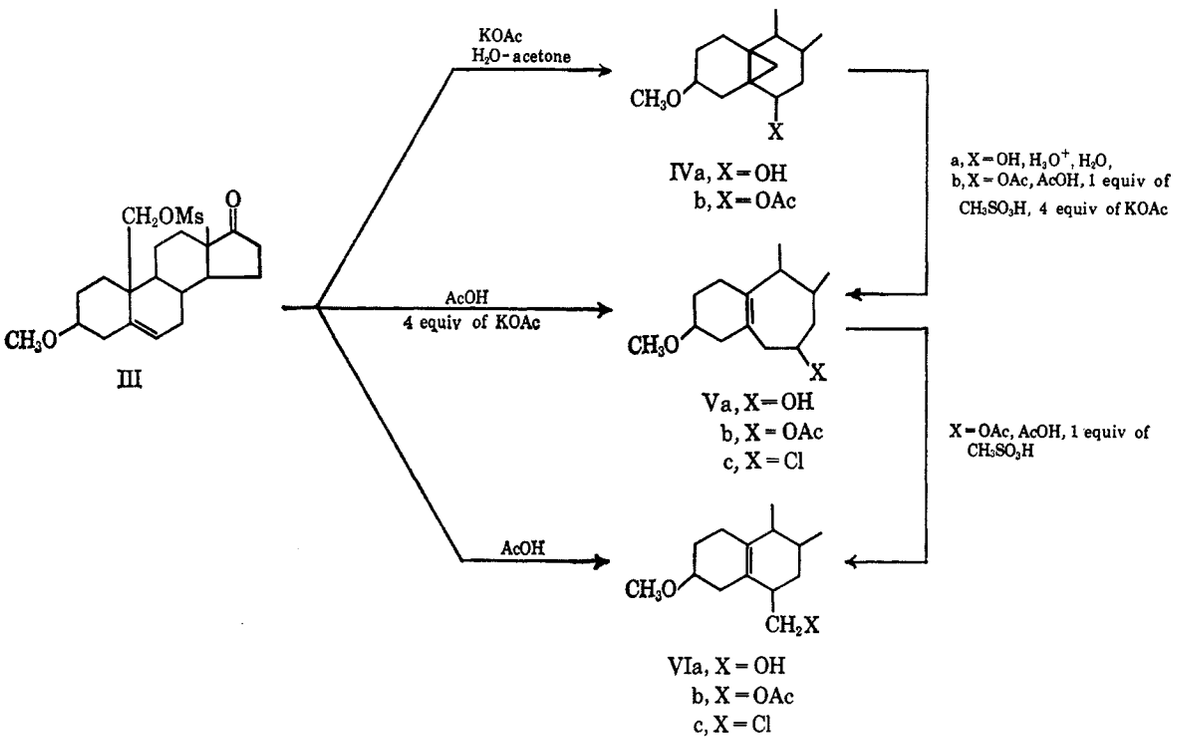
SCHEME I



It is of interest that the substitution and elimination products Vb and VII formed in the buffered acetolyses of both III and IVb must be formed from two different, isomeric homoallylic cations IX and VIII, respectively, since it has been found that the olefin formed from cation IX, which leads to the B-homo acetate Vb, is the isomeric vinylcyclopropane X.[2b,c]

It has been previously established that formation of X from the B-homosteroid Va *via* the cation IX is reversible, and that X is much less stable than VII under acidic conditions.[2b,c] The failure to isolate X as an elimination product from the buffered acetolysis of III or IVb may be explained by the fact that buffered acetolysis of X, followed by basic hydrolysis of the product with methanolic potassium hydroxide, was found to give 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (Va) in 64% yield.

Unlike the buffered acetolyses of the methanesulfonate III and the acetate IVb, both of which must occur by initial formation of cation VIII followed by rearrangement of VIII to cation IX,[2b,c] buffered acetolysis of the vinylcyclopropane X, which leads directly to cation IX, does not give the 5β,19-cyclo-6-ene VII as a by-product. This is consistent with previous observations[2b,c] which indicate a considerable energy barrier between VIII and IX, and that rearrangement of cation VIII to IX, which occurs in the conversions of III and IV to V and VI, is essentially irreversible.

These results clearly indicate that the nature of the rearrangement products formed from Δ^5-19-substituted steroids is governed by a delicate balance of kinetic and thermodynamic factors and that the kinetically favored order of products, IV > V > VI, is opposite the thermodynamically favored order. Evidence for the intermediates VIII and IX which are involved in these rearrangements has been previously described.[2b,c]

Experimental Section

Melting points were determined with a Fisher–Johns block. Optical rotations were determined with a Hilger and Watts polarimeter on 1% solutions in chloroform. Infrared spectra were determined with a Perkin–Elmer, Model 421, grating spectrophotometer with 7% solutions in deuteriochloroform. Nmr spectra were determined on solutions in deuteriochloroform unless otherwise specified with a Varian A-60 spectrometer. Nmr absorptions are reported in cycles per second relative to tetramethylsilane (TMS) as an internal standard. Woelm alumina of activity III was used for all chromatography. The petroleum ether used was a fraction boiling at 66–70°.

Acetolysis of 3β-Methoxy-19-methanesulfonoxyandrost-5-en-17-one (III). A. Unbuffered.—A solution prepared from 5.1 g of III, 250 ml of glacial acetic acid, and 5.0 ml of acetic anhydride was heated at 100° for 16 hr. The resulting black solution was cooled to room temperature and shaken with a mixture of 1.2 l. of ether and 2 l. of water. The aqueous phase was separated and extracted with 1.2 l. of ether. The ether solutions were washed in series with four 500-ml portions of water, two 500-ml portions of 5% sodium bicarbonate solution, and three 500-ml portions of water, then combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 4.23 g of a black oil.

The product was heated under reflux for 1 hr in 170 ml of 5% methanolic potassium hydroxide solution. Water (200 ml) was added, and the major portion of the methanol was evaporated under reduced pressure. The resulting aqueous suspension was diluted to 500 ml by the addition of water and extracted three times with 400-ml portions of ether. The ether solutions were washed in series with four 250-ml portions of water, then combined, and dried over anhydrous magnesium sulfate. Evaporation of the ether left 3.51 g of oil.

The product was chromatographed on 220 g of alumina. Elution with benzene (10 × 100 ml) gave 650 mg of an oil. The infrared spectrum showed the absence of hydroxyl absorption while the nmr spectrum indicated the presence of aromatic protons. Elution of the column with 1:1 ether–benzene solution gave 2.56 g of an oil which crystallized on trituration with petroleum ether. Two recrystallizations of this product from acetone–petroleum ether gave 1.38 g (34%) of 3β-methoxy-6β-hydroxymethylestr-5(10)-en-17-one (VIa): mp 128–130°; infrared, $\tilde{\nu}_{max}$ 3619, 3435, 1727 cm^{-1}; nmr spectrum, 53.5(s), C_{18}-H; 202(s), OCH_3; 218(m), 6β-CH_2 (in $CDCl_3$); 263, 268, 274 (t) OH (in CD_3SOCD_3).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.44; H, 9.50. Found: C, 75.22; H, 9.65.

B. Buffered.—The buffered acetolysis solution was prepared by heating a solution prepared from 3.5 g of anhydrous potassium carbonate, 5.0 ml of acetic anhydride, and 250 ml of glacial acetic acid under reflux overnight.

A solution prepared from 2.45 g of the methanesulfonate III and 120 ml of the buffered acetolysis solution was heated at 100° for 16 hr. The product (2.17 g of orange oil) was isolated by ether extraction as described above and then heated under reflux for 1 hr in 80 ml of 5% methanolic potassium hydroxide solution. The product (1.82 g of orange oil) was isolated by ether extraction and chromatographed on 120 g of alumina. Elution with benzene (4 × 100 ml) gave 140 mg (8%) of 3β-methoxy-5β,19-cycloandrost-6-en-17-one (VII), the infrared and nmr spectra of which were identical with those of a previously prepared sample.[2b,c]

Elution with 1:2 ether–benzene solution gave 1.52 g (77%) of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (Va), mp 105–115°. Two recrystallizations from benzene–petroleum ether yielded 1.11 g, mp 118–120°, undepressed on admixture with previously prepared material.[2] The infrared and nmr spectra of the product were identical with those of previously prepared material.

Rearrangement of 3β-Methoxy-7β-acetoxy-B-homoestr-5(10)-en-17-one (Vb)[2] under Unbuffered Acetolysis Conditions.—A solution prepared from 769 mg of Vb, 0.138 ml of methanesulfonic acid, and 2.1 ml of acetic anhydride was heated at 100° for 3 hr. The product (740 mg of black oil) was isolated by ether extraction in the usual manner and then heated under reflux for 1 hr in 25 ml of 5% methanolic potassium hydroxide solution. The product (581 mg) was chromatographed on 50 g of alumina. Elution with benzene (3 × 100 ml) gave 65 mg of orange oil. This was followed by elution with 1:1 ether–benzene solution which gave 390 mg of product. Three recrystallizations from acetone–petroleum ether solution gave 230 mg (34%) of 3β-methoxy-6β-hydroxymethylestr-5(10)-en-17-one (VIa), mp 126–128°, $[\alpha]^{25}D$ +131°, identical in all respects with the material described above.

Rearrangement of 3β-Methoxy-6β-acetoxy-5β,19-cycloandrostan-17-one (IVb) under Conditions of Buffered Acetolysis.—A solution prepared from 578 mg of IVb, 0.104 ml of methanesulfonic acid, and 31 ml of the buffered acetolysis solution, prepared as described above, was heated at 100° for 5 hr. The product (549 mg of orange oil) was isolated by ether extraction in the usual manner and then heated under reflux for 1 hr in 30 ml of 5% methanolic potassium hydroxide solution. The product (434 mg of orange oil) was chromatographed on 42 g of alumina. Elution with benzene (25 ml) and 1:15 ether–benzene solution (75 ml) gave 69 mg (14%) of 3β-methoxy-5β,19-cycloandrost-6-en-17-one (VII) identified by its infrared and nmr spectra.[2]

Elution with 1:2 ether–benzene solution yielded 323 mg (63%) of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (Va), mp 108–117°. Recrystallization from benzene–petroleum ether solution gave 248 mg, mp 117–120°, identical in all respects with previously prepared material.[2]

Buffered Acetolysis of 3β-Methoxy-5β,6β-methanoestr-9-en-17-one (X).—A solution prepared from 511 mg of the vinylcyclopropane X, 0.104 ml of methanesulfonic acid, and 31 ml of the buffered acetolysis solution described above was heated at 100° for 5 hr. The product (551 mg) was isolated by ether extraction and heated under reflux for 1 hr in 30 ml. of 5% methanolic potassium hydroxide solution, and the product (451 mg) was chromatographed on 45 g of alumina. Elution with benzene (20 ml) and 1:15 ether–benzene solution (80 ml) gave 53 mg of an oil. Nmr and infrared spectra of this material showed the absence of vinyl protons and thus the absence of 3β-methoxy-5β,-19-cycloandrost-6-en-17-one (VII). The presence in the nmr spectrum of two methoxyl absorptions of approximately equal area at 199 and 201 cps and two angular methyl absorptions at 53.5 and 54.8 cps indicated a mixture which was not characterized further.

Elution of the column with 1:2 ether–benzene solution (3 × 100 ml) yielded 345 mg. (64%) of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (Va), mp 108–115°. Recrystallization from benzene–petroleum ether solution gave 288 mg, mp 117–121°, identical in all respects with a previously prepared sample.[2]

Preparation of 3β-Methoxy-6β-acetoxymethylestr-5(10)-en-17-one (VIb) and 3β-Methoxy-6β-acetoxy-5β,19-cycloandrostan-17-one (IVb).—The acetates were prepared by treatment of the corresponding alcohols with acetic anhydride in pyridine solution as described previously.[2] Pertinent physical data are listed. 3β-Methoxy-6β-acetoxymethylestr-5(10)-en-17-one (VIb) (an oil) showed $[\alpha]^{25}D$ +124; infrared, ν_{max} 1730 cm^{-1}; nmr, 54.2(s), C_{18}-H; 125(s), $OCOCH_3$; 201(s), OCH_3; 250(s), 245, 242(d), 6β-CH_2.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.01; H, 8.86.

3β-Methoxy-6β-acetoxy-5β,19-cycloandrostan-17-one (IVb) showed mp 130–133°; $[\alpha]^{25}D$ +115°; infrared, ν_{max} 3064 and 1726 cm^{-1}; nmr, 21.4, 27.0(d), one cyclopropyl proton; 53.4(s), C_{18}-H; 124(s), $OCOCH_3$; 197(s), OCH_3; 310(m), $W_{1/2}$ = 7 cps, $C_{6\alpha}$-H.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.34; H, 8.99.

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The Skeletal Structure of Lobinaline[1]

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By a combination of degradative, spectral, and synthetic studies, lobinaline, the major alkaloid of *Lobelia cardinalis L.*, has been shown to have the skeletal structure **1a**. The degradative studies on the alkaloid proceeded by way of a Von Braun demethylation followed by dehydogenation to 5,7-diphenyl-6-(2-pyridyl)-quinoline. The latter was synthesized for comparison by a Skraup synthesis with 3,5-diphenyl-4-(2-pyridyl)-aniline which, in turn, was prepared by an unequivocal route. Various other transformations of the alkaloid as well as a synthesis of the isomeric 6,7-diphenyl-5-(2-pyridyl)quinoline are also described.

Lobinaline, the major alkaloid of *Lobelia cardinalis L.*, was first isolated in 1938 by Manske,[2] who carried out some preliminary chemical studies on the constitution of the compound. Since that time little has been published on the subject other than a report[3] on the, paper chromatographic behavior of the alkaloid. In the course of a program of routine plant screening in this laboratory, a crystalline alkaloid was isolated from *L. cardinalis* which appears to be the same as the earlier reported lobinaline. In this paper are reported the results of degradative, spectral, and synthetic studies

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