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Acid-catalyzed rearrangement of some steroidal isoxazolidines

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Abstract

Acid-catalyzed reaction of the steroidal Δ^1-unsaturated 3β,5β-epoxyimino compound **2** and Δ^3-unsaturated 1β,5β-epoxyimino products **3** and **7**, results in intramolecular rearrangement involving the *N*-CH_3 group to give the corresponding perhydro-3,1-oxazine derivatives **9**-**11**. Under similar reaction conditions, the saturated analogues **4**, **6** and **8** remain unchanged. The difference in reactivity between the unsaturated and saturated compounds is studied and elucidated by the semiempirical molecular orbital MNDO-PM3 method. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: isoxazolidines; perhydro-oxazines; seco steroids; molecular rearrangement.

Introduction

In a preliminary communication [1] we described briefly a new type of acid-catalyzed rearrangement of the steroidal isoxazolidines, *i.e.*, *N*-methyl-3β,5-epoxyimino-5β-cholest-1-ene (**2**), *N*-methyl-1β,5-epoxyimino-5β-cholest-3-ene (**3**) (Scheme 1) and *N*-methyl-1β,5-epoxyimino-19-nor-5β-androst-3-en-17β-yl acetate (**7**) (Scheme 2) to the corresponding perhydro-3,1-oxazine derivatives **9-11**, respectively (Scheme 3). In the present paper we wish to report more extensively on the observed transformation of these Δ^1- and Δ^3-unsaturated substrates and also on the behaviour of the respective saturated analogues (compounds **4**, **6** and **8**, Schemes 1 and 2), when subjected to similar acid-catalyzed conditions.

The isoxazolidines **2** and **3** were prepared (in 56% and 30% yield, respectively) [2], by heating

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[†] Our esteemed teacher, colleague and friend deceased on June 8. 1998.

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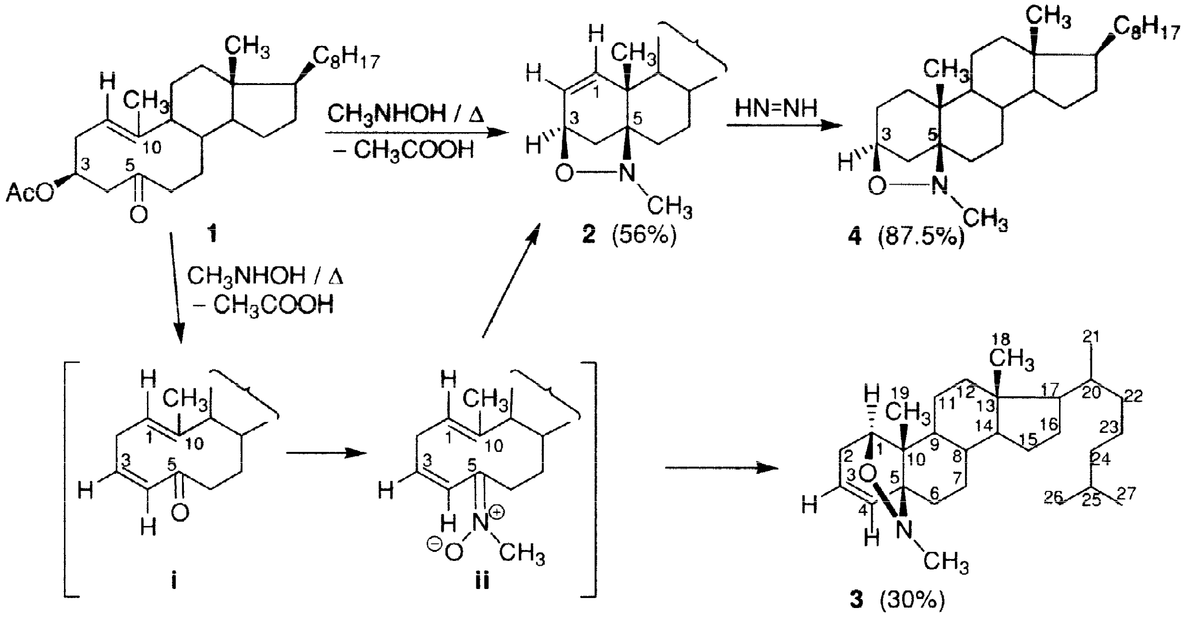
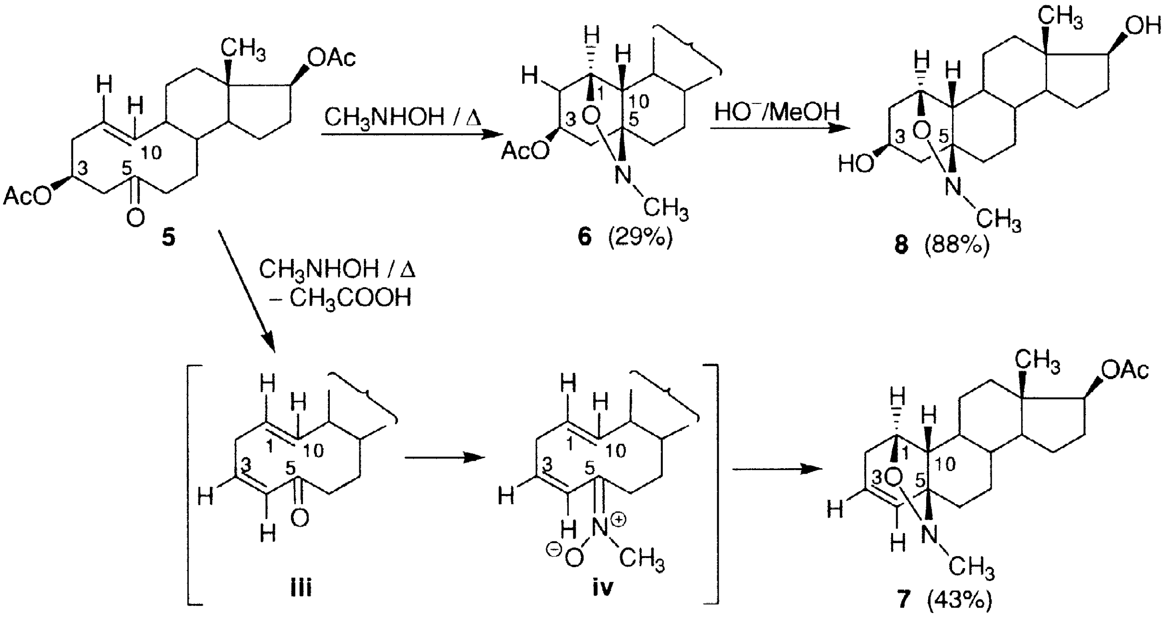


Scheme 1

(*Z*)-3β-acetoxy-5,10-secocholest-1(10)-en-5-one (**1**) with *N*-methylhydroxylamine hydrochloride in ethanol-pyridine (1:1, v/v) solution at reflux for 24 h (Scheme 1), while the corresponding 19-norandrost-3-ene analogue **7** (Scheme 2) was obtained (in 43% yield) under similar conditions starting from (*Z*)-3β,17β-diacetoxy-19-nor-5,10-secoandrost-1(10)-en-5-one (**5**); the minor product of the latter reaction being the saturated 3β-acetoxy isoxazolidine **6** (isolated in 29% yield) [3].

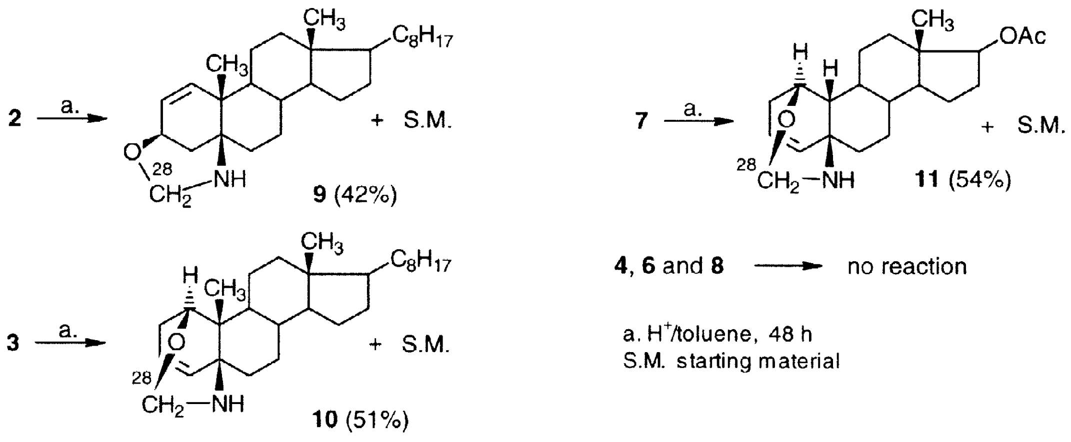


Scheme 2

Δ^3-Unsaturated isoxazolidines **3** and **7** are formed by an intramolecular, 1,3-dipolar cycloaddition of the C(5)-nitrone group of the intermediate **ii** and **iv**, respectively, to the corresponding transannular $\Delta^{1(10)}$-double bond (the reaction proceeding *via* **i** and **iii** produced by acetic acid elimination from the (*Z*)-5,10-secosteroidal ketones **1** and **5**), while Δ^{1}-isoxazolidine **2** arises from an intramolecular process in which the C(5)-nitrone function and both the $\Delta^{1(10)}$- and Δ^{3}-double bond are involved (for details see Ref. 4). On the other hand, isoxazolidine **6** is the product of transannular C(5)-nitrone 1,3-dipolar cycloaddition to the $\Delta^{1(10)}$-bond of **5** which takes place without acetic acid elimination.

Acid-catalyzed reactivity of N*-methylisoxazolidines* ***2-4*** *and* ***6-8***

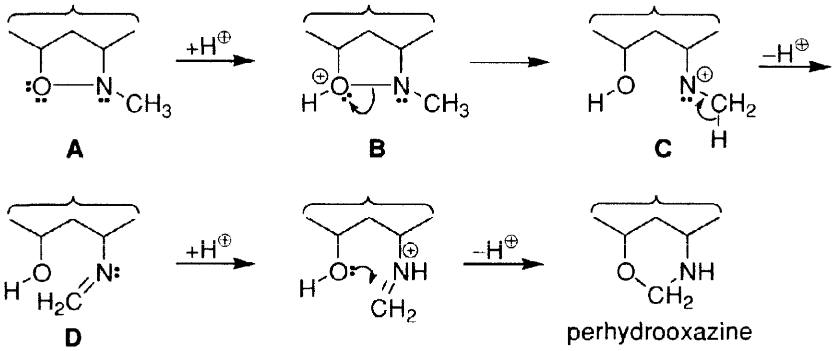
Acid-catalyzed reaction of isoxazolidines **2**, **3** and **7** was carried out in boiling toluene solution (~6 mM) with *p*-toluenesulfonic acid (~20 mol%) for 48 h. Under these conditions all three substrates underwent an intramolecular rearrangement involving their N-CH_3 group, to give (Scheme 3) the perhydro-3,1-oxazine derivative **9-11** (in 42-54% yield); the remainder being the recovered starting material (17-20%) and a complex mixture.



Scheme 3

The structure of the obtained products **9-11** was established as follows. In their ^{1}H-NMR spectra the original N-CH_3 group (singlet at δ~2.60 ppm) was missing. Instead, two doublets appeared between δ 4.18-4.32 ppm and δ 4.65-4.82 ppm, respectively, assignable to the -CH_2- group between oxygen and nitrogen, indicating the presence of the -O-CH_2-NH-C(5) fragment. The $\rangle$N-H group appeared in the IR spectra of compounds **9-11** as a new absorption at ~3300 cm^{-1}. Besides, the number of the primary, secondary, tertiary and H-free C-atoms detectable in the DEPT ^{13}C-NMR-spectra of these compounds [for **9** and **10**, 5 CH_3, 11 CH_2, 9 CH (of which 2 olefinic and 1 bearing oxazine oxygen) and 3 H-free C-atoms, and for **11**, 2 CH_3, 8 CH_2, 8 CH (of which 2 olefinic and 1 bearing oxazine oxygen) and 3 H-free C-atoms] are consistent with the proposed structures. For additional spectral characteristics confirming the structures **9-11** see Experimental.

The results obtained with the unsaturated isoxazolidines **2**, **3** and **7** prompted us to investigate the synthetic possibilities of the described transformation using as substrates the corresponding saturated analogues, *i.e.*, *N*-methyl-1β,5-epoxyimino-5β-cholestane (**4**) (obtained by diimide reduction of the Δ^1-unsaturated derivative **2**, Scheme 1) and *N*-methyl-1β,5-epoxyimino-19-nor-5β-androstane-3β,17β-diyl diacetate (**6**), as well as the corresponding 3β,17β-dihydroxy derivative (**8**) (obtained from **6** by alkaline hydrolysis, Scheme 2). However, when **4**, **6** and **8**, respectively, were subjected to similar acid-catalyzed conditions as above, *i.e.*, heating with *p*-toluenesulfonic acid in boiling toluene for 48 h, neither of these compounds was transformed to the expected perhydro-1,3-oxazine (recovery of the starting material being 68-74% (see Experimental), while the remainder was a complex mixture). This indicated that the presence of the olefinic Δ^1- or Δ^3-double bond in the steroid ring A is indispensable for the reaction to occur.



Scheme 4

The general course of the investigated transformation is presented in Scheme 4. It was anticipated [1] that the reaction is initiated by protonation of the oxygen[1] in the epoxyimino bridge (to give oxonium ion **B**), followed by cleavage of the O-N bond (to produce species **C**), and subsequent proton elimination involving, as the final step, intramolecular cyclization in which participate the imine function of the obtained intermediate **D** and the newly formed hydroxyl group.

In an attempt to get a mechanistic explanation of the observed difference in reactivity between the unsaturated isoxazolidinines **2**, **3** and **6** and their saturated analogues **4**, **7** and **8**, semiempirical M.O. methods have been applied.

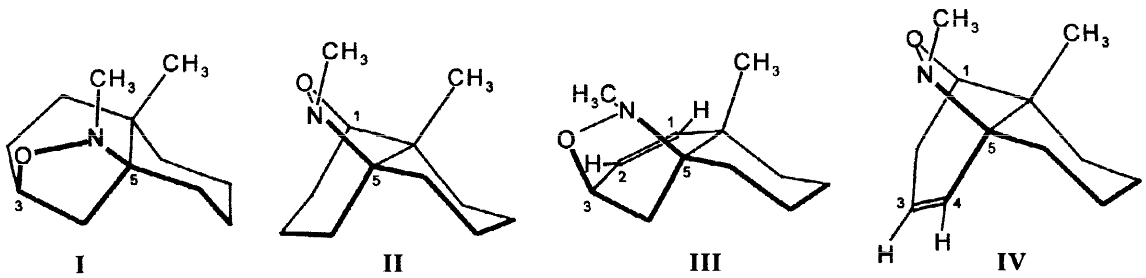


Figure 1. Structures of model compounds as computed by semiempirical MO calculations

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[1] As reported in Ref. 1, protonation of the nitrogen in the epoxyimino bridge of 1β,5β-isoxazolidines **3** and **7** results in elimination of the CH_3NH_2 fragment and formation of the unsaturated 1-oxo derivatives.

As model compounds the saturated and unsaturated *cis*-decaline-3,5- and 1,5-isoxazolidine derivatives **I-IV** (Figure 1) were selected.

Method of calculation

In our work we used the MNDO-PM3 method that proved to be highly reliable for investigating molecular properties of molecules and ions [5-17]. We used the MOPAC program package, Version 7.01. The geometries of all molecular species correspond to the energy minima in a vacuum and were optimized by the PM3 method. The transition states for all the reactions were found using the corresponding MOPAC facilities (TS, SADDLE). When needed, the obtained structures were refined by Bartel's method (Non-Linear Least Squares gradient minimization routine - NLLSQ), and transition states were further proved by vibrational analysis showing only one negative vibration. The influence of the solvent on the cations was not studied, because all the studied reactions were experimentally done in a non polar solvent.

Results and discussion

In calculations the following intuitive models have been considered:

(i) Bond strain imposed on the isoxazolidine ring upon introduction of the olefinic double bond into the steroid ring A. In the saturated systems the epoxyimino bridge is attached to the diaxial 3β,5β- (in **4**) or 1β,5β-bonds (in **6** and **8**), in contrast to the unsaturated molecules in which the β-oriented bonds next to the double bond (*i.e.*, 3β- in **2** and 5β- in **3** and **7**) assume pseudoaxial (a') orientation. Therefore, in unsaturated substrates the epoxyimino bridge should be connected to the spatially more distant a',a-3β,5β- (in **2**) and a,a'-1β,5β-positions (in **3** and **7**), thus weakening their O–N bond.

(ii) Competition between the oxygen and nitrogen of epoxyimino bridge to attract a proton; as shown in Scheme 4, only protonated oxygen can initiate reaction proceeding in the right direction.

Results given in Table 1 indicate that the lengths of the N–O bond in the *O*-protonated intermediates (of type **B**, Scheme 4) in saturated and unsaturated 3β,5β- and 1β,5β-isoxazolidines are very similar. Moreover, stretching of the N–O bond in saturated systems is somewhat greater than in the unsaturated ones, but the former compounds do not open their isoxazolidine ring under acid-catalyzed conditions.

Table 1.
N-O Bond lenghts for the species protonated at oxygen

Protonated isoxazolidine	3,5-saturated **I**	1,5-saturated **II**	Δ^1-3,5-unsaturated **III**	Δ^3-1,5-unsaturated **IV**
Distance N-O [Å]	1.814	1.816	1.781	1.807

Besides, Table 2 (in which the calculated heats of formation of various reaction intermediates are given) shows that in all investigated cases, *O*-protonated intermediates have considerably higher energies (for 16 - 20 kcal/mol) than the corresponding *N*-protonated species. Yet, reaction products of the latter intermediates were not detected in the respective reaction mixtures.

Therefore, in order to explain the acid-catalyzed reactivity of unsaturated compounds, some other factors had to be also considered. Namely, it can be safely assumed that the olefinic bond present in the molecules **2**, **3**, and **7**, is directly involved in the rearrangement process, by interaction with the electrophilic N atom in the intermediate **C**.

Table 2.
The calculated energies (ΔH_f in [kcal/mol]) of *cis*-decaline isoxazolidines **I** - **IV** and their respective reaction intermediates leading to the imino form **D**

	protonated				
I Saturated 3,5-isoxazolidine	at N	at O, **B**	open, **C**		imino form, **D**
-26.048	123.874	148.408	147.987		96.339
II Saturated 1,5-isoxazolidine	at N	at O, **B**	open, **C**		imino form, **D**
-22.454	129.481	145.965	147.741		96.332
III Δ^1- 3,5-isoxazolidine	at N	at O, **B'**	open, **C'**	pyrrolidine form	imino form, **D'**
-0.655	151.405	169.217	170.900	165.190	121.492
IV Δ^3- 1,5-isoxazolidine	at N	at O, **B''**	open, **C''**	aziridine form	imino form, **D''**
2.116	153.343	170.363	175.391	163.342	119.973

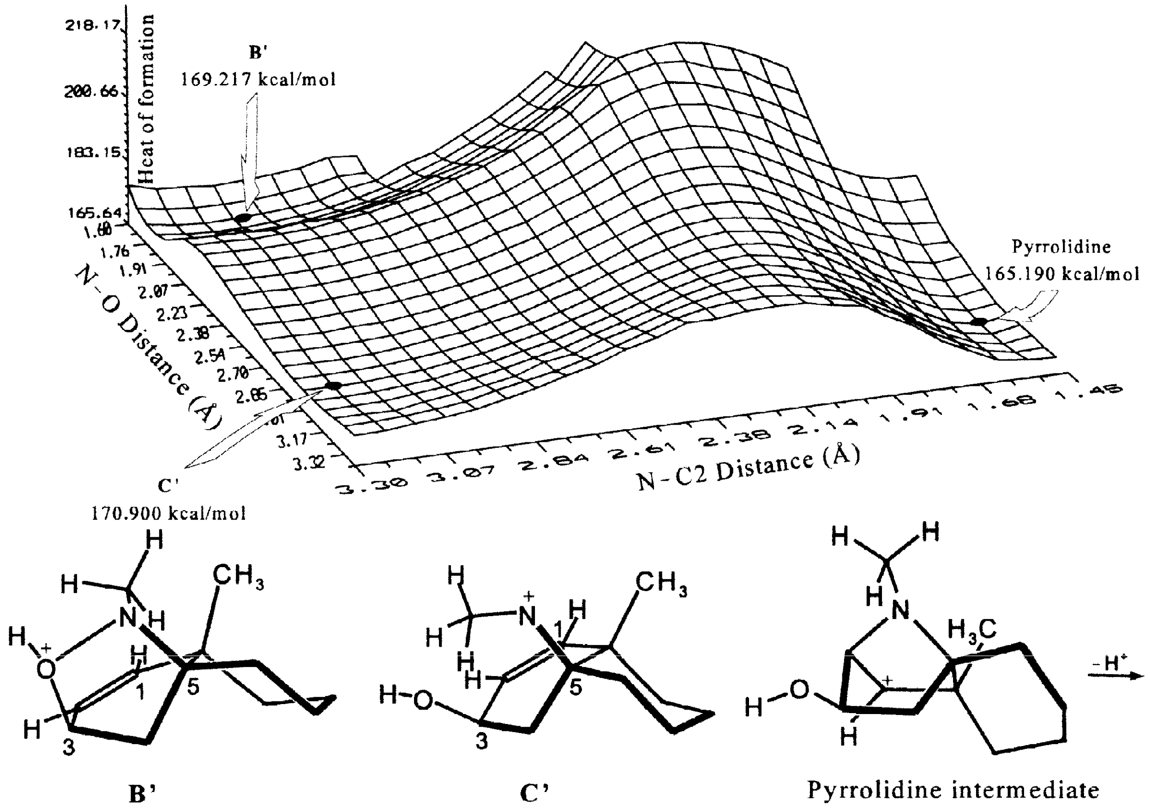

Figure 2. Potential energy surfaces of interconversions among various structures in Δ^1-3,5-isoxazolidine, **III**. On the bottom of the figure the optimized geometries are shown, that correspond to the minima on the potential energy surface.

To establish what kind of stabilization by the olefinic double bond in the model compounds **III** and **IV** is possible, extensive calculations of potential energy surfaces for these compounds have been done. As reaction coordinates were chosen the N-O distance in the course of transformation **B** to **C**, and the distance between nitrogen and one of the carbons on the double bond in the course of formation **D**.

Figure 2 shows the potential energy surface for conversion of Δ^1-3,5-isoxazolidine, **III**, to the imine **D'**. The primarily formed *O*-protonated intermediate of structure **B'** is transformed *via* the completely opened intermediate **C'** to the most stable intermediate for which the pyrrolidine structure has been computed. The latter species after proton elimination from the *N*-methyl group forms imine **D'**. Activation energies for the above transformations from **B'** to **C'** and to pyrrolidine intermediate are very low (about 2-3 kcal/mol).

Very similar results are obtained for Δ^1-3,5-isoxazolidine, **IV** (shown in Fig.3). Primarily formed, *O*-protonated intermediate (structure **B''**), after complete opening of the isoxazolidine ring gives intermediate structure **C''**, which is stabilized by participation of the Δ^3-double bond to form an aziridine intermediate. By proton elimination from the *N*-methyl group, it is transformed to imine **D''**. Activation energies for interconversions among these structures are also very low, ranging from 2 to 3 kcal/mol.

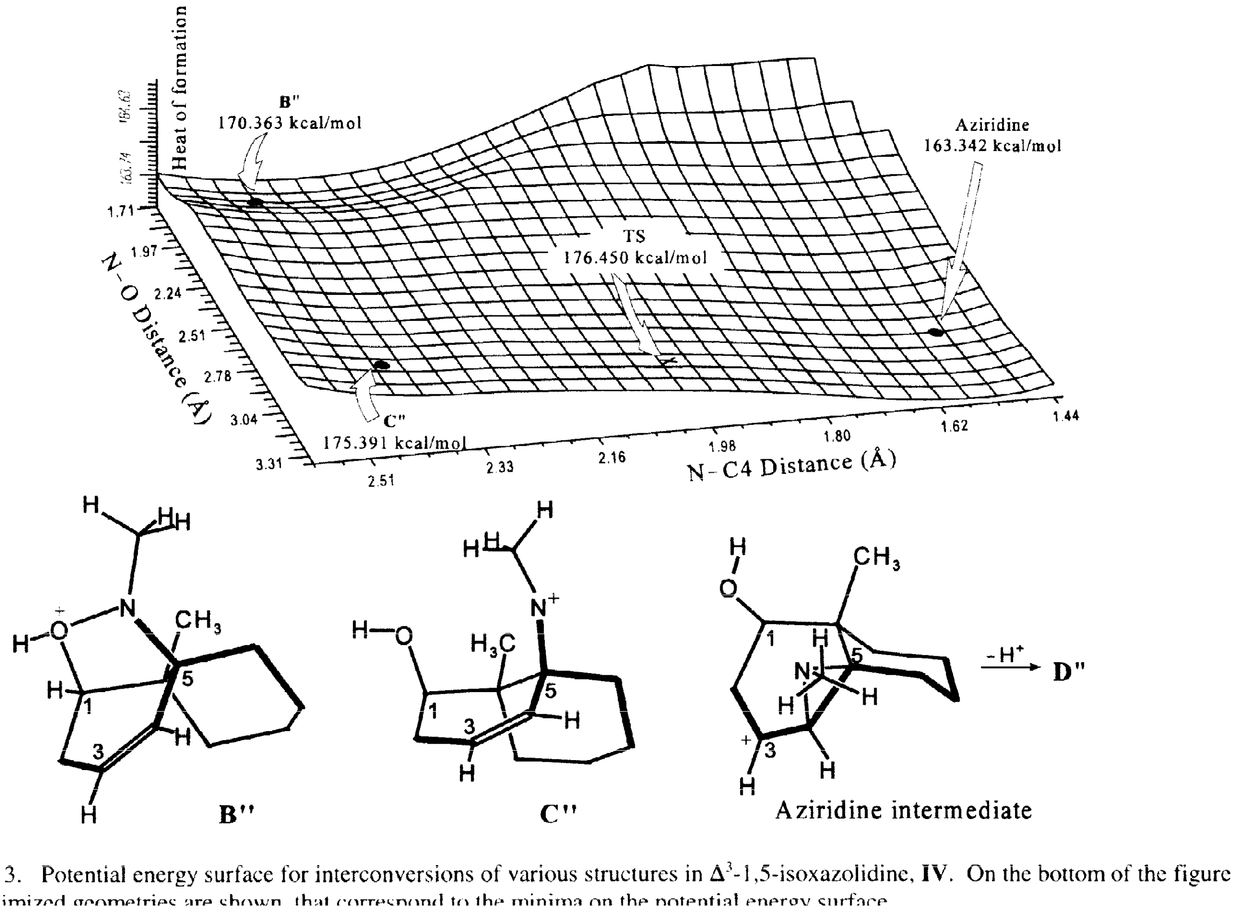

Figure 3. Potential energy surface for interconversions of various structures in Δ^3-1,5-isoxazolidine, **IV**. On the bottom of the figure the optimized geometries are shown, that correspond to the minima on the potential energy surface.

These results suggest that stabilization due to formation of the pyrrolidine structure (for **III**), and the aziridine structure (for **IV**) makes feasible the observed isomerization of unsaturated isoxazolidines leading to the corresponding imine intermediates, and further to the perhydro-1,3-oxazine derivatives. As shown by experiment, the saturated systems, in which such a stabilization is not possible, do not react under similar acid-catalyzed conditions.

Experimental

General.

Removal of solvents was carried out under reduced pressure. Prep. column chromatography: silica gel 0.063-0.200 mm. TLC: control of reactions and separation of products on silica gel G (Stahl) with benzene/AcOEt 9:1 and 7:3, toluene/AcOEt 9:1, 8:2 and 7:3 or toluene/EtOEt 9:1 and 8:2, detection with 50% aq.H_2SO_4 soln. M. ps. uncorrected. IR spectra: *Perkin-Elmer-337* spectrophotometer; ν in cm^{-1}. NMR spectra: *Brucker AM-360* or *Varian Gemini 200* (^1H at 360 or 200 MHz, ^{13}C at 90.55 or 50.28 MHz); $CDCl_3$ soln. at r. t., TMS as internal standard; chemical shifts in ppm as δ values, *J* in Hz. Mass spectra: *Finnigan-MAT 8230*. Light petroleum: fraction boiling at 40-60 °C.

Preparation of starting materials:

N-Methyl-isoxazolidines **2**, **3**, **6-8** were prepared according to the reported procedures [1,2].

N-*Methyl-3β,5-epoxyimino-5β-cholestane* (**4**). - To a stirred suspension of *N*-methyl-3β,5-epoxyimino-5β-cholest-1-ene (**2**) (0.2 g, 0.481 mmol) and potassium azodicarboxylate [18] (0.8 g, 4.12 mmol) in methanol (10 ml, distilled over $NaBH_4$) and dry methylene chloride (10 ml) cooled in an ice bath, a solution of acetic acid (0.52 ml, 8.25 mmol) in dry methanol (2 ml) was slowly added. The reaction mixture was stirred at room temperature for an additional 12 h, then poured into water and extracted with diethyl ether-methylene chloride. The organic layer was washed with water, 5% aq. $NaHCO_3$ soln., water, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from acetone, to give *N*-methyl-3β,5-epoxyimino-5β-cholestane **4** (0.176 g, 87.5%) as a white solid, m.p. 65 °C. $[\alpha]_D^{25}$= - 4.7 (c=1, $CHCl_3$). IR (KBr): 1470, 1450, 1435, 1380, 1370, 945, 930 . ^1H-NMR (360 MHz): 0.67 (*s*, CH_3(18)), 0.88 (2*d*, *J*=6, CH_3(26), CH_3(27)), 0.91 (*d*, *J*=6, CH_3(21)), 0.97 (*s*, CH_3(19)), 2.01 (*fd*, *J*=12.5, H_α-C(6)), 2.33 (*d*, *J*=12.5, H_α-C(4)), 2.51 (*s*, CH_3-N), 4.41 (*t*, *J*= 5, H-C(3)). ^{13}C - NMR (90.55 MHz): 75.0 (*d*, C(3)), 70.6 (*s*, C(5)), 56.9 (*d*, C(17)), 56.6 (*d*, C(14)), 44.8 (*d*, C(9)), 43.2 (*s*, C(13)), 42.5 (*q*, CH_3-N), 41.3 (*s*, C(10)), 40.7 (*t*, C(12)), 39.8 (*t*, C(24)), 37.3 (*t*, C(4)), 36.5 (*t*, C(22)), 36.1 (*d*, C(8)), 35.4 (*d*, C(20)), 29.6 (*t*, C(6)), 29.5 (*t*, C(2)), 28.7 (*t*, C(1)), 28.6 (*t*, C(16)), 28.3 (*d*, C(25)), 27.9 (*t*, C(7)), 24.4 (*t*, C(23)), 24.1 (*t*, C(15)), 23.0 (*q*, C(26)), 22.8 (*q*, C(27)), 22.8 (*t*, C(11)), 19.2 (*q*, C(19)), 18.9 (*q*, C(21)), 12.6 (*q*, C(18)). MS: *m/z* = 415 ($M^{+\bullet}$, 100%), 369, 194, 165, 110, 97, 81, 57, 53. Anal. calc. for $C_{28}H_{49}NO$ (415.707): C 80.90, H 11.88, N 3.37; found: C 80.59, H 11.82, N 3.18.

Acid-catalyzed reactivity of N-*methyl isoxazolidine derivatives* **2-4** and **6-8**:

Reaction of N-*methyl-3β,5-epoxyimino-5β-cholest-1-ene (2) with* p-*toluenesulfonic acid*. - A solution of **2** (50 mg) and *p*-toluenesulfonic acid (5 mg) in toluene (20 ml) was refluxed for 48 h, then diluted with diethyl ether and washed with 5% aq. $NaHCO_3$ soln. and water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on 2 g silica gel. Elution with benzene-diethyl ether (98:2) gave the starting isoxazolidine **2** (10 mg, 20%), identified by IR and ^1H-NMR spectra (which were identical to those of an authentic sample). Benzene-diethyl ether (96:4) and (94:6) eluted a complex mixture (8 mg, ~15%), which was not further investigated. Elution with benzene-diethyl ether (90:10) gave 3β,5-epoxymethyleneimino-5β-cholest-1-ene (**9**) (21 mg, 42%) as a white solid, m.p. 118 °C (from acetone-MeOH). $[\alpha]_D^{25}$= +131 (c=0.50, $CHCl_3$); IR (KBr): 3290 (-NH-), 1470, 1430, 1385, 1370, 1135, 965. ^{1}H-NMR (360 MHz): 0.66 (*s*, CH_3 (18)), 0.86 (2*d*, *J*=6, CH_3(26), CH_3(27)), 0.89 (*d*, *J*=6, CH_3(21)), 1.10 (*s*, CH_3(19)), 1.96 (*dt*, *J*=12, 5.4, H_α-C(6)), 2.23 (*fd*, *J*=12, H_2C(4)), 4.36 (*m*, H-C(3)), 4.18 and 4.65 (2*d*, *J*=11.4, H_2C(28)), 5.53 (*dd*, *J*=11.4, 5.4, H-C(2)), 6.20 (*d*, *J*=11.4, H-C(1)); ^{13}C-NMR (90.55 MHz) ($CDCl_3$): 144.1 (*d*, C(1)), 118.7 (*d*, C(2)), 68.8 (*t*, C(28)), 66.0 (*d*, C(3)), 55.9 (*d*, C(17)), 55.6 (*d*, C(14)), 51.6 (*s*, C(5)), 49.4 (*d*, C(9)), 42.0 (*s*, C(13)), 41.2 (*s*, C(10)), 39.6 (*t*, C(12)), 39.0 (*t*, C(24)), 37.1 (*t*, C(22)), 35.7 (*t*, C(4)), 35.7 (*t*, C(6)), 35.3 (*d*, C(20)), 34.8 (*d*, C(8)), 27.7 (*t*, C(16)), 27.6 (*d*, C(25)), 26.4 (*t*, C(7)), 23.8 (*t*, C(15)), 23.4 (*t*, C(23)), 22.4 (*q*, C(27)), 22.1 (*q*, C(26)), 21.6 (*t*, C(11)), 18.2 (*q*, C(21)), 14.3 (*q*, C(19)), 11.5 (*q*, C(18)); MS: *m/z* = 413 ($M^{+\bullet}$), 412 ($M^{+\bullet}$-1), 398, 384, 368, 344, 43 (100%); Anal. calc. for $C_{28}H_{47}NO$ (413.691): C 81.29, H 11.45, N 3.39; found: C 80.96, H 11.29, N 3.37.

Reaction of N-*methyl-1β,5-epoxyimino-5β-cholest-3-ene (3) with* p-*toluenesulfonic acid.* - A solution of **3** (50 mg) and *p*-toluenesulfonic acid (5 mg) in toluene (20 ml) was refluxed for 48 h and the mixture worked up as above. The residue was chromatographed on 2 g silica gel. Elution with benzene-diethyl ether (90:10) gave starting isoxazolidine derivative **3** (9.5 mg, 19%), identified by m.p., mixed m.p., IR and NMR spectra. Benzene-diethyl ether (85:15) and (80:20) eluted a complex mixture (8 mg, ca. 15%). Further elution with benzene-diethyl ether (80:20) gave 1β,5-epoxymethyleneimino-5β-cholest-3-ene (**10**) (25.5 mg, 51%) as a white solid, m.p. 145 °C (from acetone-MeOH). $[\alpha]_D^{25}$= +3 (c=0.50, $CHCl_3$). IR (KBr): 3310 (-NH-), 1470, 1440, 1375, 1135, 1025, 935. ^{1}H-NMR (360 MHz): 0.66 (*s*, CH_3(18)), 0.86 (2*d*, *J*=6, CH_3(26), CH_3(27)), 0.90 (*d*, *J*=6, CH_3(21)), 1.28 (*s*, CH_3(19)), 1.96 (*dt*, *J*=12, 6, H_α-C(6)), 2.32 (*m*, H_2-C(2)), 3.73 (*br s*, H-C(1)), 4.32 and 4.82 (2*d*, *J*=11.4, H_2-C(28)), 5.28 (*fd*, *J*=11.5, H-C(4)), 6.13 (*dt*, *J*=11.5, 5.5 H-C(3)). ^{13}C-NMR (90.55 MHz): 130.2 (*d*, C(3)), 129,8 (*d*, C(4)), 73.8 (*d*, C(1)), 70.5 (*t*, C(28)), 56.0 (*d*, C(14)), 56.0 (*d*, C(17)), 53.2 (*s*, C(5)), 43.7 (*d*, C(9)), 42.6 (*s*, C(13)), 39.6 (*t*, C(12)), 39.4 (*t*, C(24)), 38.6 (*s*, C(10)), 36.0 (*t*, C(22)), 35.6 (*d*, C(20)), 35.0 (*d*, C(8)), 33.4 (*t*, C(6)), 29.4 (*t*, C(2)), 28.0 (*t*, C(16)), 27.9 (*d*, C(25)), 27.7 (*t*, C(7)), 23.6 (*t*, C(23)), 23.9 (*t*, C(15)), 22.6 (*q*, C(26)), 22.4 (*q*, C(27)), 21.8 (*t*, C(11)), 18.6 (*q*, C(21)), 13.8 (*q*, C(19)), 12.0 (*q*, C(18)). MS: *m/z* = 413 ($M^{+\bullet}$), 412 ($M^{+\bullet}$-1), 398, 384, 368, 353, 43 (100%). Anal. calc. for $C_{28}H_{47}NO$ (413.691): C 81.29, H 11.45, N 3.40; found: C 81.70, H 11.89, N 3.29.

Reaction of N-*methyl-1β,5-epoxyimino-19-nor-5β-androst-3-en-17β-yl acetate (7) with* p-*toluenesulfonic acid.*- A solution of **7** (67 mg) and *p*-toluenesulfonic acid (7 mg) in toluene (26.8 ml) was refluxed for 48 h and the mixture worked up as above. The residue was chromatographed on 2 g silica gel. Elution with benzene-diethyl ether (85:15) afforded starting isoxazolidine derivative **7** (11.4 mg, 17%), identified by m.p., mixed m.p., IR and NMR spectra. Benzene-diethyl ether (85:15) and (80:20) eluted a complex mixture (10 mg, ~15%). Further elution with benzene-diethyl ether (80:20) gave 1β,5-epoxymethyleneimino-19-nor-5β-androst-3-en-17β-yl acetate (**11**) (27 mg, 54%) as a white solid, m.p. 110 °C (from petrolether-acetone), $[\alpha]_D^{25}$ = + 6.5 (c=0.83, $CHCl_3$). IR (KBr): 3286 (-NH-), 1739, 1451, 1374, 1248, 1046, 795. ^{1}H-NMR (200 MHz): 0.80 (*s*, CH_3(18)), 2.04 (*s*, AcO-C(17)), 4.18 (*br.s*, w/2= 13.2, H-C(1)), 4.31 and 4.78 (2*d*, *J*= 10.8, H_2-C(21)), 4.57 (*dd*, *J*= 9, 7.6 , H-C(17)), 5.33 (*d*, *J*=9.8, H-C(4)), 6.15 (*dt*, *J*=7, 3.1, H-C(3)). ^{13}C-NMR (50.28 MHz): 171.2 (*s*, Me*C*OO); 131.9 (*d*, C(3)); 128.9 (*d*, C(4)); 82.7 (*d*, C(17)); 70.6 (*t*, C(21)); 68.5 (*d*, C(1)); 50.9 (*s*, C(5)); 50.7 (*d*, C(10)); 49.3 (*d*, C(14)); 42.9 (*s*, C(13)), 41.0 (*d*, C(9)), 40.9 (*d*, C(8)), 38.7 (*t*, C(12)), 36.5 (*t*, C(2)), 28.7 (*t*, C(6)), 27.3 (*t*, C(16)), 26.9 (*t*, C(7)), 24.9 (*t*, C(11)), 23.2 (*t*, C(15)), 21.1 (*q*, *Me*COO), 12.0 (*q*, C(18)). MS: *m/z* = 346 ($M^{+\bullet}$ +1), 345 ($M^{+\bullet}$), 286 (100%). Anal. calc. for $C_{21}H_{31}NO_3$ (345.486): C 73.01, H 9.04, N 4.05; found: C 73.14, H 9.13, N 4.27.

Reaction of N-*methyl-1β,5-epoxyimino-5β-cholestane (4) with* p-*toluenesulfonic acid*.- A solution of **4** (52 mg) and *p*-toluenesulfonic acid (5.2 mg) in toluene (20.4 ml) was refluxed for 48 h and the mixture worked up as above. The residue was chromatographed on 2 g silica gel. Elution with toluene and toluene-ethyl acetate (95:5) gave a complex mixture (9 mg, 18%). Further elution with toluene-ethyl acetate (95:5) afforded starting isoxazolidine **4** (34 mg, 68%), the IR and ^{1}H-NMR spectra of which were identical to those observed for an authentic sample of **4**.

Reaction of N-*methyl-1β,5-epoxyimino-19-nor-5β-androstane-3β,17β-diyl diacetate (6) with* p-*toluenesulfonic acid*. - A solution of **6** (200 mg) and *p*-toluenesulfonic acid (20 mg) in toluene (80 ml) was refluxed for 48 h and the mixture worked up as above. The residue was chromatographed on 8 g silica gel. Elution with toluene-ethyl acetate (80:20) and (75:25) gave a complex mixture (40 mg, 20%), which was not further investigated. Toluene-ethyl acetate (70:30) eluted starting material **6** (134 mg, 67.5%), the IR and NMR spectra of which were identical to those observed for a previously described sample **6** [3].

Reaction of N-*methyl-1β,5-epoxyimino-19-nor-5β-androstane-3β,17β-diol (8) with* p-*toluenesulfonic acid*. - A solution of **8** (46 mg) and *p*-toluenesulfonic acid (5 mg) in toluene (18.4 ml) was refluxed for 48 h and the mixture worked up as above. After evaporation, the residue was recrystallized from acetone, giving the starting isoxazolidine **8** (34 mg, 73.9%), identified by m.p., mixed m.p., and spectral data [3]. The residue (6 mg, ~13%) was a complex mixture.

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