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HETEROCYCLIC RING CLEAVAGE IN 20-ISOXAZOLINYL STEROIDS UPON TREATMENT WITH BASE

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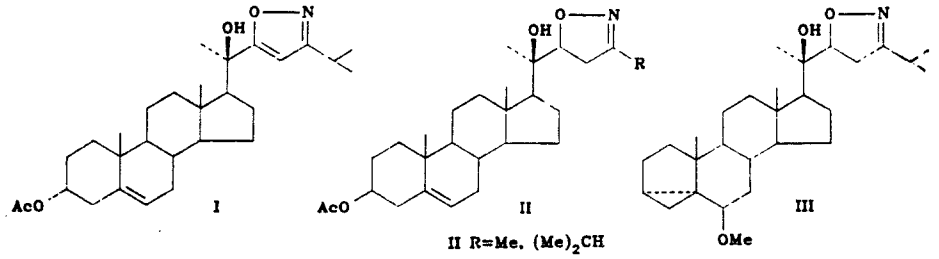
Heterocyclic ring cleavage in 20-isoxazolinyl steroids upon treatment with base has been studied. Treatment with sodium dimsyl (dimethylsulfoxide anion) has been found to result in cleavage of the isoxazoline ring and formation of an α,β-unsaturated ketoxime. The structures of the resulting products are discussed.

Continuing our studies of the synthesis of bifunctional compounds via heterocyclic ring cleavage in isoxazolines and isoxazoles [1], which are adducts formed from ntiriloxides and various unsaturated systems, and pursuant to the goal of preparing on this basis different natural products and related biologically active compounds, it was of great interest to us to examine the feasibility of this approach for the design and construction of polyfunctional steroidal side chains; the problem of stereoselective synthesis of steroidal side chains is an urgent and complex problem in contemporary steroid chemistry.

Toward this goal, we have recently synthesized 20-isoxazolyl- (I) [2] and 20-isoxazolinylsteroids (II and III) [3] via reactions of steroidal acetylenes and olefins, respectively, with nitriloxides.



In studying the catalytic hydrogenation of derivatives of I-III on a variety of catalysts (Pd, Pt, Raney Ni), we have found that there are substantial differences in the properties of these compounds. Isoxazoles I, for instance, readily undergo reductive cleavage along the N–O bond under standard conditions, leading to the corresponding enamino ketones in 100% yield [2]. Isoxazolines II and III, on the other hand, are completely stable with respect to reductive cleavage, which has prompted us to explore alternate pathways for unlocking the inherent functionality in the isoxazoline ring.

Cleavage of 2-isoxazolines II and III upon treatment with base would be of special interest. However, it was found that neither butyllithium nor alkali metal alkoxides led to the desired results. In contrast, use of the dimethylsulfoxide anion [4] as the base, prepared from DMSO upon treatment with sodium hydride, led to the formation of α,β-unsaturated ketoximes IV and VI.

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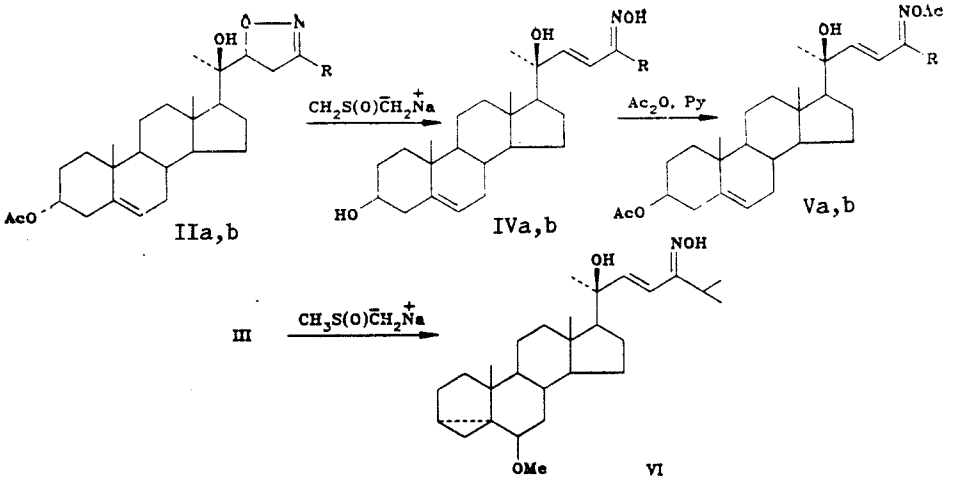
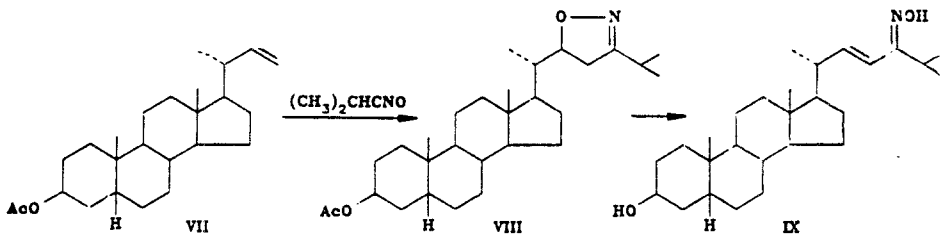
The isomeric structure of II and III (22R or 22S, structure of the A and B rings) does not affect the reaction course or the yields of products IV and VI, using either pure epimers or epimeric mixtures as the starting materials.

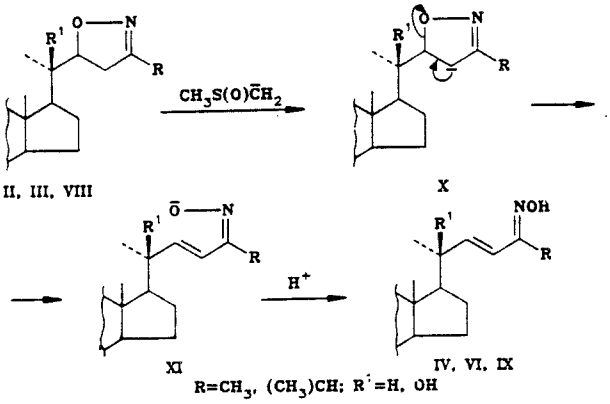


II, IV, V a $R=CH_3$; b $R=(CH_3)_2CH$

Analogous results were obtained upon reaction of 20-isoxazolinyl steroids VIII, which do not contain a hydroxyl group at $C_{(20)}$. Isoxazolines VIII were synthesized by 1,3-dipolar cycloaddition of nitrile oxides to olefin VII, which is formed upon oxidative decarboxylation of lithocholic acid [5].



The structures of the heterocyclic ring cleavage products of isoxazolinyl steroids, namely the α,β-unsaturated ketoximes IV, VI, and IX, were confirmed based on their spectral data (Table 1). Their PMR spectra contained, in addition to the signals for all of the principal molecular structural fragments in the expected regions, two olefinic proton signals for $C_{(22)}$ and $C_{(23)}$ at δ = 6.28-6.32 and 6.83-7.00 ppm, with SSCC ($J_{22,23}$ = 16.8 Hz) corresponding to an E-configuration at the Δ^{22} bond. The stereochemical structure of the product oximes can be deduced from their PMR spectral data (the presence of only one isomer) and the mechanism of cleavage of the isoxazoline ring. Based on these factors, we propose the formation of the syn-isomers of oximes IV, VI, and IX.



Our proposed mechanism for cleavage of heterocycles II, III, and VIII involves initial abstraction of an allylic hydrogen from the 4'-position, followed by isomerization of the resulting carbanion X to an enoximate anion XI, analogous to that de-

TABLE 1. Physical Characteristics of Compounds IV-IX

Compound	T, °C	PMR spectrum, δ, ppm (J, Hz)	IR spectrum, cm^{-1}	Mass spectrum, m/e	Yield %
IVa	217...218	0,82 (3H, s, 18-CH_3); 1,02 (3H, s, 19-CH_3); 1,40 (3H, s, 21-CH_3); 1,98 (3H, s, 25-CH_3); 3,52 (1H, m, $H_{(3)}$); 5,35 (1H, m, $H_{(6)}$); 6,28 (1H, d, J=16,8, $H_{(22)}$); 7,00 (1H, d, J=16,8, $H_{(23)}$)	3420, 1640, 1380	401 $[M]^+$, 383 $[M-H_2O]^+$, 365 $[M-2H_2O]^+$, 273 [M-side ch.]$^+$, 254 [M-side ch $-H_2O]^+$	61
IVb	169...172	0,84 (3H, s, 18-CH_3); 1,02 (3H, s, 19-CH_3); 1,15 (6H, 2d, J=7,2, 26- & 27-CH_3); 1,40 (3H, s, 21-CH_3); 2,81 (1H, sept, $H_{(25)}$); 3,52 (1H, m, $H_{(3)}$); 5,35 (1H, m, $H_{(6)}$); 6,33 (1H, d, J=16,8, $H_{(22)}$); 6,83 (1H, d, J=16,8, $H_{(23)}$)	3420, 1640, 1380	429 $[M]^+$, 412 $[M-H_2O]^+$, 273 [M-side ch]$^+$, 255 [M-side ch.$-H_2O]^+$	73
Va	182...185	0,83 (3H, s, 18-CH_3); 1,02 (3H, s, 19-CH_3); 1,40 (3H, s, 21-CH_3); 2,08 (3H, s, $OCOCH_3$); 2,12 (3H, s, 25-CH_3); 2,20 (3H, s, $OCOCH_3$); 4,59 (1H, m, $H_{(3)}$); 5,37 (1H, m, $H_{(6)}$); 6,43 (1H, d, J=16,8, $H_{(22)}$); 6,92 (1H, d, J=16,8, $H_{(23)}$)	3470, 1750, 1730, 1640, 1365, 1250	485 $[M]^+$, 425 $[M-AcOH]^+$, 365 $[M-2AcOH]^+$	88
Vb	159...160	0,84 (3H, s, 18-CH_3); 1,02 (3H, s, 19-CH_3); 1,24 (6H, 2d, J=7,2, 26- & 27-CH_3); 1,41 (3H, s, 21-CH_3); 2,03 (3H, s, $OCOCH_3$); 2,92 (1H, sept $H_{(25)}$); 4,59 (1H, m, $H_{(3)}$); 5,37 (1H, m, $H_{(6)}$); 6,40 (1H, d, J=16,8, $H_{(22)}$); 6,70 (1H, d, J=16,8, $H_{(23)}$)	3500, 1750, 1720, 1640, 1365, 1250, 1050	513 $[M]^+$, 463 $[M-AcOH]^+$, 413 $[M-2AcOH]^+$, 254 [M-AcOH-side ch.]$^+$	84
VI	196...200	0,88 (3H, s, 18-CH_3); 1,02 (3H, s, 19-CH_3); 1,16 (6H, 2d, 26 and 27-CH_3); 1,40 (3H, s, 21-CH_3); 2,77 (1H, m, $H_{(6)}$); 2,81 (1H, sept $H_{(25)}$); 3,33 (3H, s, OCH_3); 6,32 (1H, t, J=16,8, $H_{(22)}$); 6,83 (1H, d, J=16,8, $H_{(23)}$)	3500, 1640, 1380, 1100	444 $[M]^+$, 426 $[M-H_2O]^+$, 400 $[M-MeOH]^+$, 255 [M-MeOH-side ch,]$^+$	71
VIII	120...122	0,68 (3H, s, 18-CH_3); 0,85 (3H, d, J=7,2, 21-CH_3); 0,93 (3H, s, 19-CH_3); 1,16 & 2,70 (7H, 2d & sept, J=7,2, *iso*-C_3H_7); 2,03 (3H, s, $OCOCH_3$); 2,69 (2H, m, $H_{(3')}$); 4,62 (1H, d, $H_{(22)}$); 4,72 (1H, m, $H_{(3)}$)	1740, 1380, 1250, 1040	457 $[M]^+$, 397 $[M-AcOH]^+$	63
IX	166...169	0,68 (3H, s, 18-CH_3); 0,93 (3H, s, 19-CH_3); 1,09 (3H, d, J=7,2, 21-CH_3); 1,15 (6H, d, J=7,2, 26 and 27-CH_3); 2,83 (1H, sept, $H_{(25)}$); 3,63 (1H, m, $H_{(3)}$); 6,04 (1H, d.d., J=9,8, $H_{(22)}$); 6,62 (1H, d, J=16,8, $H_{(23)}$)	3400, 1640, 1380	416 $[M]^+$, 400 $[M-CH_3]^+$, 380 $[M-2H_2O]^+$, 273 [M-side ch]$^+$, 255 [M-side ch. $-H_2O]^+$	70

scribed in the literature [6]. Protonation of compound XI results in the formation of the corresponding α,β-unsaturated ketoximes IV, VI, and IX.

The mass spectra of enoximes IV, VI, and IX contain their respective molecular ion peaks. Subsequent fragmentation appears to be the result of elimination of a water molecule, followed by cleavage of the steroidal side chain. A few of the enoximes were characterized further in the form of their acetates Va, b. The latter have characteristic IR spectra (in particular, an additional band for the acetate group at 1740-1750 cm^{-1}), PMR spectra (the acetyl methyl group protons give rise to a signal at 2.20 ppm), and mass spectra (in addition to the presence of their molecular ion peaks, ion peaks corresponding to $[M-AcOH]^+$ and $[M-2AcOH]^+$ are also observed).

Ketoximes IV, VI, and IX can be converted to α,β-unsaturated ketones and other functionalized compounds using known methods [7].

The sequence of transformations discussed herein represents a new pathway for the formation of a polyfunctional steroidal side chain, which may be useful in the synthesis of different groups of naturally occurring polyhydroxysteroids, such as ecdy- and brassinosteroids and their biologically active analogs.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer, PMR spectra on a WM-360 (360 MHz) spectrometer versus TMS as internal standard. Mass spectra were measured on a Varian MAT-311 spectrometer at an ionizing electron energy of 70 eV. Chromatography was carried out on silica gel 5/40 μ (ChSSR). The purity of compounds was determined by TLC on Silufol UV-254 plates in the system hexane–ether, 1:3, which were visualized with sulfuric acid. Melting-point temperatures were measured on a Coffler block.

The results of C, H, and N elemental analysis for compounds IVa, b, Va, b, VI, VIII, and IX agreed with calculations.

E-(20S)-24-Hydroximino-26,27-dinorcholest-5,22-dien-3β,20-diol (IVa, $C_{25}H_{39}NO_3$). A solution of isoxazoline IIa (0.443 g, 1 mmole) [3] in 35 ml dry DMSO was added under argon over a period of 0.5 h to a solution of dimsyl sodium [prepared under an argon atmosphere by mixing sodium hydride (30 mmoles) and 40 ml dry DMSO, and heating the resulting mixture at 50-60°C until no more gas bubble evolution was observed], at 20°C. The mixture was stirred for 12 h at 20°C and for 1-2 h at 50-60°C, then poured onto ice water (150 ml), and acidified to pH 7 by the addition of 2% hydrochloric acid; the mixture was extracted with ethyl acetate (3 × 50 ml), washed with water (3 × 20 ml), and dried over sodium sulfate. The solvent was evaporated under vacuum and the resulting product was purified by column chromatography (20 × 1 cm) on silica gel. The eluent was 5:2 hexane–ether. The fractions were detected by TLC and the corresponding eluents were evaporated. The product was then crystallized from ethyl acetate–hexane. Yield of enoxime IVa 0.245 g (61%).

E-(20S)-24-Hydroximinocholest-5,22-dien-3β,20-diol (IVb, $C_{27}H_{43}NO_3$). Prepared in an analogous manner from 0.471 g (1 mmole) isoxazoline IIb [3], in 0.313 g (73%) yield.

E-(20S)-24-Hydroximino-6β-methoxy-3α,5-cyclo-5α-cholest-5,22-dien-20-ol (VI, $C_{28}H_{45}NO_3$). Prepared analogously from 0.443 g (1 mmole) isoxazoline III [3], in 0.315 g (71%) yield.

E-24-Hydroximino-5β-cholest-22-en-3α-ol (IX, $C_{27}H_{45}NO_2$). Prepared in an analogous manner from 0.457 g (1 mmole) isoxazoline VIII, in 0.291 g (70%) yield.

(22ξ)-3α-Acetoxy-20-(3'-isopropylisoxazolin-5'-yl)-5β-pregnane (VIII, $C_{29}H_{47}NO_3$). To a suspension of 0.900 g (6.8 mmoles) N-chlorosuccinimide in 20 ml dry chloroform was added 0.01 ml pyridine and 0.560 g (6.8 mmoles) isobutyral oxime. After 5 min a homogeneous solution formed and 0.503 g (1.4 mmoles) olefin VII was added [5]. This was followed by the addition over a 3-h period of 1 ml (6.8 mmoles) triethylamine in 10 ml chloroform. The resulting mixture was stirred for 20 h. The chloroform was evaporated under vacuum and the resulting material was poured onto 30 ml water and extracted with ether (3 × 75 ml). The combined ether extracts were washed with water (2 × 50 ml) and dried over sodium sulfate. The solvent was removed under vacuum and the resulting oily product was purified by column chromatography (20 × 1 cm) on silica gel (with 10:1 hexane–ether eluent). After evaporation of the eluent the residue was crystallized from a mixture of hexane and ether, to give 0.403 g (63%) of enoxime VIII.

E-(20S)-3β-Acetoxy-25-acetoxyimino-26,27-dinorcholest-5,22-dien-20-ol (Va, $C_{29}H_{43}NO_5$). To a solution of 0.200 g (0.5 mmole) enoxime IVa in 2 ml pyridine was added 1 ml acetic anhydride. The reaction mixture was allowed to stand for 24 h at 20°C, then poured into 20 ml ice water. The resulting precipitate was removed by filtration and washed with 30 ml of a 2% solution of hydrochloric acid and 20 ml water (to pH 7). The solid product was dried in air and crystallized from a mixture of ethyl acetate and hexane to give 0.214 g (88%) of enoxime acetate Va.

E-(20S)-3β-Acetoxy-24-acetoxyiminocholest-5,22-dien-20-ol (Vb, $C_{31}H_{47}NO_5$). Prepared in an analogous manner from 0.215 g (0.5 mmole) enoxime IVb in a yield of 0.216 g (84%).

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SYNTHESIS OF (–)-(4R,5R)- AND (+)-(4S,5S)-1-ALKYL-4-(4'-NITROPHENYL)-1-AZONIUM-3,7-DIOXABICYCLO[3.3.0]OCTANE HALIDES

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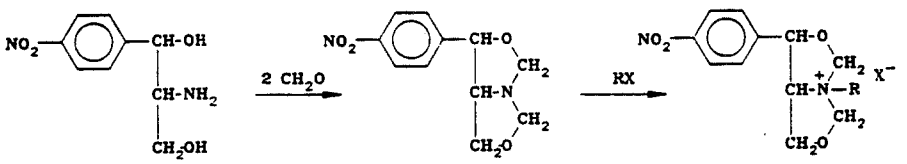
UDC 547.787.3'435.22.07

A preparative method has been proposed for the synthesis of bicyclic quaternary ammonium salts via sequential treatment of (–)-(1R,2R)- and (+)-(1S,2S)-1-(4'-nitrophenyl)-2-amino-1,3-propanediol with paraform followed by an alkyl halide.

Quaternary ammonium salts can be used as phase transfer catalysts [1-3], orientation directing agents as additive for liquid crystals [4], as well as growth-regulating substances [5], general antiseptics [6, 7], and as agents with curarelike activity [6, 8].

We have now prepared two series of salts (Table 1) from (–)-(1R,2R)- and (+)-(1S,2S)-1-(4'-nitrophenyl)-2-amino-1,3-propanediol [(–)-I and (+)-I, respectively] using a two-step reaction sequence:



(+)-I or (–)-I (+)-II or (–)-II (+)-III or (–)-III

a RX=CH_3I, b RX=C_2H_5Br, c RX=$C_6H_5CH_2Cl$, d RX=$C_6H_5CH_2Br$, e RX=CH_2=CH—CH_2Cl, f RX=CH_2=CH—CH_2Br

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