with chloroform, and the extract was washed with a saturated solution of salt and filtered through a layer of aluminum oxide. Removal of the solvents and chromatography on plates with silica gel 5/40 in ether–hexane (3:1) gave 0.025 g (18%) of hydroxy compound XIa and 0.068 g (45%) of methoxy derivative XIe. IR spectrum (film): 1617, 1675, 1735 cm^{-1}. ^1H NMR spectrum: 6.92 (t, 1H, 3-H, J = 2.4 Hz), 4.67 (1H, d t, 1-H, J = 6.8 Hz, 2.4 Hz), 4.12 (2H, q) and 1.25 (3H, t, COOEt), 3.35 (3H, s, OMe), 1.66 (4H, m, 4-H and 5-H), 2.31 (2H, t, $CH_2C{=}O$).

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REDUCTIVE CLEAVAGE OF 4,5-CYCLOALKANOISOXAZOLINES*

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UDC 547.786.3:542.942.9:543.422.25

Different variants of the reductive cleavage of 4,5-cycloalkanoisoxazolines under the influence of Raney nickel in the presence of acids were studied. The compositions, structures, and properties of the reaction products are discussed.

The ease of formation of 2-isoxazolines as a result of 1,3-dipolar addition of nitrile oxides to substituted alkenes, the possibility of the selective modification of the heteroring, and the large number of transformations, particularly those with reductive character, associated with ring opening to give various structures (amino alcohols, hydroxy nitriles, enoximes, enones) make 2-isoxazolines convenient and flexible agents of organic synthesis for the construction of the carbon skeleton of the desired compound with the necessary difunctional fragment [2-4]. The general reaction of the reductive cleavage of 2-isoxazolines to β-hydroxy ketones or the products of their dehydration – α,β-unsaturated ketones – by the action of Raney nickel in an acidic medium, which was observed and described by us for the

*See [1] for our preliminary communication.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 972-976, July, 1988. Original article submitted January 20, 1987.

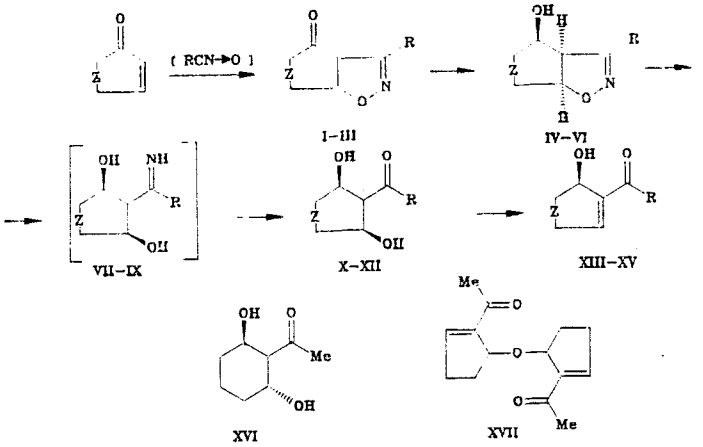
0009-3122/88/2407-0800$12.50

TABLE 1. Physicochemical Properties of the Synthesized Compounds

Compound	mp, °C	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)*	Yield, %
Ia	36—38	1630, 1750	3,75 d (8), 5,4 m	70
Ib	—	1615, 1750	3,70 d (9), 5,4 m	69
Ic	23—25	1620, 1745	3,74 d (9), 5,47 m	72
Id	31—32	1615, 1745	3,67 d (9), 5,37 m	49
Ie	93—95	1590, 1750	4,07 d (8,4), 5,5 d d (8,4; 4,0)	60
If	Oil	1620, 1750	3,50 d (8,5), 5,30 d d (8,5; 4,2)	69
IIa	18—21	1620, 1720	3,54 d (10), 4,76 m	70
IIIa	51—53	1620, 1720	3,62 d (11), 4,94 m	72
IIIb	—	1620, 1720	3,57 d (10,5), 4,87 m	45
IIIe	123—124	1550, 1705	4,08 d (9), 4,99 m	68
IVa	43—44	1630, 3400	4,42 m, 3,52 t (8,4), 4,95 m	98
IVb	—	1620, 3400	4,26 m, 3,45 t (8), 4,76 m	90
IVc	42—45	1620, 3480	4,44 m, 3,56 t (8,6), 4,95 dq	81
IVd	38—39	1615, 3400	4,42 m, 3,57 t (8,4), 4,95 dq	97
IVf	98—99	1605, 3400	4,26m, 3,34 t (9,2), 4,8 dd (9,2; 4,3)	91
Va	67—69	1630, 3370	4,08 m, 3,12m, 4,50 m	77
Ve	121—123	1560, 3390	3,50 m, 3,08 t (8), 4,47 m	70
VIa	98—99	1610, 3390	4,20 m, 3,36m, 4,70 m	85
Xa	34—36	1705, 3500	4,50m, 2H, 2,70 t (4)	33
Xd	—	1690, 3400	4,60m, 2H, 2,62 m	74
Xe	—	—	4,68 m, 2H, 3,36 t (3,6)	—
XIa	38—39	1705, 3510	4,44 m, 2H, 2,39 t (2)	65
XIIa	119—121	1700, 3420	4,40m, 2H, 2,72 t (3,5)	60
XIIIa	Oil	1670, 3450	4,9 m, 6,70 t (2,5)	39
XIIIb	Oil	1665, 3460	5,10m, 6,73 m	27
XIIIc	Oil	1660, 3460	5,12 t, d 6,4, 6,84 t (2,6)	42
XIIId	Oil	1660, 3455	5,12 m, 6,86 m	41
XIIIf	Oil	1665, 3420	—	47
XIVa	Oil	1670, 3450	4,34 m, 6,74 t (4)	49
XVa	—	1670, 3450	4,64 m, 7,02 t (4)	48

*With the exception of X-XII, the δ values of the one-proton multiplets are presented.

first time in 1979 [1], has recently found extensive synthetic application with various methodical modifications [5-7]. In the present paper we correlate the results of a study of different variants of the indicated reductive cleavage of 4,5-cycloalkanoisoxazolines.



I, IV, VII, X, XIII Z=—; II, V, VIII, XI, XIV Z=CH_2; III, VI, IX, XII, XV Z=CMe_2;
I—XV a R=Me; b R=C_5H_{11}; c R=C_6H_{13}; d R=C_7H_{15}; e R=C_6H_5; f R=$CH_2C_6H_5$

Cycloalkanoisoxazolines I-III (Table 1) were obtained in good yields in the reaction of cycloalk-2-en-1-ones with nitrile oxides generated from hydroxamic acid chlorides or primary nitro compounds. It has been previously shown [8] that cyclohexanoisoxazolines II and III are readily dehydrogenated to the corresponding isoxazoles, sometimes even spontaneously during chromatography on silica gel. In contrast to the cyclohexane analogs, oxocyclopentanoisoxazolines I and hydroxycyclopentanoisoxazolines IV displayed stability both in reductive

reactions and with respect to oxidation to the corresponding isoxazoles over a wide range of methods that are usually employed [1, 9]; this is evidently associated with the steric restrictions of the strained carbocyclic part of the molecule. The realization of the latent bifunctional character of the cyclohexano- and cyclopentanoisoxazolines is thus complicated by opposing factors: by the exceptional lability of the heteroring in the first case and its relative stability in the second case. Numerous experiments have shown that this problem is solved most successfully by the reductive cleavage of hydroxycycloalkanoisoxazolines IV-VI under the influence of Raney nickel in the presence of strong acids.

The hydroxycycloalkanoisoxazolines were obtained in high yields by reduction of the carbonyl function in I-III with sodium borohydride in alcohol (Table 1). One should note the extremely high stereoselectivity of this process, in the course of which the isomer with a cis orientation of the hydroxy function and the heteroring is formed. The other isomer could not be detected from characteristic signals in the PMR spectra recorded after primary workup of the reaction mixture.* The reductive cleavage of cycloalkanoisoxazolines IV-VI was realized by hydrogenolysis of them in aqueous solutions of strong acids (trifluoroacetic, hydrochloric, sulfuric, perchloric) under the influence of Raney nickel. Since under these conditions nickel reacts with the acid with the evolution of hydrogen, the reaction can be carried out without special feeding in of gaseous hydrogen. The successful use of Raney nickel in the presence of a strong acid as the reagent for the reductive cleavage of 2-isoxazolines is evidently ensured by the combination of the action of both reagents, since the indicated process does not occur either when other metals (zinc, iron) are used under similar conditions or in the presence of weak acids such as acetic acid [1]. The described process for the cleavage of 2-isoxazolines under the influence of an acid and Raney nickel can probably be regarded as a variant of catalytic ionic hydrogenation in which the hydride-ion donor is the gaseous hydrogen liberated from the acid and activated by the metal catalyst. We assume that the reduction of the cycloalkanoisoxazolines occurs with opening of the heteroring at the N–O bond through the intermediate formation of the imino diols VII-IX, which under the reaction conditions are hydrolyzed to keto diols X-XII. The dehydration of the keto diols under the influence of the acid under the reaction conditions leads to conjugated hydroxy enones XIII-XV. Intermediate imino diols VII-IX could not be isolated in any of the experiments. On the other hand, either keto diols X-XII together with hydroxy enones XIII-XV or exclusively hydroxy enones were isolated from the reaction mixtures depending on the conditions used to carry out the reductive cleavage.

Thus treatment of an aqueous solution of isoxazoline Va with Raney nickel and concentrated HCl at room temperature gave 2-acetylcyclohexenol (XIVa) (49% yield), which was identical to the compound previously obtained by an independent method [10]. Carrying out the reaction with cooling (0°C) and for a shorter time made it possible to isolate, in addition to hydroxy enone XIVa, diol XIa, which precedes it. A mixture of XIVa and XIa in an overall yield of 63% was also obtained as a result of the reaction at room temperature in aqueous methanol solution (1:5). The dehydration of the keto diols in situ to hydroxy enones is promoted by an increase in the reaction temperature and time. The best yields of hydroxy enones XIII-XV were obtained when 70% CF_3COOH or concentrated HCl was used; however, the use of the latter was limited by the low solubility in water of some of the starting hydroxyisoxazolines.

The cis-diol structure of X-XII follows from an analysis of their PMR spectra and serves as an additional confirmation of the established cis orientation of the hydroxy group and the heteroring in hydroxyisoxazolines IV-VI. The cis configuration of the hydroxy groups follows from the equivalence of the 1-H and 3-H carbinol protons† as a consequence of their identical coupling with the methylidyne 2-H proton and the ring methylene protons. For example, in the PMR spectrum (100 MHz) of XIIa eight lines correspond to two pairs of methylene protons, each of which constitutes the AB part of an ABX system; this constitutes evidence for equivalence of the pairs of 4-H and 6-H and 1-H and 3-H protons (equality of the δ values and SSCC) as a consequence of the symmetrical (cis) orientation of the substituents in the six-membered ring. In addition, the signal of the methylidyne 2-H proton has the form of a true triplet; this also confirms what we stated above. The orientation and character of the other resonance signals constitute evidence in favor of the high symmetry of the system.

Data from the PMR spectra of keto diols X-XII also make it possible to draw a conclusion regarding the most preferred conformation of these compounds. Thus the 1-H and 3-H signal

*A detailed review of the PMR spectra of similar compounds will be given in a subsequent publication.

†Numbering with respect to the cycloalkane.

of acetylcyclohexanediol XIa has the form of a broad singlet (4.44 ppm) with half width $W_{1/2}$ = 7 Hz, which indicates an equatorial orientation of the carbinol protons – correspondingly, the two hydroxy groups are axially oriented, while the cis-acyl group is equatorially oriented. Similar observations were made in the cyclopentane series. Thus for acetylcyclopentanediol Xa the half width of the signal of the 1-H and 3-H protons (4.48 ppm) $W_{1/2}$ was 8 Hz, while the half width of the signal of the two methylene groups at 1.86 ppm was 4 Hz; this constitutes evidence for a quasi-equatorial orientation in the half-chair conformation of the five-membered ring of the carbinol protons and a quasi-axial conformation of the hydroxy groups. This conformation with 1,3-diaxially oriented hydroxy groups is evidently stabilized by an intramolecular hydrogen bond between them.

It should be noted that keto diols (for example, Xa; c and XIa) were obtained in high yields (65-75%) by a modified method [6] – by hydrogenation of the corresponding hydroxyisoxazolines on Raney nickel in the presence of boric acid. The formation of hydroxy enones was not observed in this case. It is noteworthy that when we used this method for cleavage of cyclohexanoisoxazoline Va, from the reaction mixture, in addition to the principal product cis-keto diol XIa (65%), we were able to isolate a small amount (2%) of its trans isomer XVI, in the PMR spectrum of which the 2-H proton shows up in the form of a doublet of doublets (2.52 ppm, J equal to 12 and 2 Hz), while the carbinol protons become nonequivalent and show up in the form of two individual signals at 4.56 and 4.36 ppm. The formation of trans isomer XVI is evidently associated with epimerization in the step involving intermediate imino diol VIIIa in this variant of reductive cleavage [5].

Keto diols X-XII and the products of their dehydration – hydroxy enones XIII-XV – proved to be rather stable and do not undergo changes during storage for a long time at 0...+5°C. In addition to this, the keto diols can be converted to the corresponding hydroxy enones by dehydration of one of the hydroxy groups. However, it should be noted that the utilization of the usual methods of dehydration for these compounds was ineffective and was complicated by side reactions. Thus when we heated keto diol Xa in benzene with p-TsOH, in addition to hydroxy enone XIIIa we obtained diallyl ether XVII, the structure of which was established from the combination of the results of elementary and physicochemical analysis. The formation of these compounds can be conceived of as being the result of a side process involving the acidic dehydration of hydroxy enone XIIIa. Ether XVII is the principal reaction product in the case of more prolonged workup. The direct – in one step from hydroxyisoxazolines – preparation of hydroxy enones under the conditions proposed by us, in contrast to two-step catalytic hydrogenation–dehydration, therefore takes on special significance.

The importance of the observed reaction for obtaining the previously unknown acylcyclopentenols XIII or the preceding keto diols (X) with an aliphatic C_7-C_8-acyl chain, as well as aroyl and arylacyl chains, must be noted. Compounds of this sort are of considerable interest as precursors of steroids and prostaglandins, since they are ready-made synthone-blocks that contain a preformed side chain [11] (see our next publication).

EXPERIMENTAL

The IR spectra of KBr pellets (for the solid compounds) or films or solutions in CCl_4 (for the liquid or oily compounds) were recorded with a UR-20 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with Bruker WM-360 and Jeol PS-100 spectrometers with tetramethylsilane (TMS) as the internal standard. The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 standard plates.

The hydroxycycloalkanoisoxazolines were obtained from the corresponding cycloalk-2-en-1-ones by 1,3-dipolar cycloaddition to them of nitrile oxides and subsequent reduction of the adducts with sodium borohydride by the methods in [9, 12].

Reductive Cleavage of Hydroxyisoxazolines IV-VI by the Action of Raney Nickel in Solutions of Acids. A) A 5-g sample of Raney nickel was added to a solution of 32 mmole of the isoxazoline in 50 ml of methanol–water (5:1), after which 15 ml of concentrated HCl was added dropwise, and the mixture was stirred for 1 h. The precipitate was removed by filtration, the methanol was evaporated, and the residue was extracted with chloroform. Products X-XV were obtained after removal of the solvent and chromatographic separation of the residue on silica gel 40/100 with gradient elution with hexane–ether.

B) A 0.5-g sample of Raney nickel was added with stirring to a solution of 0.5 mmole of the hydroxyisoxazoline in 5 ml of 75% trifluoroacetic acid, after which the mixture was stirred for 3 h, neutralized to pH 5 with a saturated aqueous solution of sodium bicarbonate, and

extracted with chloroform. The combined extracts were washed with water and dried with $MgSO_4$. The residue obtained after removal of the solvent was chromatographed with a column packed with silica gel 40/100 with gradient elution with hexane–ether.

C) A 0.3-g sample of Raney nickel was saturated with hydrogen in 50 ml of methanol–water (5:1) for 20 min at atmospheric pressure, after which 0.016 mole of hydroxyisoxazoline IV-VI and 1.8 g of boric acid were added, and the mixture was hydrogenated for 3 h. At the end of the hydrogenation the reaction mixture was filtered through a layer of aluminum oxide, and the sorbent was washed with methanol. The combined filtrates were evaporated, the residue was extracted with chloroform, the solvent was evaporated, and the residue was chromatographed on silica gel 100/160.

The yields and physicochemical characteristics of starting isoxazolines I-VI and the products (X-XV) of their reductive cleavage are presented in Table 1.

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