SYNTHESIS AND SOME PROPERTIES OF SUBSTITUTED, 4,5-CYCLOPENTANO-Δ^2-ISOXAZOLINES

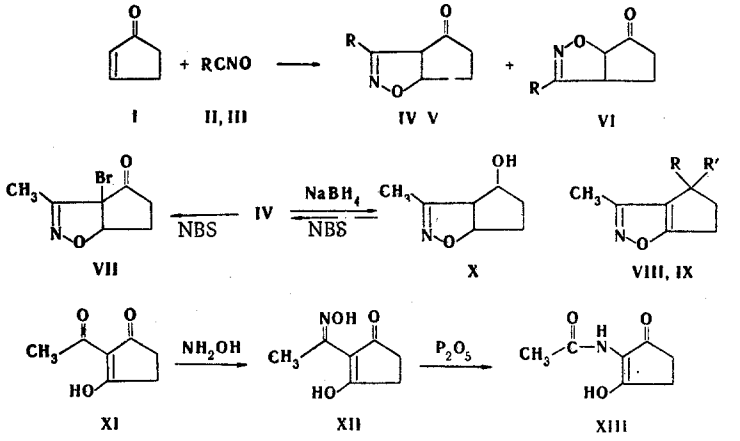
A. A. Akhrem, F. A. Lakhvich,
V. A. Khripach, I. B. Klebanovich,
and A. G. Pozdeev

UDC 547.786.31.07

The 1,3-dipolar cycloaddition of acetonitrile oxide and ethyl cyanoformate oxide to cyclopentenone and the structure and some of the properties of the resulting Δ^2-isoxazolines were studied.

The possibility of the utilization of adducts of nitrile oxides and cyclic enones — cyclohexano-Δ^2-isoxazolines — in the synthesis of 2-acyl derivatives of cyclohexane-1,3-diones seems of interest for the preparation of β-triketones of the cyclopentane series. We investigated the reaction of acetonitrile oxide (II) and ethyl cyanoformate oxide (III) with cyclopentene (I).

Nitrile oxide II reacts with enone I in situ to give isoxazoline IV in 70% yield, which, according to the PMR spectrum of the reaction mixture, is the chief (no less than 95%) cycloaddition adduct.



II, IV R = CH_3; III, V, VI R = $COOC_2H_5$; VIII R, R′ = O, IX R = OH, R′ = H

A mixture of structural isomers V and VI in a ratio of 2:3, respectively (according to the PMR spectrum of the mixture with respect to different signals of the methylidyne protons of the isomers) was obtained in 32% yield in the reaction of nitrile oxide III with cyclopentene. The decrease in the yield of the adduct and the appearance in the mixture of a product of "reverse" addition (VI) can be explained by the different (as compared with acetonitrile oxide) distribution of the electron density in the III molecule, which has an effective electron-acceptor substituent; this assumes a considerable contribution of the $R-\overset{(-)}{C}=\overset{(+)}{N}-O$ mesomeric state to the reacting particle.

Institute of Bioorganic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 625-628, May, 1976. Original article submitted March 18, 1975; revision submitted October 10, 1975.

Adduct IV and its dehydrogenation to the corresponding isoxazole seem of practical interest in connection with the object of this research. The use of o- and p-chloranil, S, Pd, Pd/S, and CrO_3 for this purpose did not lead to a hydrogenation product. Bromo derivative VII was obtained in good yield as a result of the reaction of IV with N-bromosuccinimide (NBS). The structure of the bromo derivative follows from a comparison of its PMR spectrum with the spectrum of starting isoxazoline IV. In fact, the characteristic doublet of the methylidyne proton attached to C-4 vanishes in the spectrum of the bromination product, and the signal of the proton attached to C-5 is converted to a triplet, which one should expect in the case of 4-bromoisoxazoline VII. The latter does not undergo any change on refluxing in pyridine or on treatment with triethylamine.

On the other hand, we made an attempt to obtain cyclopentanoisoxazole VIII from triketone XI by the method in [2]. In this case we obtained oxime XII. It should be noted that oximes of cyclohexane β-triketones undergo spontaneous cyclodehydration [2]. Oxime XII is not cyclized to an isoxazole under the influence of dehydrating reagents. When XII is refluxed with P_2O_5 in chloroform, it undergoes Beckmann rearrangement to give amide XIII. In addition to the signals of the protons of all of the structural elements of the molecule, a singlet of a methyl group is observed in the PMR spectrum of this compound, and this constitutes evidence in favor of structure XIII rather than an alternative N-methylamide structure. The mass spectrum of rearrangement product XIII contains, in addition to a molecular ion peak (m/e 155, relative intensity 94.8%), a peak with an intensity of 100% at m/e 113, which corresponds to the elimination of ketone. This sort of fragmentation of the molecular ion to form a rearranged ion is characteristic for secondary amides [3] and corresponds to the structure of the side chain of XIII. The peak with m/e 43 (99.7%), which corresponds to the $CH_3-C\equiv O^+$ ion, is also characteristic from this point of view. The $(M-43)^+$ fragment, which arises as a result of the loss of an acetyl radical by the molecular ion, is of lower intensity (43.5%). These types of fragmentation are the principal pathways for the molecular ion of XIII; they cannot be characteristic for the β-triketone structure of the alternative product of Beckmann rearrangement. This conclusion is confirmed by a comparison of the mass spectral characteristics of XIII and the related compounds discussed in this paper.

The difficulty involved in the preparation of cyclopentanoisoxazole VIII can evidently be explained by the high steric strain of the two-ring system, the cyclopentane ring of which contains three trigonal centers. This view, in conjunction with the data in [4,5], made it possible to count upon preparation of cyclopentanoisoxazole from hydroxy compound X or its bromo derivative. An attempt to obtain the latter by reduction of VII with sodium borohydride gave a complex mixture of products in addition to a product of hydrogenolysis of the C—Br bond. Hydroxyisoxazoline X was obtained by reduction of IV with $NaBH_4$ in alcohol solution and, in conformity with the data in [6], probably has an OH group with a cis configuration.

Oxidation of X with NBS under the allylic bromination conditions described for other isoxazolines (for example, see [7,8]) gave oxoisoxazoline IV instead of the expected isoxazole IX. Considering the above-described reaction of IV with NBS and the data on the Δ^2-isoxazolines [4], a somewhat unusual mechanism of oxidation of the secondary hydroxyl group can be assumed in this case. As a rule, the side processes take place via an ionic mechanism in which the positive bromine ion attacks either the hydroxyl group itself or the carbon atom to which it is bonded [9]. In our case, in the first step the radical mechanism via the allylic substitution scheme leads to an intermediate bromine derivative of the VII type; when it is treated with base, steric factors evidently are responsible for the more facile elimination of HBr, leading to the enol, which is a tautomer of IV. This sort of mechanism may occur in those cases in which the α-carbon atom of the secondary alcohol is simultaneously an allylic carbon atom and the conditions under which the reaction is carried out correspond to allylic substitution.

EXPERIMENTAL

The melting points were measured with a Kofler block. The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra were recorded with the spectrometer of the JNM-PFT-100 system with tetramethylsilane as the internal standard. The mass-spectrometric data were obtained with a Varian MAT-311 spectrometer at an ionizing-electron energy of 70 eV.

Woelm, LSL-254, and $H_2SiO_3 \cdot nH_2O$ silica gels, Brockmann Al_2O_3, and Silufol UV-254 plates were used for thin-layer chromatography (TLC) and column chromatography. The chromatograms were developed in iodine vapors and in UV light.

8-Methyl-2-oxo-6-oxa-7-azabicyclo[3.3.0]-7-octene (IV). A solution of 3 g of acetylhydroxamic acid chloride in 200 ml of ether and a solution of 5 g of Et_3N in 200 ml of other were added simultaneously at room temperature from two dropping funnels to a vigorously stirred solution of 4.1 g of cyclopentenone in 50 ml of anhydrous ether. The next day, the precipitated $Et_3N \cdot HCl$ was removed by filtration, and the solvent and excess reagents were removed by vacuum distillation. The oily residue was chromatographed with a column filled with Al_2O_3 with gradient elution with a hexane—ether system to give 3 g (70%) of IV with mp 36-38° (from ether). IR spectrum (KBr): 1630, 1750, 2870, and 2970 cm^{-1}. PMR spectrum (CCl_4): 1.90 (CH_3, s, 3H), 2.22 (CH_2, m, 4H), 3.48 (1-H, d, J = 9 Hz, 1H), and 5.15 ppm (5-H, m, 1H). Found: C 60.6; H 6.6; N 10.1%; M 139 (mass spectrometrically). $C_7H_9NO_2$. Calculated: C 60.4; H 6.5; N 10.1%; M 139.16.

8-Carbethoxy-2-oxo-6-oxa-7-azabicyclo[3.3.0]-7-octene (V) and 6-Carbethoxy-2-oxo-8-oxa-7-azabicyclo[3.3.0]-6-octene (VI). A procedure similar to that described above was used to obtain 141 mg of VI from 0.9 g of ethyl chloroiminoacetate, 12 g of cyclopentenone, and 0.9 ml of Et_3N after chromatography of the reaction mixture with a column filled with silicic acid (150 mesh). PMR spectrum (CCl_4): 1.40 (CH_3, t, J = 7 Hz, 3H), 2.28 (CH_2, m, 4H), 4.32 (CH_2, q, J = 7 Hz, 2H), 4.23 (5-H, m, 1H), and 4.76 ppm (1-H, d, J = 11 Hz, 1H). Subsequent elution gave 236 mg of a mixture of V and VI (9:5, respectively). The overall yield of the mixture of isomers was 32%, and the yield of VI was 19%. PMR spectrum of V (in CCl_4): 1.35 (CH_3, t, J = 7 Hz, 3H), 2.36 (CH_2, m, 4H), 3.92 (1-H, d, J = 9 Hz, 1H), 4.24 (CH_2, q, J = 7 Hz, 2H), and 5.52 ppm (5-H, m, 1H).

8-Methyl-1-bromo-2-oxo-6-oxa-7-azabicyclo[3.3.0]-7-octene (VII). A mixture of 4.17 mg of IV, 534 mg of NBS, 5 mg of benzoyl peroxide, and 7.5 ml of CCl_4 was refluxed for 30 min. The precipitated succinimide was removed by filtration, and the solvent was vacuum evaporated. Preparative TLC of the residue on silica gel (LSL-254, 5-40μ) yielded 479 mg (73%) of VII. IR spectrum (thin layer): 1750, 2860, and 2950 cm^{-1}. PMR spectrum (CCl_4): 2.08 (CH_3, s, 3H), 2.53 (CH_2, m, 4H), and 5.36 ppm (5-H, t, J = 6 Hz, 1H). Molecular weight 217;219 (mass spectrometrically).

8-Methyl-2-hydroxy-6-oxa-7-azabicyclo[3.3.0]-7-octene (X). A 0.61-g sample of $NaBH_4$ was added with stirring to a solution of 2.22 g of IV in 150 ml of ethanol after which stirring was continued for 3 h. The solution was then concentrated, diluted with water, and extracted with $CHCl_3$. The extract was dried with $MgSO_4$, the solvent was removed, and the residue was recrystallized from ether to give 1.63 g (72%) of X with mp 41.5-43.5°. IR spectrum (KBr): 1630, 2870, 2980, and 3320 cm^{-1}. PMR spectrum (CCl_4): 1.85 (CH_2, m, 4H), 2.04 (CH_3, s, 3H), 2.82 (OH, broad s, 1H), 3.48 (1-H, m, 1H), 4.40 (2-H, m, 1H), and 4.89 ppm (5-H, m, 1H). Found: C 59.6; H 7.9; N 9.9%; M 141 (mass spectrometrically). $C_7H_{11}NO_2$. Calculated: C 59.7; H 7.9; N 9.9%; M 141.17.

Reaction of X with NBS. A mixture of 7.5 ml of CCl_4, 314 mg of X, 395 mg of NBS, and 5 mg of benzoyl peroxide was refluxed for 30 min, after which the solvent was removed, the residue was treated with Et_3N (2 ml), and the mixture was allowed to stand overnight. Water (50 ml) was added to the mixture, after which it was extracted with ether. The extract was dried with $MgSO_4$, the solvent was removed, and the residue was chromatographed with a column filled with Al_2O_3 with gradient elution with a hexane—ether system to give 60 mg (19%) of isoxazoline IV.

2-(α-Hydroxyimino)ethylcyclopentane-1,3-dione (XII). A mixture of 400 mg of triketone XI, 201 mg of $NH_2OH \cdot HCl$, and 115 mg of NaOH in 5 ml of 50% ethanol was allowed to stand for 4 days, after which the resulting precipitate was removed by filtration to give 400 mg (90%) of XII with mp 177.5-179° (from ethyl acetate). IR spectrum (KBr): 1520, 1535, 1600, 1650, and 3420 cm^{-1}. PMR spectrum (CF_3COOH): 2.79 (CH_3, s, 3H) and 3.02 ppm (CH_2, s, 4H). Found: C 54.3; H 5.8; N 9.1%; M 155 (mass spectrometrically). $C_7H_9NO_3$. Calculated: C 54.2; H 5.8; N 9.0%; M 155.15.

N-(2,5-Dioxocyclopentyl)acetamide (XIII). A solution of 400 mg of XII in 10 ml of $CHCl_3$ was refluxed in the presence of P_2O_5 for 10 h. Workup of the reaction mixture gave

270 mg (68%) of XIII with mp 167.5-169°. IR spectrum (KBr pellet): 1540, 1550, 1600, and 3280 cm^{-1}. PMR spectrum (in $CDCl_3$): 2.24 (CH_3, s, 3H), 2.58 (CH_2, unresolved multiplet, 4H), 8.64 (NH, broad s, 1H), and 13.56 ppm (OH, s, 1H). Found: C 54.4; H 5.9; N 9.2%; M 155 (mass spectrometrically). $C_7H_9NO_3$. Calculated: C 54.; H 5.8; N 9.2%; M 155.15.

LITERATURE CITED

1. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, Dokl. Akad. Nauk SSSR, 216, 1045 (1974).
2. H. Smith, J. Chem. Soc., 803 (1953).
3. H. Budzikiewicz, C. Djerassi, and D. H. Williams Interpretation of Mass Spectra of Organic Compounds, Holden-Day (1964).
4. G. Bianchi, A. Gamba, and R. Gandolfi, J. Chem. Soc., C, 2375 (1971).
5. L. I. Klimova and N. N. Suvorov, Zh. Obshch. Khim., 34, 1357 (1964).
6. G. Bianchi, C. Micheli, and R. Gandolfi, J. Chem. Soc., Perkin I, 1711 (1972).
7. G. S. King, P. D. Magnus, and H. S. Rzepa, J. Chem. Soc., Perkin I, 437 (1972).
8. A. Krishnamurthy, K. S. R. Krishnamohanrao, and N. Subbarao, Indian J. Chem., 10, 38 (1972).
9. R. Filler, Chem. Rev., 63, 21 (1963).

RECYCLIZATION REACTIONS OF HETEROCYLES.

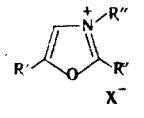
XVII*. HYDRAZINATION OF 1,3,4-OXADIAZOLIUM SALTS

V. I. Fomenko and O. P. Shvaika

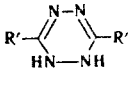
UDC 547.793.4

2,5-Diaryl-3-alkyl-1,3,4-oxadiazolium salts react with hydrazine to give acyclic hydrazinolysis products or products of recyclization with participation of the carbon atom in the 2 position of the oxadiazole ring, i.e., dihydro-sym-tetrazines and N-amino-sym-triazoles (with hydrazine) and 2-phenyl-5-aryl-1,3,4-oxadiazoles (with benzoylhydrazine) or formazans (with phenylhydrazine).

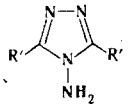
Perfluoroalkyl-, monoaryl-, and amino-1,3,4-oxadiazoles, 1,3,4-oxadiazolones, and oxadiazolethiones react with hydrazines to give acyclic compounds or undergo recyclization to



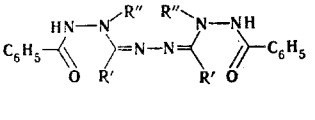
I a-d



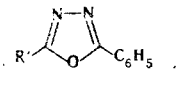
II a-c



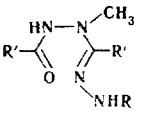
III a-c



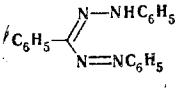
IV a, b



V a, b



VI a, b



VII

I—VI a $R'=C_6H_5$; I—III, V b $R'=p\text{-}CH_3OC_6H_4$; IV b $R'=CH_3$; VI b $R'=C_6H_5$; I—III c $R'=C_{10}H_7$; I d $R'=CH_3$; I, IV a $R''=CH_3$; I b,c $R''=CH_3$; I d IV b $R''=C_6H_5$; VI a R= $=C_6H_5$, b $R=COC_6H_5$; I a-c X=TsO, d $X=ClO_4$

*See [1] for communication XVI.

Institute of Physical Organic Chemistry and Coal Chemistry, Academy of Sciences of the Ukrainian SSR, Donetsk.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 629-634, May, 1976. Original article submitted October 29, 1974; revision submitted May 15, 1975.