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SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES.

35.* REGIOSELECTIVITY AND STEREOSELECTIVITY OF THE [2+3]-CYCLOADDITION OF PHENYL NITRONES TO 1-DECENE

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It was shown by spectroscopic methods that the [2+3]-cycloaddition of C,C,N-triphenyl nitrone to 1-decene is regiospecific and leads to 2,3,3-triphenyl-5-octylisoxazolidine as the only reaction product, whereas Z-C,N-diphenyl nitrone with the same alkene forms a mixture of stereoisomeric 2,3-diphenyl-5-octylisoxazolidines. The regiochemistry of the reaction was explained in terms of PMO theory.

The [2+3]-cycloaddition of nitrones to alkenes has found wide use in organic chemistry [2-4]. From the isoxazolidines synthesized by this reaction it is easily possible to obtain certain representatives of the alkaloids [3], vitamins [5], macrocyclic compounds [6], β-lactams [7], and other types of compounds [2]. At the same time the regio- and stereoselectivity of the reaction has been insufficiently investigated [3, 4]. We studied these aspects of [2+3]-cycloaddition, using C,C,N-triphenyl nitrone (I), Z-C,N-diphenyl nitrone (II), and 1-decene (III) as models.

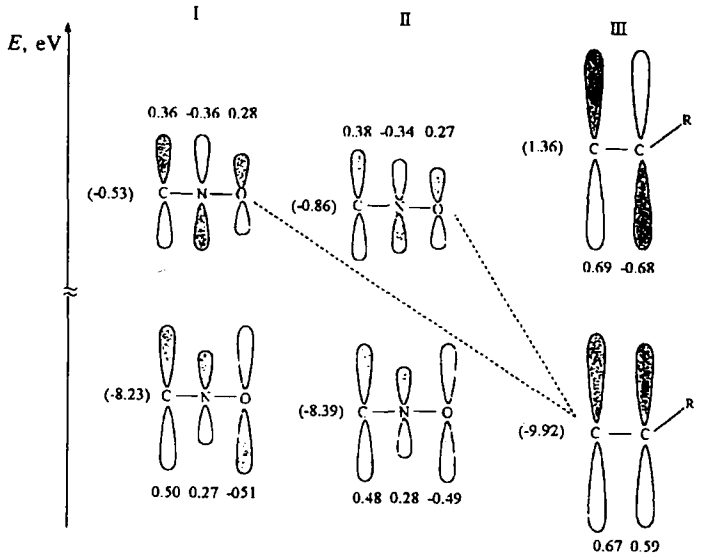

Fig. 1. Correlation diagram for the [2+1]-cycloaddition of the nitrones (I) and (II) to the decene (III) according to data from AM-1 calculations. (The energies of the MOs are given in parentheses.)

*For Communication 34, see [1].

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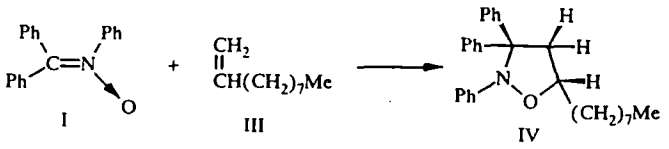
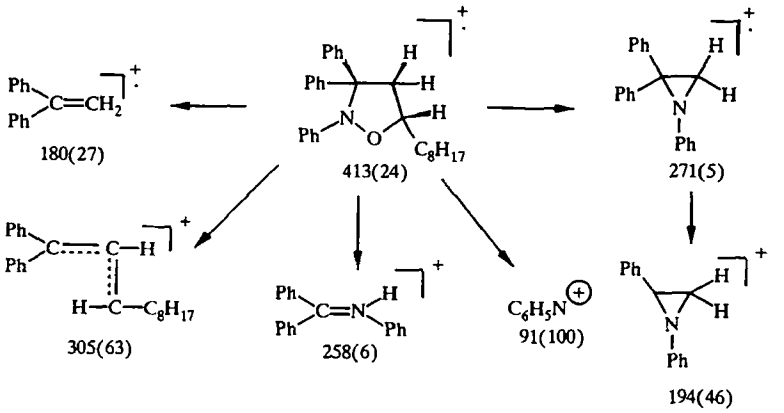
The cycloaddition of these substrates was conducted at 80°C in dry toluene with a tenfold excess of the alkene. The reaction was monitored by the disappearance of the nitrone using TLC. At the end of the reaction the solvent and the excess of the decene were removed under vacuum, and the solid residue was investigated by physicochemical methods.



It was established that the [2+3]-cycloaddition of triphenyl nitrone (I) and decene (III) is regiospecific and leads to 2,3,3-triphenyl-5-octylisoxazolidine (IV) as the only reaction product.

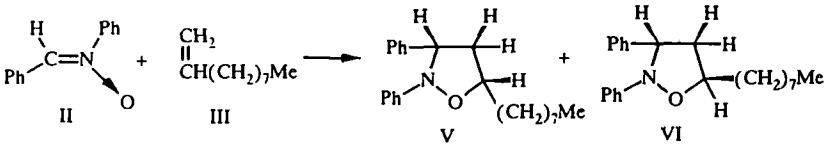
The structure of the cyclic adduct (IV) was confirmed by the data from elemental analysis and IR, mass, and ^{1}H NMR spectroscopy. It was shown that its elemental composition corresponds to the formula $C_{29}H_{35}NO$. The absorption bands discovered in the IR spectrum indicate the presence of monosubstituted benzene rings and also the N–O and C–O bonds of the azoline ring [4]. As expected, the protons of the heterocyclic ring correspond in their resonance characteristics to a spin system of the ABX type, the spectral parameters of which were calculated using the familiar algorithm [8]. The mass spectrum of (IV) is typical of 2,3,5-substituted isoxazolidines [4]. The molecular peak relates to the fragmentation ions. The presence of the two phenyl rings at position 3 and one at position 2 leads to the appearance of a large number of fragment ions, formed as a result of concurrent fragmentation processes in the isoxazolidine ring with rupture (in pairs) of the following bonds: N–O and $C_{(3)}$–$C_{(4)}$, N–O and $C_{(3)}$–N, N–$C_{(3)}$ and $C_{(4)}$–$C_{(5)}$, N–$C_{(3)}$ and O–$C_{(5)}$, N–O and $C_{(4)}$–$C_{(5)}$. The strongest signal corresponds to the C_6H_5N fragment. The main fragmentation paths are shown in Scheme 1.

Scheme 1

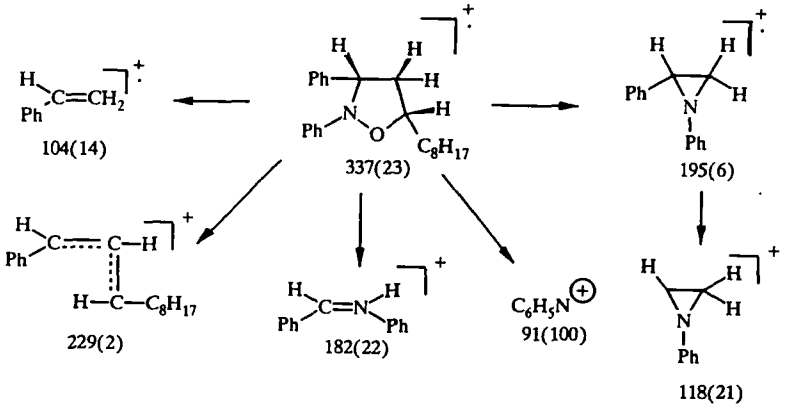


As established by TLC and ^{1}H NMR spectroscopy, [2+3]-cycloaddition of diphenyl nitrone (II) and decene (III) under analogous conditions leads to a mixture of two products in a ratio of approximately 20:1. However, only one of them was isolated in the pure form as a colorless crystalline substance, whereas the other, formed in insignificant amounts, was isolated in the form of a contaminated liquid. The first compound has the empirical formula $C_{23}H_{31}NO$ and is characterized by IR absorption typical of substituted isoxazolidine. Its mass spectrum contains a relatively stable molecular ion (Scheme 2), the fragmentation of which is similar to that described above for 2,3,3-triphenyl-5-octylisoxazolidine. In the ^{1}H NMR spectra, apart from the protons of the phenyl rings and alkyl radical, there are four protons, which form a spin system of the ABXY type. Analysis of the spin–spin coupling constants using the PCMODEL-4 program favors the structure of 2,3-diphenyl-5-octylisoxazolidine (V), in which the phenyl ring at $C_{(3)}$ and the C_8H_{17} radical are in the *cis* position. On the basis of the ^{1}H NMR, mass, and IR spectra and also by analogy with the results of the reaction between the C,N-diphenyl nitrone and ethoxyethylene [9] the product, isolated in small amounts, was assigned the structure of 2,3-diphenyl-5-octylisoxazolidine (VI), in which the phenyl fragment at $C_{(3)}$ and the C_8H_{17} radical are in the *trans* position.

Thus, the reaction of the diphenyl nitrone (II) with the decene (III) is completely regiospecific but not stereospecific.



Scheme 2



The regiochemistry of the investigated reactions can be explained easily in terms of the theory of molecular orbital perturbation [10]. In particular, it becomes clear from the diagram of the interaction of the frontier molecular orbitals of the substrates (I-III) (Fig. 1) that in both cases the interaction between the LUMO of the 1,3-dipole and the HOMO of the dipolarophile is predominant, since the energy gap between them is less than the energy gap between the LUMO of the dipolarophile and the HOMO of the 1,3-dipole. The degree of these interactions can be assessed by means of the Salem–Klopman equation [11] for the energy changes accompanied by orbital overlap of the molecules participating in the cycloaddition reaction. According to this equation, the preferred transition state will be the state in which the orbitals with the largest coefficients of the atomic orbitals overlap. As seen from Fig. 1, the largest coefficients of the atomic orbitals for the LUMO of the 1,3-dipoles (I) and (II) are at the carbon atom, while in the HOMO of the dipolarophile they are at the terminal carbon atom. This must lead to the formation of regioisomers of the "head-to-tail" type, i.e., to 2,3,3-triphenyl-5-octylisoxazolidine.

The fact that the reaction of the diphenyl nitrone with the 1-decene leads to a mixture of two stereoisomers can be explained by steric factors. From the AM-1 calculations of the transition states (Fig. 2) it follows that the approach of the 1,3-dipole to the C=C double bond in the case of the formation of the *trans* stereoisomer (VI) (the *endo* form of the transition state) is more sterically hindered than in the case of the formation of the stereoisomer (V) (the *exo* form of the transition state). The *cis* isomer (V) must therefore predominate in the reaction mixture.

EXPERIMENTAL

The melting points were determined on a Boetius microheater bench and were not corrected. The ^1H NMR spectra were recorded on a BS-487C instrument (80 MHz) at room temperature with TMS as internal standard. The chemical shifts are given on the δ scale. The IR spectra were recorded on a UR-20 spectrometer. The mass spectra were recorded on an LKB 9000S mass spectrograph at 70 eV. The reactions and the purity of the products were monitored by TLC on Merck Kieselgel 60 F_{254} plates in the 95:5 cyclohexane–ethyl acetate system. Elemental analysis for C, H, N was conducted on a Perkin-Elmer instrument. The quantum-chemical calculations by the semiempirical AM-1 method were performed on a Convex 3220 computer (Cyfronet, Krakow) using the MOPAC-7 software (QCPE, Indiana University, Bloomington, USA). The calculations by the PCMODEL-4 software were carried out on a Pentium 133 computer. The nitrones (I) and (II) were obtained by the method described in [13].

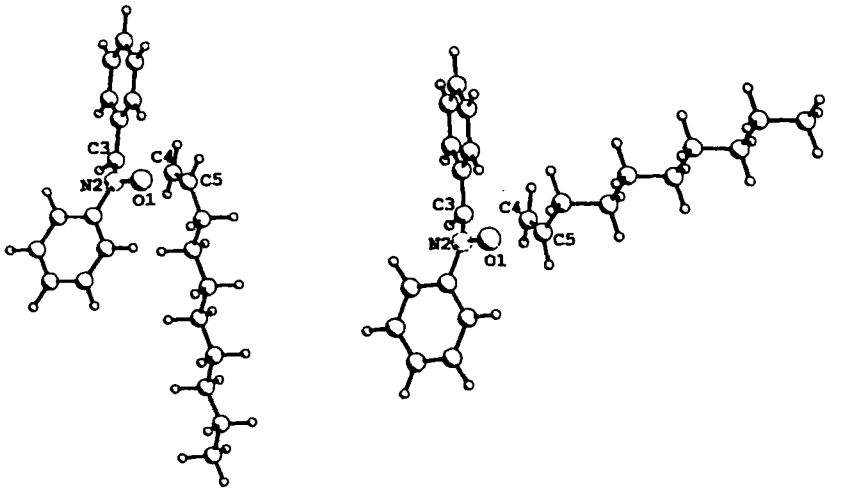


Fig. 2. PLUTO representation of the *endo* and *exo* transition states of the reaction of the nitrone (II) with the decene (III) (data from [12]).

2,3,3-Triphenyl-5-octylisoxazolidine (IV). A solution of 1.36 g (5 mmole) of C,C,N-triphenyl nitrone and 7 g (50 mmole) of 1-decene in 20 ml of dry toluene was heated at 80°C for 24 h. The solvent was evaporated to dryness, and the residue was investigated by TLC and ^{1}H NMR spectroscopy, after which it was recrystallized from ethanol. The yield was 1.8 g (87%); mp 37-38°C. IR spectrum, cm^{-1} (tablets with potassium bromide): 705, 755, 760 (C_6H_5), 1035 (C−O), 1270 (N−O). ^{1}H NMR spectrum, ppm (deuterochloroform): 0.9 (3H, t, J = 7); 1.7-1.0 (14H, m); 2.8 (1H, dd, J = 12.3, 8.8); 3.1 (1H, dd, J = 12.3, 6.4); 4.4 (1H, m); 7.6-6.6 (15H, m). Found %: C 84.4; H 8.5. $C_{29}H_{35}NO$. Calculated %: C 84.2; H 8.4.

2,3-Diphenyl-5-octylisoxazolidines (V, VI). These compounds were obtained from Z-C,N-diphenyl nitrone (0.98 g, 5 mmole) and 1-decene (7 g, 50 mmole) by the procedure described for 2,3,3-triphenyl-5-octylisoxazolidine. The residue after study by TLC and ^{1}H NMR spectrometry was separated into the components by fractional crystallization from ethanol. The yield was 1.5 g (89%) of *cis*-2,3-diphenyl-5-octylisoxazolidine (V) in the form of colorless needles; mp 43-44°C. IR spectrum, cm^{-1} (tablets with potassium bromide): 705, 755, 760 (C_6H_5), 1035 (C−O), 1270 (N−O). ^{1}H NMR spectrum, ppm (deuterochloroform): 0.9 (3H, t, J = 6.8); 1.7-1.0 (14H, m); 2.0 (1H, ddd, J = 11.7, 9.8, 8.0); 2.9 (1H, ddd, J = 11.7, 5.1, 8.0); 4.1 (1H, m); 4.8 (1H, t, J = 8.0); 7.6-6.6 (10H, m). Found %: C 82.0; H 9.3; N 4.1. $C_{23}H_{31}NO$. Calculated %: C 81.9; H 9.2; N 4.2.

By evaporating the mother solution we obtained 0.15 g of a dark-brown oil, from which we obtained 0.05 g (3%) of *trans*-2,3-diphenyl-5-octylisoxazolidine (VI) in the form of a yellow oil by preparative TLC on Kieselgel 60 F_{254} plates (Merck) 2 mm thick with 95:5 cyclohexane−ethyl acetate as eluant. IR spectrum, cm^{-1} (tablets with potassium bromide): 705, 755 (C_6H_5), 1035 (C−O), 1270 (N−O). ^{1}H NMR spectrum, ppm (deuterochloroform): 0.9 (3H, t, J = 6.8); 1.7-1.0 (14H, m); 2.3 (1H, ddd, J = 11.7, 10.0, 6.0); 2.5 (1H, dd, J = 11.7, 7.0); 4.1 (1H, m); 4.6 (1H, dd, J = 7.0, 10.0); 7.6-6.6 (10H, m). Mass spectrum (*m/z*): 337 (21), 195 (10), 191 (6), 182 (26), 104 (19), 91 (100).

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