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HETARENES WITH A BRIDGE NITROGEN ATOM.
6.* AMBIDENT PROPERTIES OF THE OXAZOLO[3,2-*a*]PYRIDINIUM NUCLEUS IN REACTIONS WITH NUCLEOPHILES: PREDICTION AND EXPERIMENT

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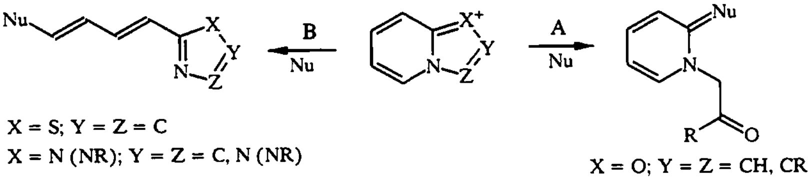
We have studied the problem of ambident opening of five-membered and six-membered rings of the heteroaromatic oxazolo[3,2-a]pyridinium cation. A quantum chemical SINDO1 calculation of the energies of isomeric adducts of this cation with nucleophiles predicts preferential formation of the $C_{(9)}$-adduct in the case of OH and SH ions with opening of the oxazole fragment, while for nitrogen-containing nucleophiles (NH_2, NMe_2) attack at the $C_{(5)}$ atom is also likely with opening of the pyridine fragment. We have experimentally observed that this cation undergoes opening of the five-membered ring in reaction with NaSH, opening of the six-membered ring in reaction with piperidine, and opening of both rings in reaction with ammonia.

We know that aromatic oxazolo[3,2-*a*]pyridinium cations (I) in reactions with nucleophiles (base [2], primary amines [3,4], carbanions [1,5]) undergo opening and recyclization of exclusively the five-membered oxazole fragment (direction A, Scheme 1). Moreover, in a number of analogous bridged azolopyridinium cations (containing a thiazole nucleus annelated at the C–N bond and other azoles) when treated with a broad range of nucleophiles, opening of the pyridinium fragment has been observed [6-8] (direction B, Scheme 1).

Scheme 1



Is the oxazolo[3,2-*a*]pyridinium system capable of opening of the six-membered ring and, in a broader sense, of exhibiting ambident properties in reactions with nucleophiles? In order to answer this question, in this work we have undertaken theoretical analysis of the reactivity of cation I with respect to reactions of addition of various nucleophiles. The experimentally verified results allowed us to observe the first example of opening of the six-membered ring in this cation and also to accomplish a number of previously unknown recyclizations, including a step involving opening of the five-membered ring.

Quantum chemical analysis of the reactivity of cation I was done by the semiempirical SINDO1 method [9]. The charge distribution in cation I is given in Scheme 2.

Although in cation I there are several electron-deficient centers (the $C_{(9)}$, $C_{(7)}$, $C_{(5)}$, and $C_{(2)}$ atoms), nevertheless the greatest positive charge is concentrated on the bridge $C_{(9)}$ atom. This does not provide a clear basis for conclusions that this is an ambident system with respect to nucleophilic attack.

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*For communication 5, see [1].

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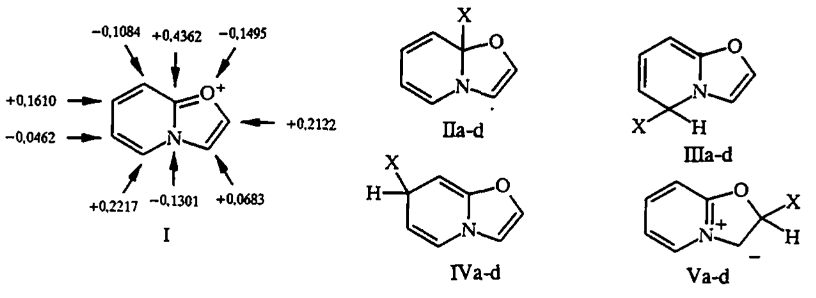
Scheme 2



II–V a X = OH, b X = SH, c X = NH_2, d X = NMe_2

Distribution of total charges in the oxazolo[3,2-*a*]pyridinium cation I and the structures of isomeric adducts of cation I with nucleophiles.

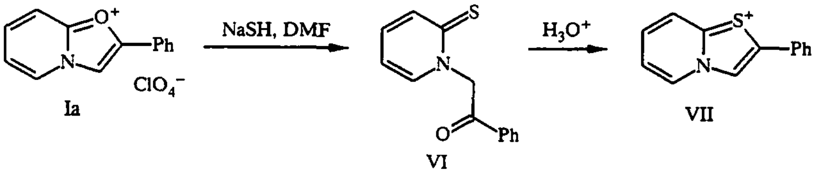
The selectivity of nucleophilic attack in cation I can be determined in another way: by comparing the energies of isomeric adducts with a nucleophile at different positions of the nucleus. Such calculations were done for isomeric $C_{(9)}$-, $C_{(7)}$-, $C_{(5)}$-, and $C_{(2)}$-adducts; as the nucleophilic residues, we selected OH, SH, NH_2, and $N(CH_3)_2$ groups (see Table 1). As we see, the $C_{(9)}$-adduct (structures IIa-d), an intermediate for opening of the five-membered ring (Scheme 1A), proves to be the most thermodynamically stable in all cases.

The next most stable for all the considered cases proves to be the adduct at the $C_{(5)}$ position (structures IIIa-d), an intermediate for opening of the six-membered ring (Scheme IB) (see Table 2).

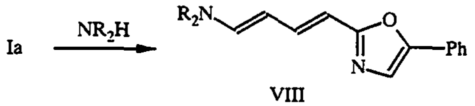
As we see from the data in Table 2, on going from O- and S-nucleophiles to nitrogen-containing groups (NH_2, NM_2), the energy difference between the $C_{(9)}$ and $C_{(5)}$ adducts is smoothed out, and the energies of the isomeric adducts are closest in the case of the dimethylamino group (structures IId and IIId). Accordingly, secondary amines might be the most promising nucleophiles, potentially capable of causing opening of the six-membered ring (according to Scheme 1B).

We note that in the known reaction of cation I with base [2], the product of opening of the five-membered ring is unambiguously formed: N-(β-oxoalkyl)-2-pyridone (according to Scheme 1A), in full agreement with the presented calculations. Nevertheless, secondary amines, like the simplest nucleophiles under discussion (ammonia and hydrosulfide ion) widely used for transformation of oxygen-containing heterocycles, so far have not been used as reagents capable of causing opening (recyclization) of oxazolopyridines.

We found that in the reaction of 2-phenyloxazolo[3,2-*a*]pyridinium perchlorate (Ia) with a solution of sodium hydrosulfide in DMF, we see smooth formation of N-phenacylpyridine-2-thione (VI) (90% yield). The latter in acid medium easily closes the thiazolium ring [2], forming a thiazolopyridinium cation VII.



We also observed that when treated with piperidine, the 2-phenyloxazolo[3,2-*a*]pyridinium perchlorate (Ia) undergoes opening of the six-membered fragment with formation of 1-piperidyl-4-(5-phenyl-2-oxazolyl)butadiene (VIII).



NR_2H = piperidine

The structure of the aminobutadiene obtained was proven by a series of spectral data. In the mass spectrum, we observe a molecular ion peak (formally corresponding to the 1:1 adduct of the original cation with the amine), and also an intense peak

TABLE 1. Total Energy (au) of Isomeric Adducts of Cation I with Nucleophiles

Nucleophile (a-d), adduct (II-V)	OH (a)	SH (b)	NH2 (c)	N(CH3)2 (d)
II $C_{(9)}$- adduct	-86,620425	-80,698696	-81,398581	-95,195569
III $C_{(5)}$- adduct	-86,613322	-80,691706	-81,395822	-95,194263
IV $C_{(7)}$- adduct	-86,600707	-80,686487	-81,384776	-95,183500
V $C_{(2)}$-adduct	-86,603989	-80,682971	-81,383291	-95,182777

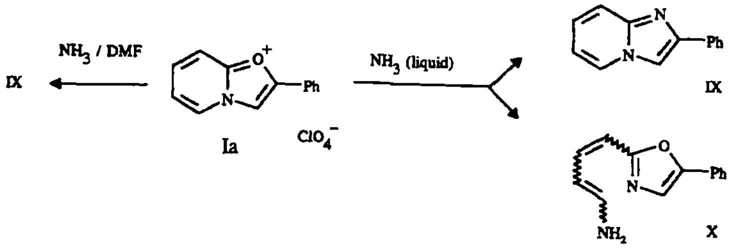
TABLE 2. Differences in Energies (kcal/mole) for Isomeric Adducts Relative to the Most Stable Adduct at the $C_{(9)}$ Atom

Nucleophile (a-d), adduct (II-V)	OH (a)	SH (b)	NH2 (c)	N(CH3)2 (d)
II $C_{(9)}$- adduct	0	0	0	0
III $C_{(5)}$- adduct	4,46	4,39	1,73	0,82
IV $C_{(7)}$- adduct	12,37	7,66	8,66	7,57
V $C_{(2)}$- adduct	10,31	9,87	9,59	8,03

with *m*/z 196 (loss of the piperidine fragment), probably corresponding to intramolecular cyclization of the molecular ion VIII to cation Ia. In the UV spectrum of the diene, there is an intense long-wavelength absorption band at 382 nm; and in the IR spectrum we see the vibrational frequencies characteristic for dienes at 1628 cm^{-1}. The PMR spectrum of oxazolylbutadiene VIII is similar to the spectra for known thia analogs (α-amino-ω-thiazolylbutadienes [8]). The spin–spin coupling constants observed in the PMR spectrum (J_{12} = 13.1; J_{23} = 11.2; J_{34} = 15.5 Hz) allow us to assign a *trans-trans* geometry to diene VIII. The observed direction of the reaction is the first example of opening of the six-membered ring in an aromatic oxazolo[3,2-*a*]-pyridinium system and opens up a synthesis route for α-amino-ω-(2-oxazolyl)butadienes, which were previously difficult to obtain. We note that although butadiene VIII proved to be unstable and difficult to purify, its other analogs, in particular those we obtained from 2-(*p*-nitrophenyl)oxazolopyridinium, proved to be quite stable crystalline compounds. Their synthesis and properties will be the subject of a separate report.

Thus the different behavior of cation Ia in reaction with hydrosulfide (opening according to Scheme 1A) and in reaction with a secondary amine (opening according to Scheme 1B) is qualitatively consistent with data from the calculation done for the model cation I. Probably the slight difference between the energies of the $C_{(5)}$ and $C_{(9)}$ adducts in the reaction of oxazolo[3,2-*a*]pyridinium cation with a secondary amine (see Table 2) proves to be sufficient for the occurrence of the process according to Scheme 1A with rupture of the $C_{(5)}-N$ bond. The lack of a product of opening of the five-membered ring in this case is probably connected with the possible instability of the zwitterionic compound which might be formed on rupture of the $C_{(9)}-O$ bond in adduct IId.

The results obtained did not allow us to make a clear prediction of the direction of the reaction of cation I with ammonia. We have found that when a solution of the 2-phenyloxazolo[3,2-*a*]pyridinium cation in DMF is treated with gaseous ammonia, the reaction selectively occurs with formation of exclusively 2-phenyl[1,2-*a*]imidazopyridine (IX) (63% yield). Moreover, when this cation is dissolved in liquid ammonia, we isolate a mixture of the same imidazopyridine IX (the product of recyclization of the five-membered ring) and a small amount of an orange compound which, based on all the spectral data (NMR, UV, and mass spectrum), was assigned the structure of the product of opening of the six-membered fragment of cation I, i.e., the aminobutadiene X.



The UV, PMR, and mass spectra of aminobutadiene X is quite similar to the spectra of piperidylbutadiene VIII (see Experimental section).

The observed schemes for exchange of an oxygen heteroatom of cation I by a sulfur atom (a two-step process) and by a nitrogen atom ("one-pot" conversion), analogous to the Yur'ev reaction in a number of five-membered hetarenes, have not been used so far in syntheses of bridged heterocycles VII and IX [10]. Regarding the preparative aspect of these recyclizations, we should note that both heteroatom exchange processes proved to be quite sensitive to the presence of traces of water. Thus when using aqueous solutions of sulfides and hydrosulfides of alkali metals or aqueous ammonia in the reaction with cation Ia, an appreciable byproduct proved to be N-phenacyl-2-pyridone, which as has been noted is easily formed in base hydrolysis of cation I.

Thus, depending on the nature of the nucleophile used, cation I exhibits ambident properties, undergoing opening either of the five-membered ring (solutions of ammonia and hydrosulfide) or the six-membered ring (secondary amine) or finally any of the rings (liquid NH_3).

EXPERIMENTAL

The quantum chemical calculation was done by the SINDO1 method [9] (WS5, Theoretische Chemie, Hannover). The IR spectra were taken on a UR-20 in Vaseline oil. The UV spectra were taken on a Varian-K325. The PMR spectra were recorded on Bruker AM-400 and AC-200 spectrometers, internal standard TMS. The course of the reactions was monitored by TLC on Silufol UV-254 plates. Chromatographic separation was done on Silpearl columns.

The starting 2-phenyloxazolo[3,2-*a*]pyridinium perchlorate (Ia) [11] and the N-phenacylpyridine-2-thione (VI) [2] and 2-phenylimidazo[1,2-*a*]pyridine (IX) [12] used for comparison were obtained by the procedures described.

Reaction of Cation Ia with Sodium Hydrosulfide. 2-Phenyloxazolo[3,2-*a*]pyridinium perchlorate (Ia) (0.504 g, 1.7 millimoles) was dissolved in 10 ml absolute DMF and then 0.125 g (2.23 millimoles) NaSH was added to the solution. The mixture acquired a brownish color. After 30 min of stirring, the mixture was allowed to stand overnight at room temperature. The transparent solution obtained was poured with stirring into 100 ml ice water. The precipitate was filtered off, washed with water, and dried. Obtained: 0.35 g (90%) N-phenacylpyridine-2-thione (VI), identical in properties (T_{mp}, chromatographic behavior, IR spectrum) to a known sample. IR spectrum: 1693 cm^{-1} (C=O).

***trans*–*trans*-1-Piperidino-4-(5-phenyl-2-oxazolyl)butadiene (VIII).** 1 ml piperidine was added to 0.2 g (0.68 millimoles) oxazolopyridinium perchlorate Ia and stirred at room temperature for 2 h. Then 50 ml water was added and the precipitated aminobutadiene VIII (0.127 g, 67%) was washed a few times with water and then dried in air. The material was additionally purified by passing through a layer of silica gel. Compound VIII (viscous amorphous material, decomposes in storage) did not give satisfactory elemental analysis. Mass spectrum: *m/z* (I_{rel}, %): 280 (34, M^+), 196 (100, M^+-$C_5H_{10}N$). UV spectrum in $CHCl_3$, λ_{max} (lg ε): 268 (3.99); 281 (4.05); 382 (4.38) shoulder, 454 (3.44) nm. IR spectrum: 1628 cm^{-1} (C=C). PMR spectrum ($CDCl_3$): 7.64-7.59, 7.41-7.35 (5H, m, 5-Ph); 7.25 (1H, s, H-oxazolyl); 7.21 (1H, dd, J_{23} = 11.2, J_{34} = 15.2 Hz, 3-H); 6.53 (1H, d, J_{12} = 13.1 Hz, 1-H); 5.97 (1H, d, J_{34} = 15.2 Hz, 4-H); 5.31 (1H, dd, J_{12} = 13.1, J_{23} = 11.2 Hz, 2-H); 3.15-3.05 (4H, m, piperidyl); 1.82-1.44 ppm (6H, m, piperidyl).

Reaction of 2-Phenyloxazolo[3,2-*a*]pyridinium Perchlorate with Gaseous Ammonia. Oxazolopyridinium perchlorate Ia (0.165 g, 0.563 millimoles) was dissolved in 15 ml absolute DMF and saturated with dry ammonia. The solution was allowed to stand for 24 hours, after which it was poured into 50 ml water. The precipitate was filtered off, washed with water, and dried. Obtained: 0.053 g of material. The aqueous layer was additionally extracted with chloroform, the extract was evaporated, the oily residue was treated with water, and an additional 0.016 g of material was obtained. Overall yield, 63% of 2-phenylimidazo[1,2-*a*]pyridine (IX), identical in properties (T_{mp}, chromatographic behavior, IR spectrum) to a known sample.

Reaction of 2-Phenyloxazolo[3,2-*a*]pyridinium Perchlorate with Liquid Ammonia. By cooling with liquid nitrogen, ammonia was condensed down to a volume of 5 ml in a test tube with 0.8 oxazolopyridinium perchlorate Ia. The temperature of the mixture was kept no warmer than −35°C for 24 hours, then the temperature was raised to room temperature. The orange-red mixture obtained was extracted a few times with chloroform and the solvent was driven off. The material obtained (orange oil, 0.435 g) was dissolved in benzene and chromatographed (Silpearl, gradient elution by a benzene–acetone mixture from 3:1 to 1:2). The main fraction was collected (R_f 0.7, benzene–acetone, 1:1), from which after driving off the solvent we obtained 0.208 g (40%) 2-phenylimidazo[1,2-*a*]pyridine (IX). From the second fraction, we isolated 0.033 g (5%) 1-amino-

4-(5-phenyl-2-oxazolyl)butadiene (X) (orange needles, T_{mp} 157-159°C). Mass spectrum: m/z (I_{rel}, %): 212 (41, M^+), 196 (100, M^+-NH_3). UV spectrum in $CHCl_3$, λ_{max} (lgε): 275 (3.75); 348 (3.80); 435 (4.05) nm. PMR spectrum (DMSO-D_6−$CDCl_3$, 1:1): 7.71-7.62, 7.50-7.30 (5H, m, 5-Ph); 7.34 (1H, s, H-oxazolyl); 7.19 (1H, dd, J_{23} = 11.1, J_{34} = 15.2 Hz, 3-H); 6.64 (1H, d, J_{12} = 12.8 Hz, 1-H); 6.21 (1H, d, J_{34} = 15.2 Hz, 4-H); 5.78 (1H, dd, J_{12} = 12.8, J_{23} = 11.1 Hz, 2-H); 3.70-3.30 ppm (2H, broad m, 1-NH_2).

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