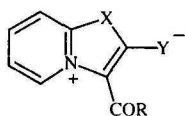


Eugene V. Babaev

Chemistry Department, Moscow State University, Moscow 119899, Russia

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Mesoionic azolopyridines of the general formula **I** are related to the family of condensed munchnones [1].

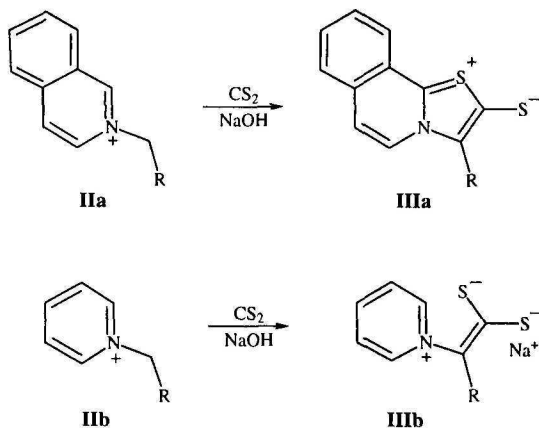
**I**

- a X = Y = O
- b X = NR, Y = S, O, NR
- c X = S, Y = S
- d X = S, Y = O
- e X = S, Y = NR

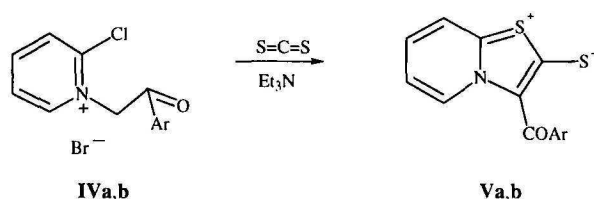
Although the chemistry of *b*-fused oxazolones **Ia** [2] and imidazopyridine derivatives **Ib** [3] is well reviewed, no data are reported yet about the synthesis of the mesoionic thiazolopyridines **Ic-e**. In the first part of this review we discuss novel strategy to the synthesis of condensed thiazoles **Ic-e** and describe structural features of munchnones **Ia** and **Ic** for which we report X-ray data for the first time. In the second part we introduce the concept of *recyclization tandems*: Mesoionic system **Ia** may be easily transformed to highly reactive oxazo[3,2-*a*]pyridinium cation which, in turn, undergoes variety of ring opening/transformation reactions leading to novel classes and subclasses of heterocyclic compounds.

Synthesis of Novel *b*-Fused Munchnones.

Krohnke first attempted to prepare mesoionic thiazoles **Ic** by cycloaddition of carbon disulfide to pyridinium and isoquinolinium ylides [4]. Although in the case of isoquinolines **IIa** the desired mesoionic product **IIIa** was obtained, the reaction of pyridinium salt **IIb** led only to the stabilized compound **IIIb** and not to the parent munchnone.

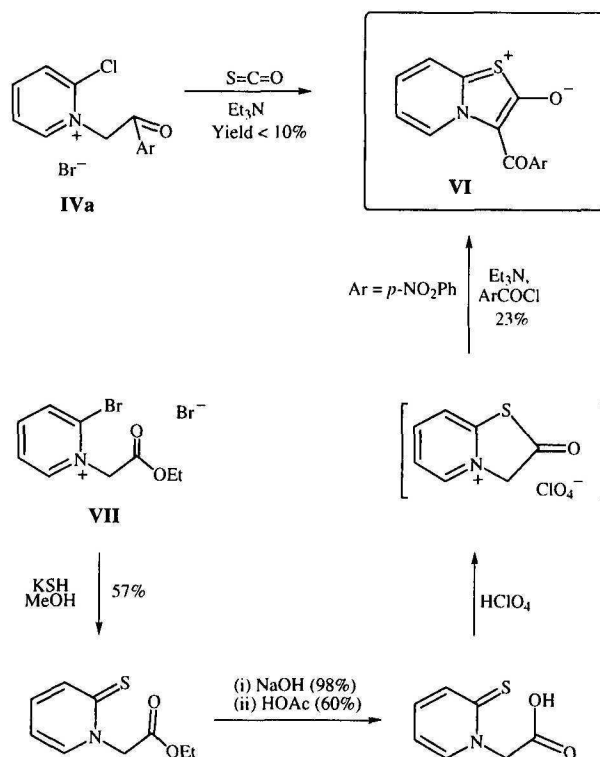


This result can be clearly explained in terms of higher electron deficiency of the isoquinolinium than that of the pyridinium ring. The presence of a leaving group at α -position of the initial pyridinium salt would favor cyclization. We found that 2-chloropyridinium salts **IVa,b** in reaction with carbon disulfide at room temperature form the desired mesoionic thiazolopyridines **Va,b** [5]. Structure of the compound **Va** was confirmed by X-ray analysis.

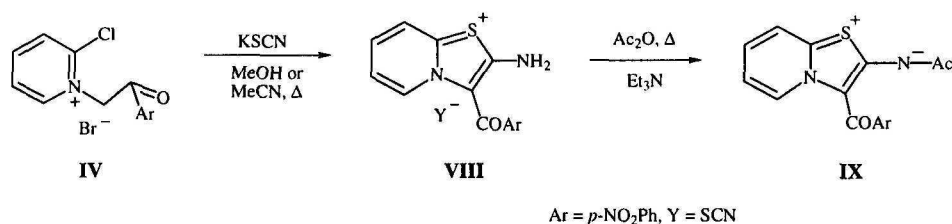


- a AR = *p*-NO₂Ph (20%)
- b *p*-ClPh (36%)

Analogous reaction between carbon oxosulfide and the salt **IVa** led to another mesoionic system **VI**; the yield, however, was low (<10%), and we performed a multistep synthesis of compound **VI** starting from the available 2-bromopyridinium salt **VII** [6].



Thiocyanate anion is isoelectronic with both carbon disulfide and carbon oxosulfide. It is, therefore, not surprising that reaction between the salt **IVa** and potassium thiocyanate proceeds similarly with incorporation of CS fragment into the newly formed thiazole ring. According to X-ray data, the resulting product was thiocyanate of 2-amino-3-(*p*-nitrobenzoyl)thiazolo[3,2-*a*]pyridinium **VIIIa** [7]. The yield of the product **VIIIa** was quantitative, and further heating of this salt with acetic anhydride led to unknown mesoionic system **IX** [8]. No change in the selectivity of the reaction was observed when potassium thiocyanate has been changed to silver thiocyanate.

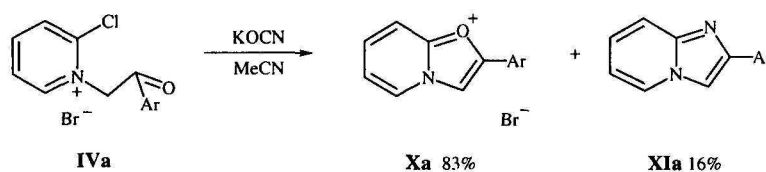


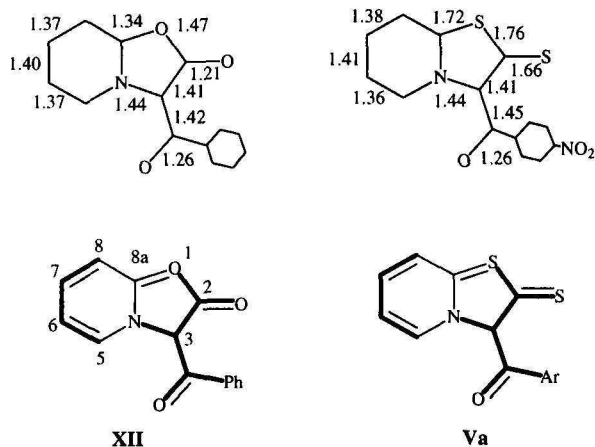
As is evident from the reaction scheme, two halogen anions -- bromide and initially covalent chlorine atom -- were removed from the starting structure. Trying to involve various 2-chloropyridinium bromides **IV** in this reaction we found [8] that, according to ionic chromatography data, the salts **VIII** were generally the mixtures of chlorides, bromides, and thiocyanates. The nature of the counterion Y in the salts **VIII** depends on the ratio of starting materials and on the nature of aryl group in the initial salts **IV**. One possibility to obtain compounds **VIII** with single counterion was to convert them into perchlorates. Another original strategy to obtain pure chlorides **VIII** was using the perchlorate of the starting salt **IV** and aqueous methanol as the solvent [9].

One would expect similar behavior of cyanate anion in reaction with cation **IV**. However, no formation of mesoionic derivatives was observed when the salt **IVa** and potassium cyanate were refluxed in acetonitrile. Instead, the reaction resulted in an unexpected formation of 2-(*p*-nitrophenyl)oxazolo[3,2-*a*]pyridinium bromide (**Xa**) and 2-(*p*-nitrophenyl)imidazo[3,2-*a*]pyridine (**XI**) [10].

Structure of *b*-Fused Munchnones.

Analysis of crystal structures of munchnones **Va** [5] and **XII** (Ar = Ph) [11] may clarify the problem of "correct" resonance structure(s) that should be assigned to such mesoionic compounds. Assigning single and double bonds (shown in bold) according to the observed bond lengths, one could obtain the following diagrams:



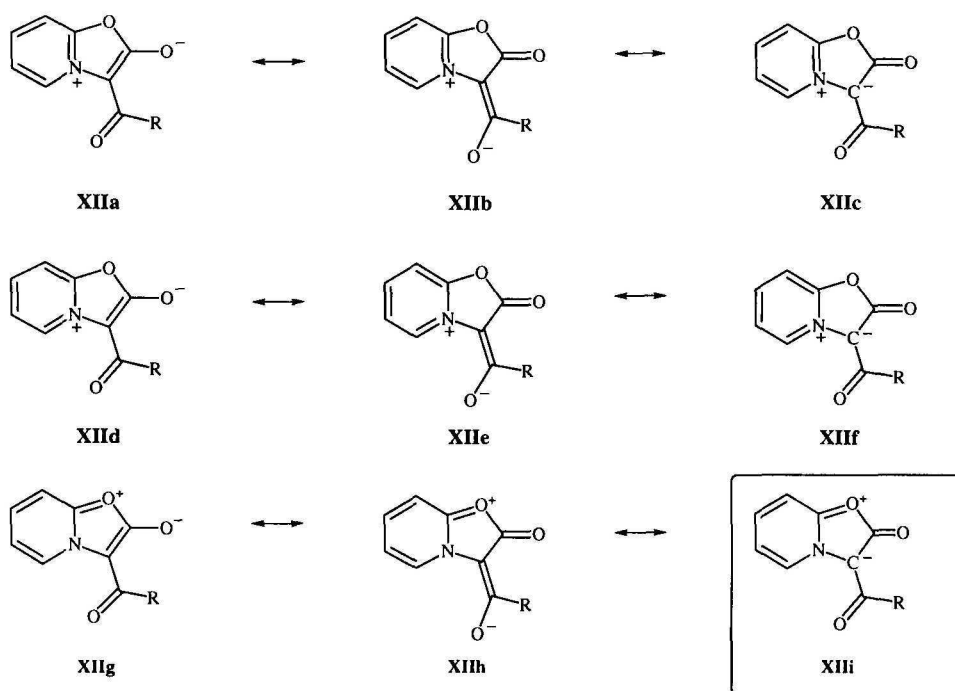


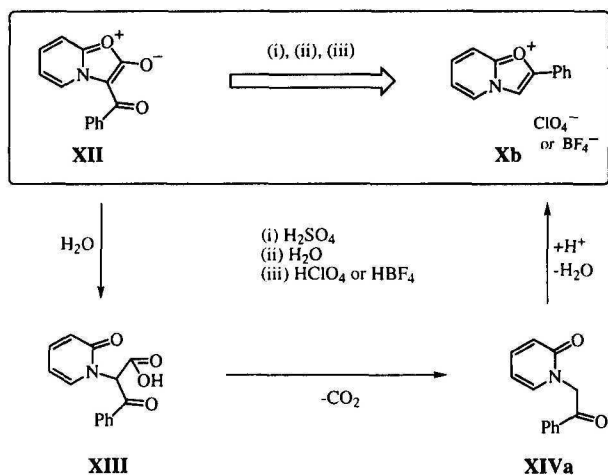
In both structures three C-C bonds adjacent to the carbon atom C3 were rather long (1.41 - 1.45 Å), whereas the lengths of CO bonds of benzoyl groups were short. Furthermore, the exocyclic C2-Y bonds (Y = O and S) were also very short. This may lead to an intriguing conclusion: the negative charge is located at position 3 without significant conjugation of carbanionic center of the ylide with exocyclic CO groups. (This conjugation, if it exists, would increase the CO bond length.) Hence, the best of resonance structures possible for mesoionic sys-

tems **I** would be formulas **XIIc,f,i** which resemble pyridinium ylides. Moreover, because the bond C8a-O is shorter than the bond C2-O and due to an alternation of bond lengths along the pyridine fragment C5-C6-C7-C8, the best remaining structure seems to be **XIII**. The geometry observed in the crystal of munchnone **XII** perfectly corresponds to the geometry theoretically calculated by ab initio method and, therefore, may reflex the structure of the isolated molecule.

Reactivity of *b*-Fused Oxazolones and Oxazolo[3,2-*a*]pyridinium Salts. The Concept of Recyclization Tandems.

The reactivity of mesoionic oxazolones **I** is well studied [2], and we paid attention to the fact that 3-benzoyloxazolo[3,2-*a*]pyridinium-2-olate (**XII**) readily underwent hydrolytic degradation to *N*-phenacyl-2-pyridone (**XIVa**) [2a]. It is also well known, that in sulfuric acid the compound **XIVa** undergoes closure of the oxazolium ring forming 2-phenyloxazolo[3,2-*a*]pyridinium cation **Xb** [12]. We found that the conversion of mesoionic derivative **XII** to cation **Xb** may proceed as one-pot recyclization [13] with the yield 83%, and the structure of the perchlorate **Xb** was confirmed by X-ray data. It was somewhat difficult to find optimal conditions for a reaction which, in fact, is *hydration* and *dehydration* simultaneously. We found that a vigorous reaction occurred when the starting material was dissolved in sulfuric acid, and the water was carefully added to the reaction mixture (thus, violating the common laboratory rule "put acid into water"). Synthetic advantages of this strategy are clear:





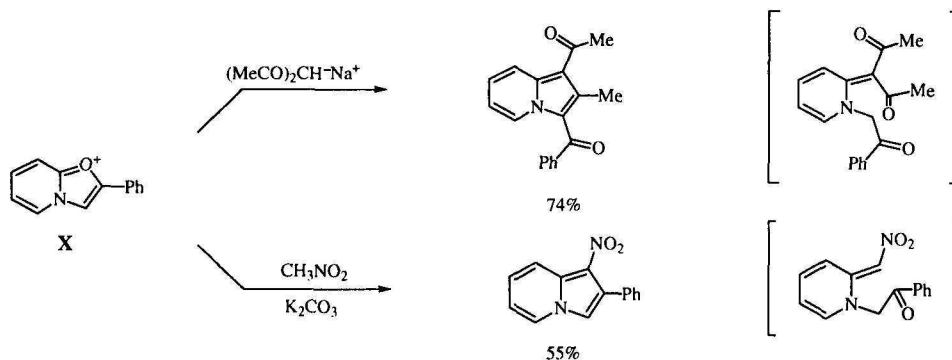
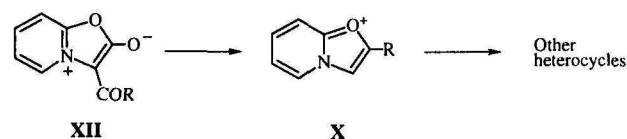
aryl group in oxazolopyridinium salts, which usually originates from α -bromoketones (*cf.* synthesis of *N*-phenacylpyridones **XIV**), in our conversion originates from aroyl chloride used for the synthesis of munchnone **XII** [14].

Discovery of this recyclization has stimulated our interest in the chemistry of oxazolo[3,2-*a*]pyridinium salts. According to literature [15], such salts may undergo transformation of oxazolium fragment ("heteroatom exchange" reactions) leading, for example, to 1-phospha-, 1-arsa- and 1-azaindolizines. One would expect the possibility of

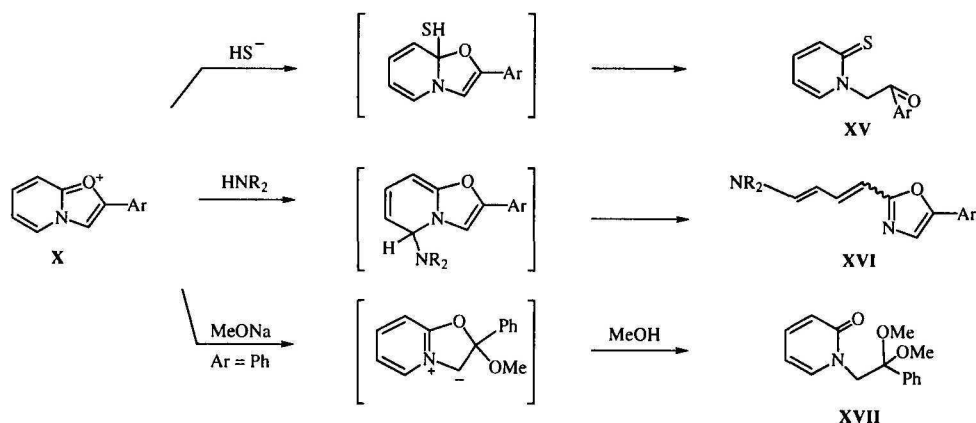
other -- quite diverse -- recyclizations involving oxazolo[3,2-*a*]pyridinium salts. Early we developed rather general structural classification of recyclizations [16] and suggested the strategy of computer assisted predictions of all possible ring transformations for a given heterocycle. Considering oxazolopyridine as a concrete example, we have published a forecast for several most promising recyclizations of this heterocycle [17]. During the last few years several of our predictions were confirmed experimentally (see review [18]).

Now we may formulate our general result as the concept of *recyclization tandems*: a stable reactive structure, obtained by a recyclization, may be involved in further recyclizations.

First, we studied reactions of the salts **X** with carbanions. Both in reaction with nitromethane [19] and with acetylacetone [20] we obtained indolizine derivatives.

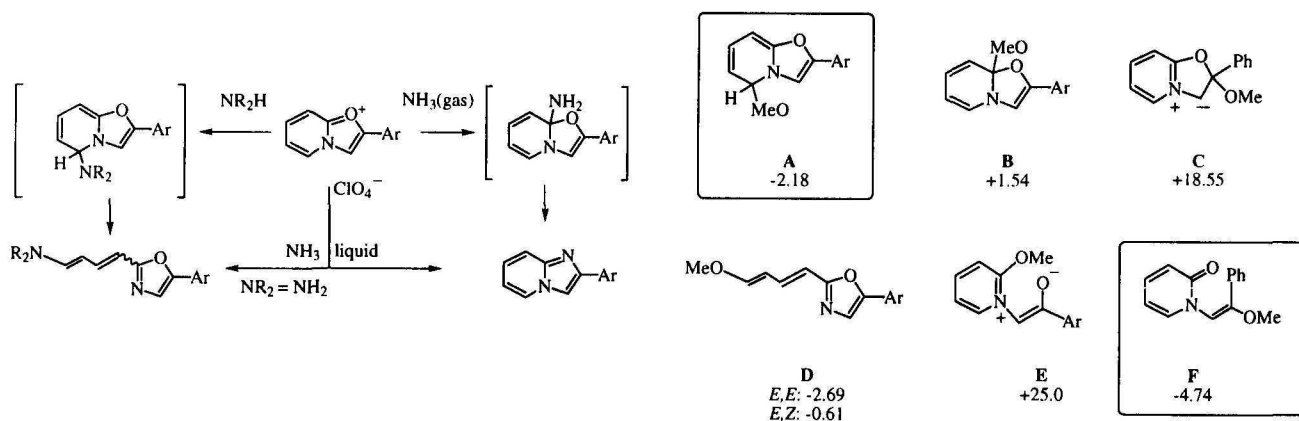


We have found that the direction of ring opening of the salts **X** depends on the nature of nucleophile. Thus, the reaction of salts **X** with sodium hydrosulfide led to *N*-phenacylpyridine-2-thiones **XV** [21]; here, as in the case of carbanions, the cleavage of C8a-O bond occurred. However, in reactions with secondary amines [22] the cleavage of the six-membered fragment occurred, leading to oxazolyldienes **XVI** with the yields 62-96%. The configuration of dienes **XVI** was either *1E,3E* or *1E,3Z* depending on the reaction temperature. An unexpected result was observed in the reaction of oxazolopyridinium salt **Xb** with sodium methoxide [23]. Here according to X-ray data, the reaction product was ketal **XVII**, and the only hypothesis to explain its formation was an assumption that the initial attack of nucleophile occurred at position 2 followed by cleavage of C2-O bond.

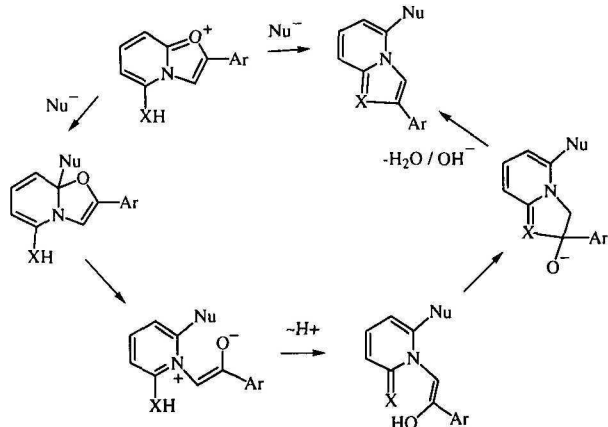


Ambident behavior of the salts **X** was observed in the reaction with ammonia. Thus, reaction of the salts **X** with gaseous ammonia led exclusively (and almost quantitatively) to imidazopyridine, whereas in liquid ammonia the by-product of pyridine ring opening was detected [21].

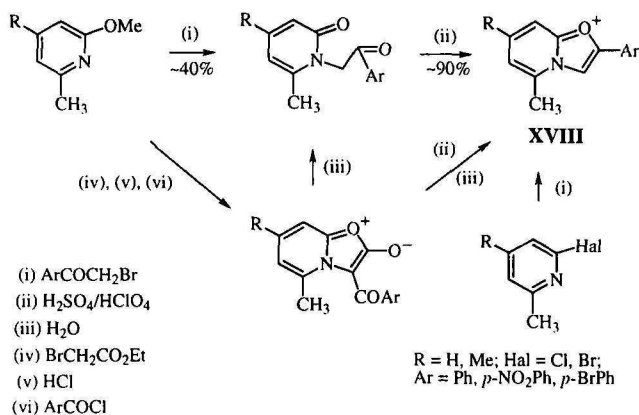
With the goal to explain the selectivity of reactions of the salts **X** with nucleophiles, we performed quantum chemical MNDO calculations of energies of the isomeric adducts of oxazolopyridinium cation with methoxide anion and also of the corresponding ring opening products [23].



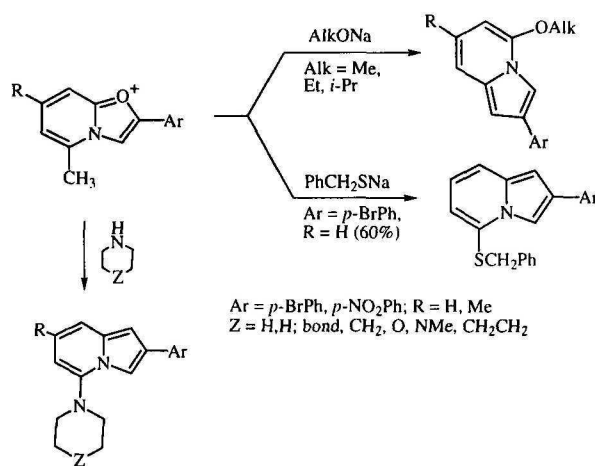
Results (energy in kcal) are presented on the diagram, and the most stable intermediates are in squares. These results indicate that the most stable initially formed adduct may not correspond to the most stable open chain intermediate. An especially interesting type of intermediates was the most unstable zwitterion of the type E, which had to be postulated in the observed reactions of salts **X** with carbanions and hydrosulfide. We have supposed that if the initial cation **X** would have a donor group XH at position 5, and if the ring cleavage would proceed *via* an intermediate of the type E, then such an intermediate may undergo ring closure involving group XH. This hypothetical scheme may be presented as follows:



Such a reaction would correspond to previously unknown recyclization type, and the problem was to synthesize oxazolopyridinium salts with suitable group XH. We have considered the case XH to be methyl group and performed the synthesis of previously unknown homologs **XVIII**. The chosen strategies involved cyclization of 6-methyl-1-phenacyl-2-pyridones [24] or recyclization of corresponding homologous mucchnones [25].



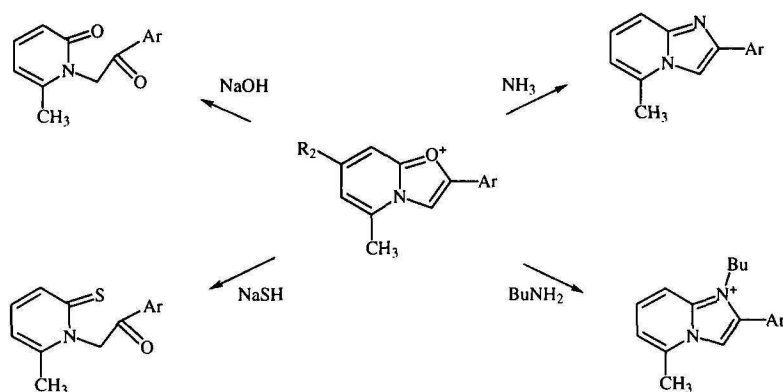
Homologous salts **XVIII** in reaction with secondary amines, sodium alcoholates and sodium salt of benzylmercaptan underwent recyclization leading to previously unknown indolizines with donor group at position 5 [26].



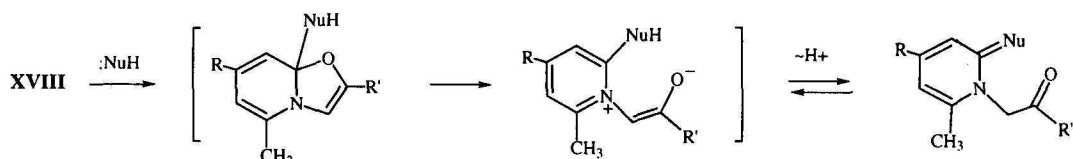
Reaction Yields

Substituents	Yield %
2-Ar,7-R (in XVIII), Z (in NR ₂)	
<i>p</i> -NO ₂ Ph, H, CH ₂	66
<i>p</i> -NO ₂ Ph, H, O	79
<i>p</i> -NO ₂ Ph, H, (CH ₂) ₂	65
<i>p</i> -NO ₂ Ph, H, HH	37
<i>p</i> -NO ₂ Ph, H, NMe	74
<i>p</i> -NO ₂ Ph, H, bond	60
<i>p</i> -BrPh, H, O	38
<i>p</i> -NO ₂ Ph, Me, bond	45
<i>p</i> -NO ₂ Ph, Me, CH ₂	83
<i>p</i> -NO ₂ Ph, Me, (CH ₂) ₂	63
2-Ar, 7-R in XVIII , OAlk	
<i>p</i> -NO ₂ Ph, H, OMe	48
<i>p</i> -NO ₂ Ph, H, OEt	20
<i>p</i> -NO ₂ Ph, H, <i>i</i> -PrO	63
<i>p</i> -NO ₂ Ph, Me, Meo	39

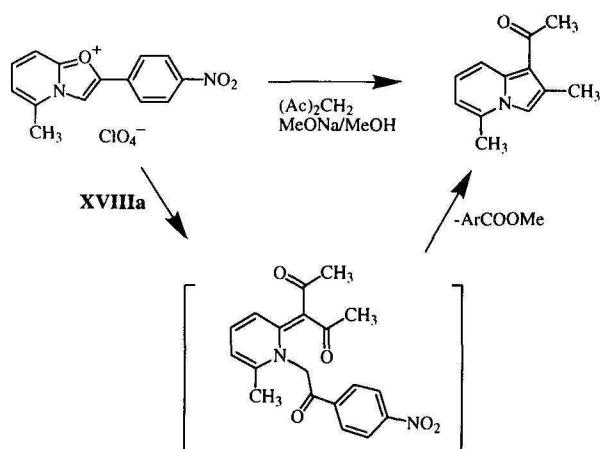
If in reactions with the salts **XVIII** the nucleophilic agents had additional hydrogen atoms, no indolizine derivatives were formed; the resulting compounds were either ring opening monocyclic structures (phenacylpyridones or thiones) or the products of "heteroatom exchange" reaction -- imidazopyridines or their salts [24, 27].



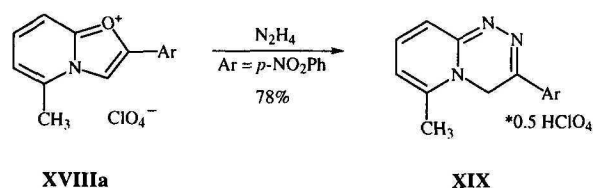
Rationalization of these results is evident, because of the possibility of tautomerism in the product of ring opening. Such tautomerism transforms zwitterionic intermediate (precursor of indolizine) to a stable pyridone-like structure:



A sort of concurrence between intramolecular (involving methyl group) and intermolecular (involving functions of an external reagent) cyclization of intermediate was possible for reactions of homologous salts **XVIII** with carbanions. We found that in reaction of the salt **XVIIIa** with acetylaceton the product was 3-acetyl-2,5-dimethylindolizine [28]; the crystal structure of the product was determined. Here the fragment of acetylaceton was incorporated into the novel pyrrole ring, and the reaction is followed by removal of aryl fragment.



Reaction of the salt **XVIIIa** with hydrazine gave an example of ring expansion reaction [27]. The structure of the fused pyridotriazine semiperchlorate **XIX** was confirmed by X-ray data, and, in contrast to the earlier hypothesis of Bradsher [28], we found no evidence for an intramolecular hydrogen bond for this structure.



Acknowledgements.

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