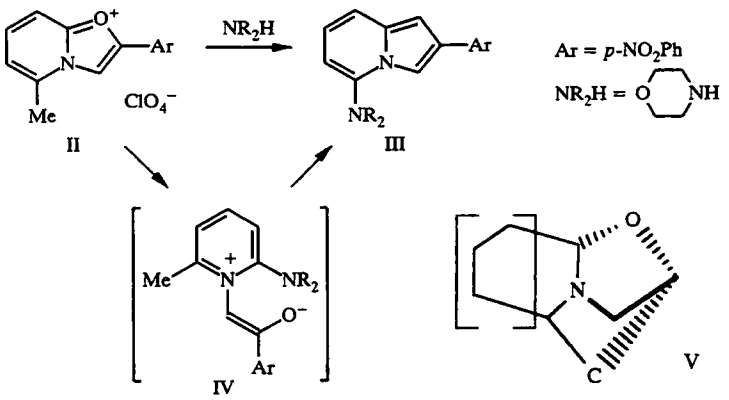
Chemistry of Heterocyclic Compounds, Vol. 33, No. 7, 1997

HETEROCYCLES WITH A BRIDGE NITROGEN ATOM. 8.* NOVEL APPROACH TO SYNTHESIS OF THE INDOLIZINE NUCLEUS AND THE CLASS OF 5-AMINOINDOLIZINES BY RECYCLIZATION OF THE 5-METHYLOXAZOLO[3,2-*a*]PYRIDINIUM CATION: ALTERNATE CONFIRMATION OF A COMPUTER PREDICTION

E. V. Babaev and A. V. Efimov

We previously proposed two novel synthesis schemes for the indolizine nucleus by recyclization of the oxazolo[3,2-*a*]pyridinium cation nucleus I when treated with CH-acids [2,3]. In both cases, the oxazole moiety of the bicycle was transformed to a pyrrole moiety. In the first scheme (when using nitromethane), the oxygen heteroatom of the oxazole moiety of cation I was formally replaced by a binucleophilic one-carbon moiety [2], while in the second scheme the two-atom moiety $C_{(2)}-O$ of cation I was substituted by the two-carbon $-CH_2CO-$ moiety of the CH-acid [3].

Detailed analysis of the polar structure of the intermediates formed in opening of the oxazole moiety of cation I allowed us to propose [4] that one of the unknown recyclization strategies for constructing an indolizine nucleus might be transformation of homologs of cation I, and specifically 5-methyloxazolo[3-2-*a*]pyridines. It is precisely such a skeleton of the starting heterocycle (as the precursor of the indolizines) which was predicted in computer generation of unknown transformations of bridged azolopyridines in [4]. We previously proposed a simple approach to obtaining such 5-methyl-substituted cations in [5]. In this report, we have observed that 5-methyl-2-(*p*-nitrophenyl)oxazolo]3,2-*a*]pyridinium perchlorate II when treated with secondary amine in fact undergoes a previously unknown recyclization with formation of 5-aminoindolizine III:



Perchlorate II (0.846 millimoles), obtained according to the procedure in [5,6], was dissolved in 1.5 ml morpholine and boiled for 15 min. The cooled mixture was poured into water; the precipitate formed was filtered and chromatographed on a column (Silpearl, $CHCl_3$). Orange-red crystals of 5-(morpholyl-1)-2-(*p*-nitrophenyl)indolizine (III) were obtained in 79% yield. T_{mp} 232°C. PMR spectrum (400 MHz, $CDCl_3$): 8.19 (2H, m, *p*-NO_2Ph); 7.77 (2H, m, *p*-NO_2Ph); 7.71 (1H, s, 3-H); 7.18 (1H, d, J_{78} = 8.8 Hz, 8-H); 6.77 (1H, s, 1-H); 6.75 (1H, dd, J_{78} = 8.8, J_{67} = 6.8 Hz, 7-H); 6.13 (1H, d, J_{67} = 6.8 Hz,

M. V. Lomonosov Moscow State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 998-1000, July, 1997. Original article submitted April 9, 1997.

0009-3122/97/3307-0875$18.00

6-H); 3.95 (4H, m, morpholyl); 3.11 (4H, m, morpholyl). UV spectrum in ethanol, λ_{max} (lgε): 263 (4.72), 360 (4.25). Mass spectrum, *m/z* (%): 323 (100) [M^+], 266 (40), 238 (48) [$M-C_4H_7NO]^+$, 191 (23). Found, %: C 67.01; H 5.25; N 13.10. $C_{18}H_{17}N_3O_3$. Calculated, %: C 66.86; H 5.30; N 13.00.

As follows from the PMR spectrum, the signal from the methyl group (present in the original system) is missing in the spectrum of the recyclization product. Moreover, a new aromatic signal appears in the spectrum along with signals from aliphatic protons of the morpholine moiety. The number and multiplicity of the peaks correspond to the structure of 2-aryl-5-substituted indolizine. Assignment of the structure of the compound obtained to 5-aminoindolizine also follows from the absence of a downfield signal from the 5-H proton, which is quite characteristic for indolizines [7]. Like other representatives of this class, indolizine III gives a characteristic blue color with *p*-dimethylaminobenzaldehyde (the classical Ehrlich test).

The mechanism of the observed elegant conversion probably includes attack by the secondary amine at the angular carbon atom of the bicycle. Opening of the oxazole moiety as needed should lead to formation of the zwitterionic open form IV (pyridinium moiety, containing a negatively charged enol moiety at the nitrogen atom). Such an intermediate can form a pyrrole moiety as a result of cyclocondensation at the methyl group. We should note that cations I (not containing a methyl group at the $C_{(5)}$ atom) react with secondary amines with breaking of the CN bond of the pyridine moiety [8], while the first step of the recyclization II → III under discussion obviously requires breaking the CO bond of the oxazole moiety.

As we see, the overall scheme for the conversion involves formal elimination of the oxygen heteroatom from the starting heterocycle. The structural scheme for the conversion found can be described with the help of the recyclization graph V. Let us recall that recyclization graphs are defined [9,10] as the superpositions of the skeletons of the original and final heterocycles. (The dotted lines indicate the breaking and newly forming bonds; the thick lines indicate the skeletal bonds which are common to both the original and final rings. Such details of the structure as, for example, the annelated moiety enclosed in brackets in diagram V, are not given in the recyclization graph.) It is not difficult to see that diagram V exactly corresponds to the recyclization scheme we predicted earlier (Scheme 5 in [4]).

The observed reaction allows us to arrive at a previously unknown class of 5-aminoindolizines. Preliminary experiments have shown that a synthetic limitation of this reaction may be instability of the 5-aminoindolizines. Thus, the analogs of cation II achieved in [5] (containing a phenyl or *p*-bromophenyl residue in the 2 position) in reaction with secondary amines also lead to the corresponding indolizines. The compounds formed (giving a positive Ehrlich test), however, are extremely easily oxidized and cannot be isolated in pure form. The instability of π-rich heterocycles substituted by donor substituents is quite well known; this feature is also characteristic for indolizines. In the case of 5-aminoindolizine III, the stability of the compound is probably determined by the additional presence of an acceptor *p*-nitrophenyl group in the 2 position. We note that the use of other secondary amines in the reaction with cation II allows us to expand the range of 5-aminoindolizines obtained. Discussion of these reactions (and also the variation in nucleophilic agents) will be the subject of a separate report.

We would like to acknowledge the Russian Foundation for Basic Research (grant 96-03-32953), the Center for Basic Natural Science, St. Petersburg (grant 95-0-9.4-222), and the foundation Volkswagen Stiftung for financing our work.

REFERENCES

1. E. V. Babaev and I. A. Orlova, Khim. Geterotsikl. Soedin., No. 4, 569 (1997).
2. E. V. Babaev, S. V. Bozhenko, and D. A. Maiboroda, Izv. Rossk. Akad. Nauk, Ser. Khim., No. 11, 2298 (1995).
3. E. V. Babaev and S. V. Bozhenko, Khim. Geterotsikl. Soedin., No. 1, 141 (1997).
4. E. V. Babaev and N. S. Zefirov, Khim. Geterotsikl. Soedin., No. 10, 1564 (1996).
5. E. V. Babaev, A. V. Efimov, and D. A. Maiboroda, Khim. Geterotsikl. Soedin., No. 8, 1104 (1995).
6. E. V. Babaev, A. V. Efimov, D. A. Maiboroda, and K. Jug, Ann. (in press).
7. E. V. Babaev, V. N. Torocheshnikov, and S. I. Bobrovskii, Khim. Geterotsikl. Soedin., No. 9, 1235 (1995).
8. E. V. Babaev, K. Yu. Pasichnichenko, and D. A. Maiboroda, Khim. Geterotsikl. Soedin., No. 3, 397 (1997).
9. E. V. Babaev and N. S. Zefirov, Khim. Geterotsikl. Soedin., No. 6, 808 (1992).
10. E. V. Babaev, D. E. Lushnikov, and N. S. Zefirov, J. Am. Chem. Soc., **115**, 2416 (1993).