Chemistry of Heterocyclic Compounds, Vol. 30, No. 5, 1994

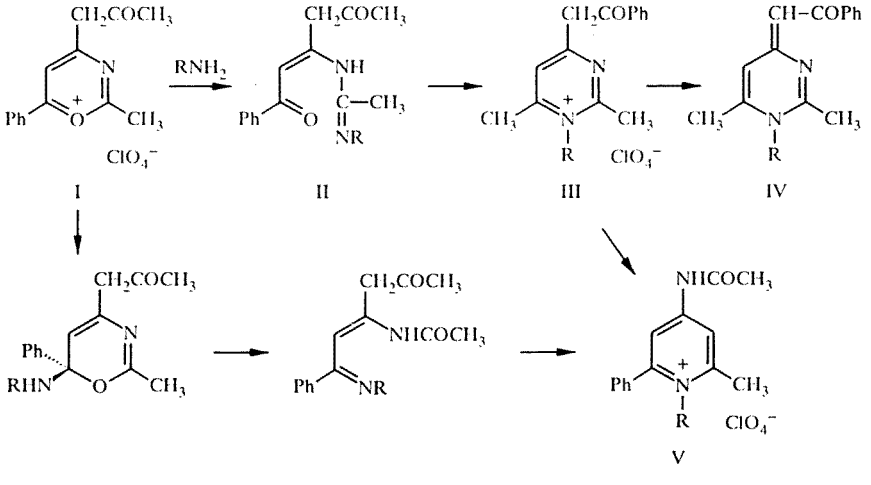
AMBIDENTATE REACTIVITY OF 3-AZAPYRYLIUM SYSTEMS IN NUCLEOPHILIC ATTACK REACTIONS

S. V. Borodaev, M. E. Kletskii, and N. V. Shibaeva

It has been shown that recyclization of 4-acylmethyl-3-azapyrylium salts under the influence of primary amines affords 4-(β-hydroxystyryl)pyrimidinium salts, which, upon further heating with the amine, are recyclized to form 4-acylaminopyridinium salts. It has been established that nucleophilic attack of 6-acylmethyl-substituted 3-azapyrylium salts in aqueous NaOH solution leads to functionally substituted pyridines. By means of MNDO quantum-chemical calculations with an accounting for solvation effects, in a continuum model, it has been shown that two directions of nucleophilic attack of the azapyrylium ring – at positions 2 and 6 – are equally probable.

In the chemistry of functionally substituted 3-azapyrylium salts, an important place is occupied by recyclization reactions that lead to new heterocyclic systems [1]. Interaction of the reactant with nucleophiles plays a decisive role in these reactions. Because of the lack of any reliable data on the site of nucleophilic attack, it has been difficult to arrive at any understanding of the mechanism of the chemical process taking place in the system. Indeed, from our point of view, the results of earlier studies [2], indicating preference for nucleophilic attack at position 6 of the 3-azapyrylium ring, from our point of view are not at all convincing. Those results were based entirely on an investigation of the structure of the final reaction products (thermodynamic control).

The potential energy surface of these systems has a far more complex multichannel structure than had been assumed previously. This conclusion is consistent with the formation of the salt III as the sole product from interaction of the perchlorate I with aromatic amines, which add at position 2 of the ring.



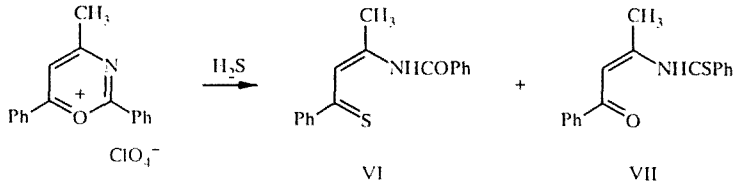
(1)

Such a direction of the reaction is a consequence of kinetic control, as thermodynamic control is inconsistent with rearrangement of the pyrimidinium perchlorates III to 4-acylaminopyridinium salts, which takes place upon prolonged refluxing (24 h) with primary amines.

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov State University, Rostov-on-Don 344010. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 697-700, May, 1994. Original article submitted April 18, 1994.

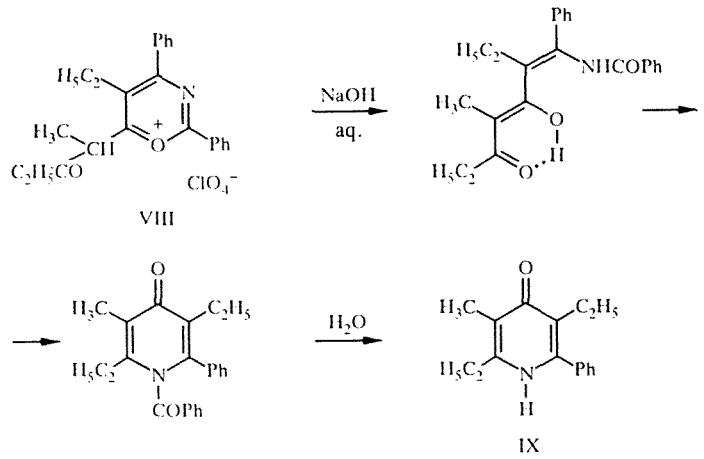
 0009-3122/94/3005-0612$12.50

We obtained the first convincing evidence of equal probabilities of nucleophilic attack at positions 2 and 6 in a study of the interaction of 2,6-diphenyl-4-methyl-3-azapyrylium perchlorate with H_2S, which yields the isomers VI and VII in a 2:1 ratio:



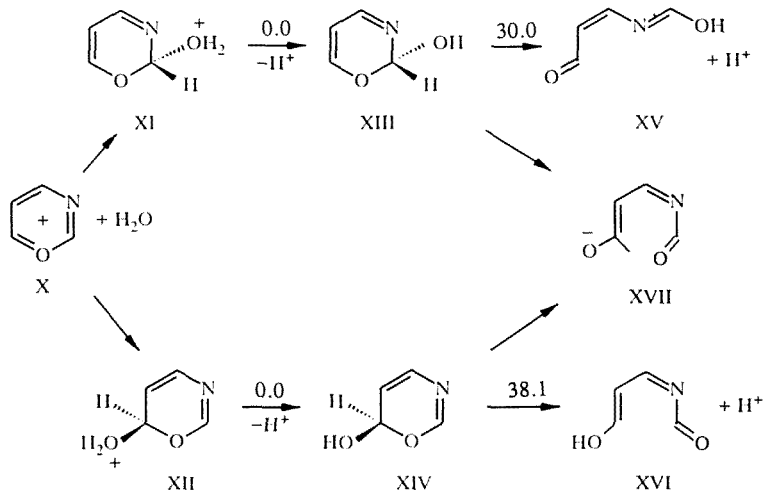
(2)

This result is in good agreement with many analogous examples that have been found for heteroanalogs of the 3-azapyrylium cation – namely, pyrimidines and their salts. An interesting conversion that we have found is the recyclization of the salt VIII to the difficulty accessible pyridones IX:



(3)

Since both directions of nucleophilic attack of the salt VIII (at positions 2 and 6) lead to exactly the same acyclic compound, it is extremely difficult to distinguish experimentally between the two reaction paths. With the aim of a more fundamental investigation of nucleophilic addition reactions of the type of (2) and (3), we carried out quantum-chemical calculations of the model reaction (4) by means of the semiempirical MNDO method [4]. Solvation effects were taken in account by means of a continuum model [5].



(4)

The quantum-chemical calculations predict that the hydroxonium ions XI (XII) will be formed in the first stage of the reaction. (The numbers written above the arrows denote the calculated magnitudes of the energy barriers in the individual stages.) The first stage is followed by an essentially barrierless deprotonation of the cations and cleavage of the rings of XIII (XIV) to form the structures XV (XVI). In addition, we found one other reaction channel on the potential energy surface of the system X: X + H_2O → XI (XII) → (XIII) (XIV) + H^+ → XVII + $2H^+$. Other reaction paths for cleavage of the azapyrylium ring, according to our calculations, are energetically less favorable.

Thus, our new experimental and calculated data indicate that, in contrast to earlier experimental results, equal probabilities exist for two directions of nucleophilic attack, at positions 2 and 6 of the azapyrylium ring.

EXPERIMENTAL

IR spectra were taken in white mineral oil on a Specord IR-75 instrument; PMR spectra were taken on a Tesla BS-487 C instrument (80 MHz), internal standard HMDS. The ratio of isomers VI and VII in the mixture obtained by the procedure of [2] was determined on the basis of relative intensities of CH_3 group signals in the PMR spectrum. The procedures used in the quantum-chemical calculations are described in [6].

Elemental analyses for C, H, Cl, and N matched the calculated values.

1-(p-Methoxyphenyl)-2,6-dimethyl-4-(β-hydroxystyryl)pyrimidium perchloride (III, $C_{21}N_{21}ClN_2O_6$). To a suspension of 10 mmoles of 2-methyl-4-acetonyl-6-phenyl-3-azapyrylium perchlorate (I) in 20 ml of dichloroethane, 1.3 g (10 mmoles) of p-anisidine was added, and the mixture was heated to boiling. After cooling, the precipitate was filtered off, recrystallized from acetic acid, and washed with ether; mp 251°C. IR spectrum, cm^{-1}: 1648, 1604, 1087. PMR spectrum, ppm (CF_3COOH): 1.80 (3H, s, 6-CH_3); 2.20 (3H, s, 2-CH_3); 3.53 (3H, s, OCH_3); 6.11 (1H, s, =CH); 6.63-7.78 (10H, m, Ar-H). Yield 65%.

1-(p-Methoxyphenyl)-2-methyl-4-acetylamino-6-phenylpyridinium perchloride (V, $C_{21}H_{21}ClN_2O_6$). A suspension of 2.16 g (5 mmoles) of the perchlorate III in 20 ml of ethanol with 0.65 g (5 mmoles) of p-anisidine was refluxed for 24 h. The alcoholic solution was diluted with 200 ml of ether; after 48 h, the precipitate was filtered off and recrystallized from a 10:1 mixture of ethyl acetate and isopropanol; mp 165°C. IR spectrum, cm^{-1}: 3275, 1727, 1623, 1580, 1100. PMR spectrum, ppm (CF_3COOH): 2.04 (5H, s, 2-CH_3 and CH_3CONH); 3.39 (3H, s, OCH_3); 6.33-7.3 (9H, m, Ar-H); 7.77-7.84 (for 1H, s, 3-H and 5-H); 9.20 (1H, s, NH). Yield 1.4 g (65%).

1-(p-Methoxyphenyl)-2,6-dimethyl-4-benzoylmethylene-1,4-dihydropyrimidine (IV, $C_{21}H_{20}N_2O_2$). A suspension of 5.5 mmoles of the pyrimidinium perchlorate III in 30 ml of benzene, with 3 g of triethylamine, was refluxed for 20 min. The benzene solution was separated by decantation from the oily precipitate of triethylamine perchlorate; the solution was removed under vacuum, and the residue was recrystallized from toluene; mp 220°C. IR spectrum, cm^{-1}: 1644, 1585, 1567. PMR spectrum, ppm ($CDCl_3$): 1.96 (3H, s, 6-CH_3); 2.33 (3H, s, 2-CH_3); 3.53 (3H, s, OCH_3); 6.31 (1H, s, =CH); 6.85-8.0 (9H, m, Ar-H); 8.08 (1H, s, =CH). Yield 85%.

2,4-Diphenyl-5-ethyl-6-(1-methylbutan-2-one-1-yl)-3-azapyrylium perchlorate (VIII, $C_{23}H_{24}ClNO_6$). To a solution of 1.48 g (10 mmoles) of butyrophenone and 2.1 g (20 mmoles) of benzonitrile in 6.5 g (50 mmoles) of propionic anhydride, there was added a mixture of 3.9 g (30 mmoles) of propionic anhydride and 1 ml (10 mmoles) of 70% $HClO_4$ (cooled while mixing); the final mixture was allowed to stand at room temperature for 3-6 days. The precipitate was filtered off and washed with a small quantity of chloroform and then with ether; mp 157-159°C. IR spectrum, cm^{-1}: 1728, 1595, 1567, 1087 cm^{-1}. PMR spectrum, ppm (100 MHz, Ph−NO_2-d_5): 1.16 (3H, t, $CH_2\underline{CH_3}$), J = 7 Hz; 1.36 (3H, t, $CH_2\underline{CH_3}$, J = 7 Hz); 2.09 (3H, d, CH_3, J = 7 Hz); 3.04 (2H, g $\underline{CH_2}CH_3$, J = 7 Hz); 3.28 (2H, g, $\underline{CH_2}CH_3$, J = 7 Hz); 5.16 (1H, g, CH, J = 7 Hz); 7.3-8.60. (10H, m, Ar−H). Yield 1.9 g (43%).

2-Phenyl-3,6-diethyl-5-methylpyridone-4(1H) (IX, $C_{16}H_{19}NO$). A mixture of 4.46 g (10 mmoles) of the 3-azapyrylium perchlorate VIII, 100 ml of ether, and 100 ml of a 10% aqueous NaOH solution was stirred at room temperature for 4-5 h. The precipitate was filtered off and recrystallized from toluene; mp 238°C. IR spectrum, cm^{-1}: 2360-2800, 1625, 1604, 1591. PMR spectrum, ppm (100 MHz, $CDCl_3$): 0.86 (3H, t, $CH_2\underline{CH_3}$, J = 7 Hz); 1.2 (3H, t, $CH_2\underline{CH_3}$, J = 7 Hz); 1.84 (3H, s, CH_3); 2.14 (2H, g, $\underline{CH_2}CH_3$, J = 7 Hz); 2.74 (2H, g, $\underline{CH_2}CH_3$, J = 7 Hz); 7.20 (5H, s, Ar−H); 10.88 (1H, s, NH).

REFERENCES

1. N. V. Shibaeva, S. V. Borodaev, I. A. Yudilevich, A. P. Knyazev, A. D. Dubonosov, A. I. Pyshchev, and S. M. Luk'yanov, Khim. Geterotsikl. Soedin., No. 2, 265 (1991).
2. R. R. Shmidt, Synthesis, **7**, 333 (1971).
3. C. Henk and H. C. van der Plas, Tetrahedron, **41**, 237 (1985).
4. M. J. S. Dewar and W. Thiel, J. Am. Chem. Soc., **99**, 4899 (1977).
5. A. J. Duben and S. Miertus, Chem. Phys. Lett., **88**, 395 (1982).
6. M. E. Kletskii, S. V. Borodaev, N. V. Shibaeva, A. I. Pyshchev, O. V. Zubkova, S. M. Luk'yanov, and R. M. Minyaev, Zh. Org. Khim., **27**, 2479 [year not given].