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On the Structure of Reaction Products of 2,3-Disubstituted *N*-Phthalimidoaziridines with Dimethyl Acetylenedicarboxylate

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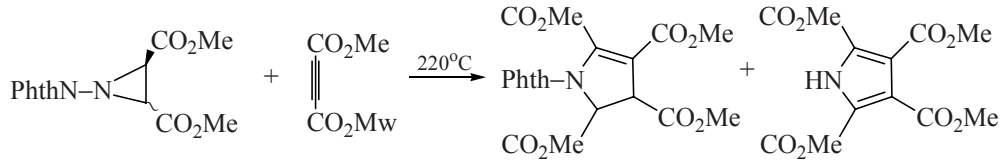
Abstract—



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1,3-Dipolar cycloaddition of azomethine ylides to various unsaturated compounds is widely used for nitrogen heterocycles construction [1, 2]. One of the general methods for azomethine ylides generation is a thermally or photochemically induced cleavage of strained aziridine cycle at the C–C bond. However *N*-aminoaziridine derivatives almost were not involved in such reactions. The articles of Person et al. [3, 4] on the reactions between several three- and tetrasubstituted *N*-phthalimidoaziridines and one of the most active dipolarophiles, DMAD (dimethyl acetylenedicarboxylate), were an exception. Reactions there described gave *N*-phthalimidosubstituted 3-pyrrolines *ex ante* but their spatial structure was not established.

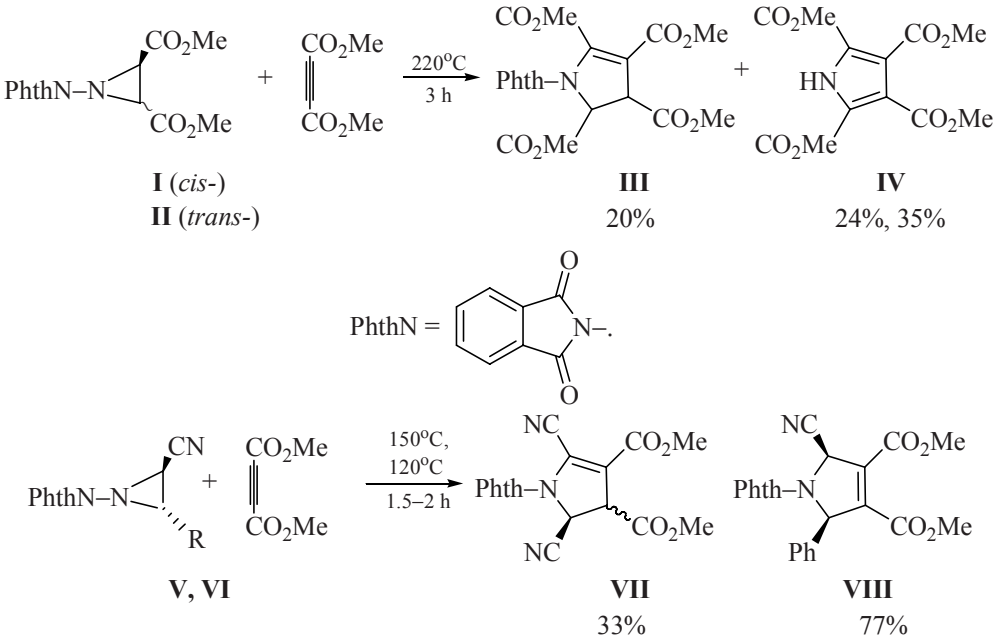
Due to a possible convenience of this reaction for the synthesis of five-membered unsaturated *N*-aminoheterocycles the main goal of this research was an investigation of its applicability for less substituted *N*-aminoaziridine derivatives and an attempt to elucidate its stereochemical features. To this end we have carried out thermolysis in the presence of DMAD of several *N*-phtalimidoaziridines with electron-withdrawing groups CN, COOMe facilitating the aziridine cleavage.

Starting *N*-phthalimidoaziridines **I, II, V,** and **VI** were synthesized by *N*-aminophthalimide oxidation in the presence of the corresponding olefins using a standard procedure [5]. Their thermolysis in the presence of DMAD was carried out in sealed ampoules and/or in a hermetically closed thermostable vial with the 150–300% excess of dipolarophile. Benzene (aziridines **V** and **VI**) and more high-boiling chlorobenzene (aziridines **I** and **II**) were used as solvents. The optimal temperature for the reaction products formation was 220°C (for aziridines **I** and **II**), 150°C (for aziridine **V**), and 120°C (for aziridine **VI**), considerably higher than for three- and tetrasubstituted compounds [3, 4]. It is in agreement with the reaction conditions becoming more stringent with the decrease in the number of substituents stabilizing the intermediate azomethine ylide.

The formation of products obtained in all cases may be understood as a result of 1,3-dipolar cycloaddition of the corresponding azomethine ylides to DMAD: 2-pyrrolines **III** and **VII**, 3-pyrroline **VIII,** and pyrrole **IV**. An assortment of products was much wider than found earlier [3, 4]. 3-Pyrrolines initially formed after cycloaddition appear to undergo further transformations under the severe reaction conditions: A proton migration leading to 2-pyrrolines and/or a loss of phthalimide molecule leading to pyrrole.

The formation only of products mentioned was confirmed by ^{1}H NMR spectra of the reactions mixtures just after heating. The composition of compounds **III, IV, VII,** and **VIII** is confirmed by elemental analysis data; their structures agree with ^{1}H and ^{13}C NMR spectra and mass-spectra.

A special feature of all *N*-phthalimidopyrrolines obtained is a retarded rotation around the N–N bond in the NMR time scale. A conformation with a



R = CN (**V**), R = Ph (**VI**).

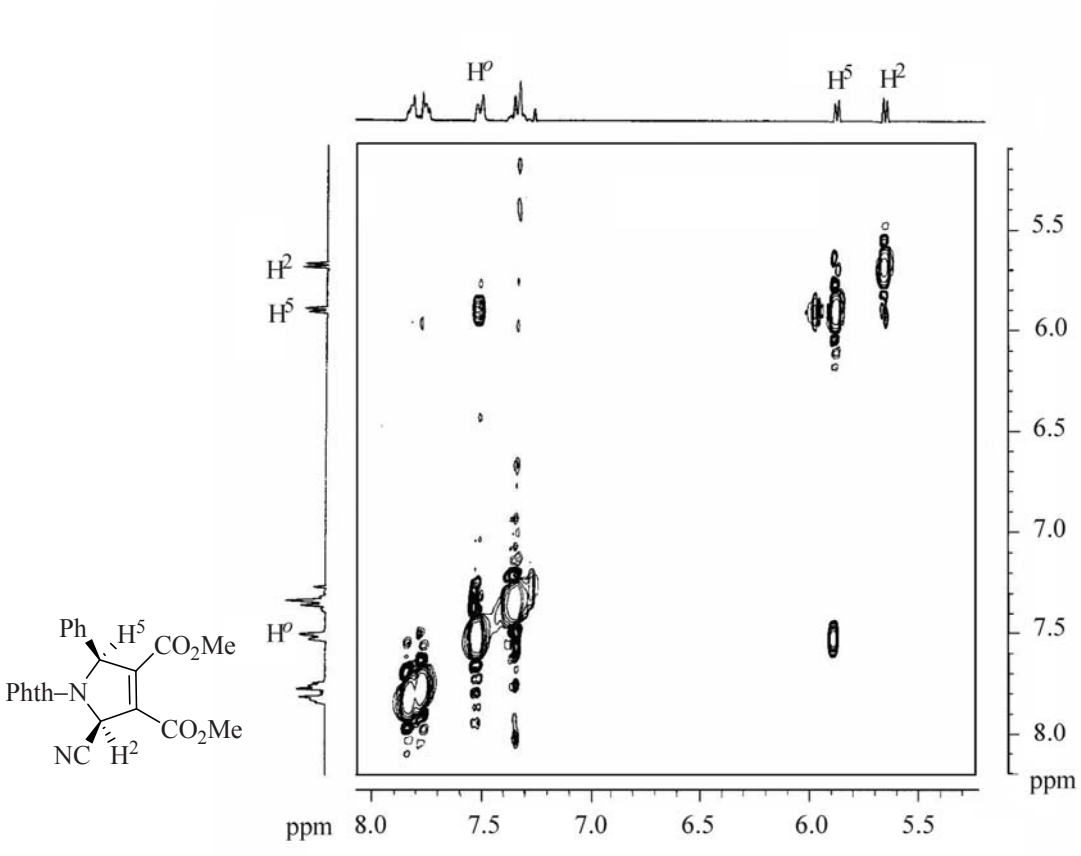
perpendicular arrangement of phthalimide and pyrroline fragments is considerable more stable than others and appears to be a primary form. That is why in ^{13}C NMR spectra of 2-pyrrolines **III, VII** appeared a double set of carbon signals of phthalimide group. For 3-pyrroline **VIII** a hindered rotation of phthalimide group becomes apparent in ^{13}C NMR spectra in a widening of $C^{a,b}$ signals and disappearance of imide carbon signals.

The major product of interaction between DMAD and stereoisomeric aziridines **I, II** in both cases is tetramethyl pyrroletetracarboxylate (35% with aziridine **I**, 42% with aziridine **II**), its physicochemical characteristics are in full agreement with literature data [6]. Alongside this compound 2-pyrroline **III** was isolated in 20% yield from the reaction mixture of the thermolysis of aziridine **I** in the presence of DMAD. It is worth mentioning that a single isomer **III** was formed but the complete establishment of its structure was difficult. In the case of aziridine **V** an inseparable mixture of stereoisomeric 2-pyrrolines **VII** was obtained. The ratio of the stereo- isomers spectrally measured was ~2:1, however it was difficult to determine on the base on vicinal spin-coupling constants in the five-membered cycles which of the isomers prevailed in the mixture. A position of the double bond in adducts **III, VII** was easily defined without additional spectral methods. No elements of symmetry were found in these molecules that leds to appearance of two doublets of protons of pyrrolidine cycle with the constants $^3J(H^4–H^5) > 8$ Hz in their ^1H NMR spectra. In an alternative structure of 3-pyrroline both heterocyclic protons would give one singlet signal.

Remarkable feature of compound **VIII** is an unexpectedly great value $^4J(H^2–H^5) = 5.1$ Hz. Low NOE between these protons (see figure) demonstrates their arrangement on one side of five-membered cycle. It corresponds to concerned cycloaddition to DMAD of *cis*-azometine ylide formed from *trans*-aziridine **VI** in agreement with the rules of preservation of orbital symmetry under thermal conditions.

EXPERIMENTAL

NMR spectra were recorded on Bruker DPX-300 spectrometer (300.13 MHz for ^1H and 75.47 MHz for ^{13}C) in $CDCl_3$ or DMSO-d_6 and were referenced to the residual proton signals of the solvent (δ_H 7.26 and 2.50 ppm) and the solvent carbon signals (δ_C 77.16 and 39.52 ppm, respectively). Elemental analyses were performed on anautomatic Hewlett–Packard CHN–analyzer HP–185B. Mass spectra were measured on a Finnigan MAT INCOS–50 spectrometer in the positive-ion mode using electron impact (ionizing voltage 70 eV, direct input). Thin-layer chromato-



NOESY spectrum of compound **VIII**.

graphy for reaction monitoring and purity control was performed on ALUGRAM SILG/UV_{254} plates using UV visualization. *N*-aminophthalimide was obtained by method [7].

Tetramethyl 2.3-dihydro-1*H*-pyrrole-2.3.4.5-tetracarboxylate (III). A solution of dimethyl *rel*-(2*R*,3*S*)-1-phthalimidoaziridine-2.3-dicarboxylate **I** (304 mg, 1 mmol) and dimethyl acetylenedicarboxylate (0.37 ml, 426 mg, 3 mmol) in anhydrous benzene (10 ml) in a sealed ampoule was heated on an oil bath at 220°C for 3 h. After cooling to r.t. the solvent was removed in vacuo. The residue was separated by column chromatography on silica eluting with a mixture dichloromethane:diethyl ether = 10:1. Yield of tetramethyl 1*H*-pyrrole-2.3.4.5-tetracarboxylate **IV** is 125 mg (42%); yield of compound **III** is 90 mg (20%), m.p. 166–168°C. ^{1}H NMR, $CDCl_3$, δ, ppm (*J*, Hz): 3.71 s (3H, MeO), 3.74 s (3H, MeO), 3.75 s (3H, MeO), 3.82 s (3H, MeO), 4.43 d (1H, ^3J = 9.4), and 4.97 d (1H, ^3J = 9.4) $H^{2,3}$, 7.70–7.95 m (4H, PhthN). ^{13}C NMR, $CDCl_3$, δ, ppm: 48.80 (C^3); 52.24, 53.17, 53.29, and 53.37 (4MeO); 68.21 (C^2), 109.18 (C^4), 124.11, and 124.43 ($C^{b,b'}$), 129.44 and 129.85 ($C^{a,a'}$), 135.01, and 135.19 ($C^{c,c'}$), 146.21 (C^5); 160.29, 162.99, 168.25, and 170.28 (4COO). EI–MS, *m/z* (I_{rel}, %): 446(6), [M^+], 387(15), 355(100), 299(15), 268(17), 236(21), 147(13), 104(15), 76(15), 59(15). Found, %: C 53.82, H 4.14, N 6.27. $C_{20}H_{18}N_2O_{10}$. Calculated, %: C 53.82, H 4.06, N 6.28.

Tetramethyl 1*H*-pyrrole-2.3.4.5-tetracarboxylate (IV). A solution of dimethyl *rel*-(2*R*,3*R*)-1-phthalimidoaziridine-2.3-dicarboxylate **II** (304 mg, 1 mmol) and dimethyl acetylenedicarboxylate (0.19 ml, 213 mg, 1.5 mmol) in anhydrous benzene (15 ml) in a sealed ampoule was heated on an oil bath at 220°C for 3 h. After cooling to r.t. the solvent was removed in vacuo. The residue was separated by thin-layer chromatography on silica eluting with mixture dichloromethane:diethyl ether = 10:1. Yield 150 mg (50%), colorless crystals, mp 123–125°C (127–128°C [6]). ^{1}H NMR, $CDCl_3$, δ, ppm (*J*, Hz): 3.89 s (6H, 2MeO), 3.92 s (6H, 2MeO), 10.00 br.s (1H, NH). ^{13}C NMR, $CDCl_3$, δ, ppm: 52.08 and 52.26 (4MeO), 120.58 ($C^{3,4}$), 122.75 ($C^{2,5}$), 159.41, and 163.45 (4COO).

Dimethyl 2.5-dicyano-1-phthalimido-2.3-dihydro-1*H*-pyrrole-3.4-dicarboxylate (VII) (the ratio of stereo isomers ~1.8:1). A solution of aziridine **V** (240 mg, 1 mmol) and dimethyl acetylenedicarboxylate (0.37 ml, 426 mg, 3 mmol) in anhydrous benzene (12 ml) in a hermetically closed thermo stable vial was heated on an oil bath at 150°C for 1.5 h. After cooling to r.t. the solvent was removed in vacuo. The residue was separated by column chromatography on silica eluting with mixture hexane:dichloromethane:diethyl ether = 2:1:0 up to 0:2:1. Yield of the mixture of two stereoisomeric esters **VII** (the ratio ~1.8:1) 125 mg (33%). ^{1}H NMR, $CDCl_3$, δ, ppm (*J*, Hz): 3.88 s (MeO of the main isomer) and 3.90 s (MeO of the minor isomer), 6H in sum; 4.45 d (^3J = 8.3, H^3 of the main isomer) and 4.51 d (^3J = 11.6, H^3 of the minor isomer), 1H in sum; 5.17 d (^3J = 8.3, H^2 of the main isomer) and 5.23 d (^3J = 11.6, H^2 of the minor isomer), 1H in sum; 7.87–8.00 m (4H, PhthN). ^{13}C NMR of the mixture of isomers, $CDCl_3$, δ, ppm: 49.59 and 51.18 ($2C^2$); 53.06, 53.89 and 54.05 (4MeO); 56.87 and 57.21 ($2C^3$); 108.29, and 112.92 ($2C^4$); 114.48, 117.91, and 118.58 (4CN); 124.61, 124.70, 125.13, and 125.19 ($4C^b$); 128.85, 128.93, 129.30, and 129.43 ($4C^a$); 129.52 and 130.54 ($2C^5$); 135.60, 135.70, 135.96, and 136.05 ($4C^c$); 160.58, 160.61, 162.58, 163.21, 164.76, 165.57, 166.66, and 167.76 (4CON and 4COO). EI–MS, *m/z* (I_{rel}, %): 380(8) [M^+], 353(11), 322(29), 321(44), 289 (100), 202(19), 148(42), 147(60), 130(25), 104 (77), 90(27), 76(64), 59(31), and 50(23). Found, %: C 56.82, H 3.44, N 14.83. $C_{18}H_{12}N_4O_6$. Calculated, %: C 56.85, H 3.18, N 14.73.

Dimethyl 2-cyano-5-phenyl-1-phthalimido-2.5-dihydro-1*H*-pyrrole-3.4-dicarboxylate (VIII). A solution of aziridine **VI** (289 mg, 1 mmol) and dimethyl acetylenedicarboxylate (0.37 ml, 426 mg, 3 mmol) in anhydrous benzene (12 ml) in a hermetically closed thermo stable vial was heated on an oil bath at 120°C for 2 h. After cooling to r.t. the solvent was removed in vacuo. The oily residue was diluted with diethyl ether (2 ml). On the next day a precipitate was collected by filtration and washed with diethyl ether. Yield 307 mg (71%), colorless crystals, mp 163°C. ^{1}H NMR, $CDCl_3$, δ, ppm (*J*, Hz): 3.64 s (3H, MeO), 3.88 s (3H, MeO), 5.67 d (1H, ^4J = 5.1) H^2, 5.89 d (1H, ^4J = 5.1) H^5, 7.32–7.39 m (3H, $H^{m,p}$), 7.50–7.53 m (2H, H^o), 7.74–7.85 m (4H, PhthN). ^{13}C NMR, $CDCl_3$, δ, ppm: 52.90 and 53.13 (2MeO); 58.58 (C^2), 74.37 (C^5); 115.81 (CN), 124.05 br.s. (C^b), 124.56 (C^3), 128.15, and 128.82 ($C^{m,o}$); 129.52 (C^p), 129.63 br.s. (C^a), 134.59 (C^i), 135.00 (C^c); 147.02 (C^4), 160.26 and 162.64 (COO). Carbon imide signals are not found due to strong widening. EI–MS, *m/z* (I_{rel}, %): 431(2) [M^+], 284(70), 253(100), 221(19), 195(10), 147(30), 140 (13), 104(36), and 76(28). Found, %: C 64.36, H 4.15, N 9.79. $C_{23}H_{17}N_3O_6$. Calculated, %: C 64.04, H 3.94, N 9.74.

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REFERENCES

1. Lown, J.W., *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed., New York: Wiley, 1984, p. 653.
2. Harwood, L.M and, Vickers, R.J., *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Padwa, A., Ed., Pearson W.H. Hoboken: Wiley. 2003, p. 169.
3. Person, H., Luanglath, K., Baudru, M., and Foucaud, A., *Bull. Soc. Chim*., 1976, nos. 11–12, p. 1989.
4. Charrier, J., Foucaud, A., Person, H., and Loukakou, E., *J. Org. Chem*., 1983, vol. 48, p. 481.
5. Gladstone, W.A.F. and Norman, R.O.C., *J. Chem. Soc., C*., 1966, p. 1536.
6. Metra, P. and Hamelin, J., *J. Chem. Soc., Chem. Commun*., 1980, vol. 21, p. 1038.
7. Drew, H.D.K. and Hatt, H.H., *J. Chem. Soc.*, 1937, p. 16.