Chemistry of Heterocyclic Compounds, Vol. 44, No. 7, 2008

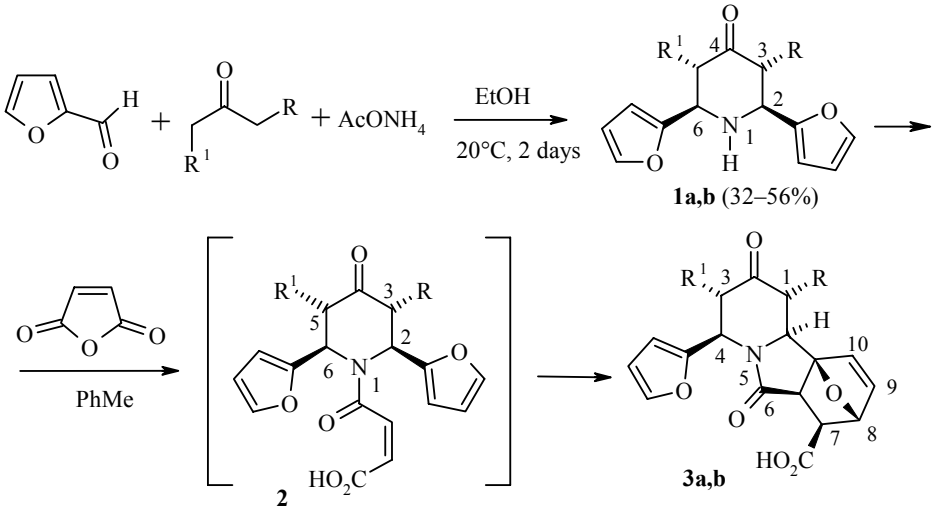
LETTERS TO THE EDITOR

THE FIRST SYNTHESIS OF 8,10a-EPOXYPYRIDO[2,1-*a*]ISO-INDOLO-7-CARBOXYLIC ACIDS

F. I. Zubkov[1], V. P. Zaytsev[1], E. V. Nikitina[1], R. S. Borisov[1], I. K. Airiyan[1], K. F. Turchin[2], and A. V. Varlamov[1]

Keywords: 2,6-difurylpiperidinone-4, pyrido[2,1-*a*]isoindole, furfurylamine, [4+2] intramolecular cyclocondensation, Diels-Alder reaction.

In our study of the cyclocondensation of derivatives of unsaturated acids with heterocycles containing furfurylamine fragment [1], we turned our attention to the reaction of 2,6-difurylpiperidinone-4 **1** with maleic anhydride [2]:



3 a R = R[1] = Me (86%); **b** R[1] = H, R = Me (76%)

It was established that the reaction of maleic anhydride with piperidone **1** began even at room temperature, but the maximum yields of the adducts **3** were obtained with short boiling of the solution in toluene. By analogy with our previous work [1, 3], the nitrogen atom is initially acylated with subsequent intramolecular [4+2] cycloaddition into the maleinamides **2**.

---

[1]Peoples' Friendship University of Russia, Moscow 117198; e-mail: fzubkov@sci.pfu.edu.ru. [2]Center for Chemistry of Drugs, All-Russian Institute for Chemical and Pharmaceutical Research, Moscow 119815, Russia; e-mail: turchin@drug.org.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, 1101-1103, July 2008. Original article submitted April 17, 2008.

As a large number of examples have shown [4], thermal intramolecular Diels-Alder reactions in N-alkenyl-substituted furfurylamines proceed stereospecifically to give products of *exo* addition, **3**. In the case of the asymmetrically substituted piperidone, **1b**, unexpectedly for us the process was highly regioselective. In the intermediate maleinamide **2b** the unsaturated unit reacted with the furan ring at position 2 of the piperidine ring to form a single regioisomer **3b**.

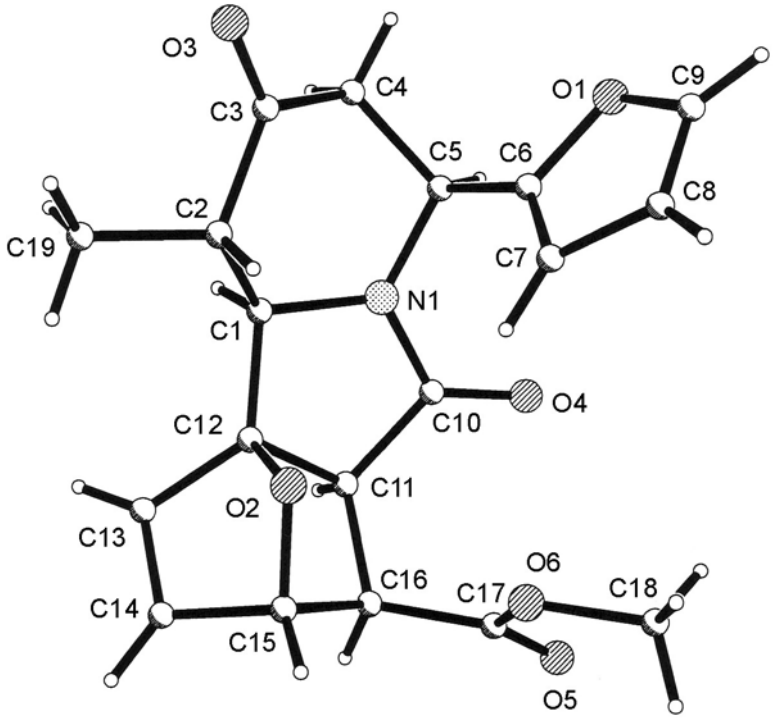


Fig. 1. Spatial Structure of the Methyl Ester of Acid **3b.**

In order to determine the direction of the cycloaddition unambiguously acid **3b** was esterified with methanol and the spatial structure of the methyl ester (1*R*,4R*,6aR*,7S*,8R*,10aS*,10bR**)-4-(furyl-2)-1-methyl-2,6-dioxo-1,3,4,6,6*a*,7,8,10*b*-octahydro-2H-8,10*a*-epoxypyrido[2,1-*a*]isoindolo-7-carboxylic acid was determined by X-ray crystallography.

Reagents from Acros Organics were used without further purification. IR spectra of KBr tablets were recorded on an Infralum FT-801 Fourier spectrometer. ^{1}H NMR spectra of DMSO-d_6 solutions were recorded on a Bruker WH-400 (400 MHz) at 30°C with the residual proton signals of the solvent as internal standard (2.49 ppm, DMSO-d_6). ^{13}C NMR spectra of DMSO-d_6 solutions were recorded on a Bruker Advance 600 (100 MHz), with the central signal of the DMSO-d_6 multiplet (39.96 ppm) as internal standard. Assignments in the spectra were based on HMQC and COSY-45 two-dimensional correlation experiments. Mass spectra (EI, 70 eV) were recorded with an HP MS 5988 instrument with direct insertion of the sample into the ion source.

8,10*a*-Epoxypyrido[2,1-*a*]isoindolo-7-carboxylic acids 3 (General Method). A mixture of piperidone **1** (1.5 mmol) and maleinic anhydride (1.5 mmol) in toluene (15 ml) was boiled for 4h and then left overnight, The precipitated crystals were filtered off, washed with ether, and dried in air. The Diels-Alder adducts **3** were obtained as colorless powders. The characteristics of adduct **3a** are: mp 237-238°C. IR spectrum, ν, cm^{-1}: 1677 (N–C=O), 1730 and 1713 (O–C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (3H, d, *J* = 6.9, 1-CH_3); 1.31 (3H, d, *J* = 7.7, 3-CH_3); 2.63 (1H, dq, *J* = 6.9, *J* = 12.2, H-1); 2.95 (1H, dq, *J* = 7.7, *J* = 2.3, H-3), 2.57 (1H, d, *J* = 9.2, H-6a); 2.99 (1H, d, *J* = 9.2, H-7); 4.58 (1H, d, *J* = 12.2, H-10b); 4.93 (1H, br. d, *J* = 2.3, H-4); 5.12 (1H, d, *J* = 1.7, H-8); 6.46 (1H, dd, *J* = 5.7, *J* = 1.7, H-9); 6.59 (1H, d, *J* = 5.7, H-10); 6.44 (1H, dd, *J* = 0.8,

J = 3.2, H-β Fur); 6.28 (1H, dd, J = 1.8, J = 3.2, H-β Fur); 7.50 (1H, dd, J = 1.8, J = 0.8, H-α Fur) . ^{13}C NMR spectrum, δ, ppm: 210.9, 173.6, 171.2, 153.2, 142.8, 136.8, 135.7, 110.8, 108.0, 90.7, 81.5, 57.0, 52.5, 51.1, 46.9, 45.3, 43.9, 17.1, 10.4. Mass spectrum, *m/z* (I_{rel}, %): 357 $[M]^+$ (13), 258 (14), 243 (9), 242 (60), 221 (11), 203 (20), 177 (14), 176 (100), 175 (16), 174 (14), 162 (11), 148 (8), 135 (16), 122 (24), 108 (41), 107 (16), 99 (9), 94 (10), 80 (10), 79 (27), 77 (14). Found, %: C 63.65; H 5.41; N 3.83. $C_{19}H_{19}NO_6$. Calculated, %: C 63.86; H 5.36; N 3.92.

Adduct 3b. Mp 219°C. IR spectrum, ν, cm^{-1}: 1658 (N–C=O), 1711 and 1737 (O–C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.99 (3H, d, J =6.9, 1-CH_3); 2.49 (1H, dq, J =6.9, J = 11.7, H-1); 2.56 (1H, d, J = 9.3, H-6a); 2.76 (1H, dd, J = 6.1, J = 16.6, H-3A); 2.97 (1H, d, J = 9.3, H-7); 3.28 (1H, dd, J = 1.9, J = 16.6, H-3B); 4.62 (1H, br. dd, J = 1.9, J = 6.1, H-4); 5.11 (1H, d, J = 1.7, H-8); 5.18 (1H, d, J = 11.7, H-10b); 6.46 (1H, dd, J =5.7, J = 1.7, H-9); 6.60 (1H, d, J = 5.7, H-10); 6.34 (1H, dd, J = 1.0, J = 3.4, H-β Fur); 6.27 (1H, dd, J = 1.8, J = 3.4, H-β Fur); 7.50 (1H, dd, J =1.8, J = 1.0, Hz Fur). Mass spectrum, *m/z* (I_{rel}, %): 343 $[M]^+$ (24), 244 (26), 235 (9), 228 (62), 207 (7), 189 (17), 176 (24), 162 (100), 148 (7), 135 (39), 122 (45), 108 (80), 99 (27), 94 (88), 79 (37), 65 (56), 55 (19), 45 (11), 39 (40). Found, %: C 63.96; H 4.85; N 4.19. $C_{18}H_{17}NO_6$. Calculated, %: C 62.97; H 4.97; N 4.08.

This work was carried out with a financial grant, of Russian Foundation for Basic Resarch, grant 07-03-00083.

REFERENCES

1. A. V. Varlamov, E. V. Boltukhina, F. I. Zubkov, E. V. Nikitina, and K. F. Turchin, *J. Heterocycl. Chem.,* **43**, 1479 (2006).
2. S. Z. Vatsadze, Yu. V. Krainova, M. A. Kovalkina, and N. V. Zyk, *Khim. Geterotsikl. Soedin.,* 1370 (2000). [*Chem. Heterocycl. Comp.,* **36**, 1185 (2000)].
3. F. I. Zubkov, E. V. Boltunkhina, K. F. Turchin, R. S. Borisov, and A. V. Varlamov, *Tetrahedron,* **61,** 4099 (2005).
4. E. V. Boltukhina, F. I. Zubkov, and A. V. Varlamov, *Khim. Geterotsikl. Soedin.,* 1123 (2006). [*Chem. Heterocycl. Comp.,* **42**, 971 (2006)].