Chemistry of Heterocyclic Compounds, Vol. 45, No. 7, 2009

SYNTHESIS OF THE NEW HETEROCYCLIC SYSTEM, INDOLO[2,1-*b*]BENZOXAZINE

V. A. Osyanin[1]* and Yu. N. Klimochkin[1]

The previously unknown heterocyclic system, indolo[2,1-b][1,3]benzoxazine, has been synthesized by condensation of iodomethylates of 2-[(dimethylamino)methylphenols] and 2-bromomelatonins. The highly reactive o-methylenequinone is proposed as an intermediate.

Keywords: 2-bromomelatonins, indolo[2,1-*b*][1,3]benzoxazines, iodomethylates of 2-[(dimethylamino)-methyl]phenols, *o*-methylenequinones.

The high biological activity of melatonin [1], a series of derivatives of pyrrolo[2,1-*b*]benzoxazines [2], with antibacterial activities, and 3,4-dihydro[1,3]oxazino[3,2-*a*]indole [3,4], which is a selective antagonist of the 5-HT_4 receptor, stimulate the synthesis of benzannelated analogs of these heterocyclic systems.

In developing methods for the construction of condensed systems based on *o*-methylenequinones [5, 6] we proposed a simple one-step method for the preparation of substituted indolo[2,1-*b*][1,3]benzoxazines **1-3** which included the interaction of 2-bromo- and 2,4-dibromomelatonins with iodomethylates of 2-[(dimethylamino)methyl]phenols on boiling in DMF in the presence of K_2CO_3.

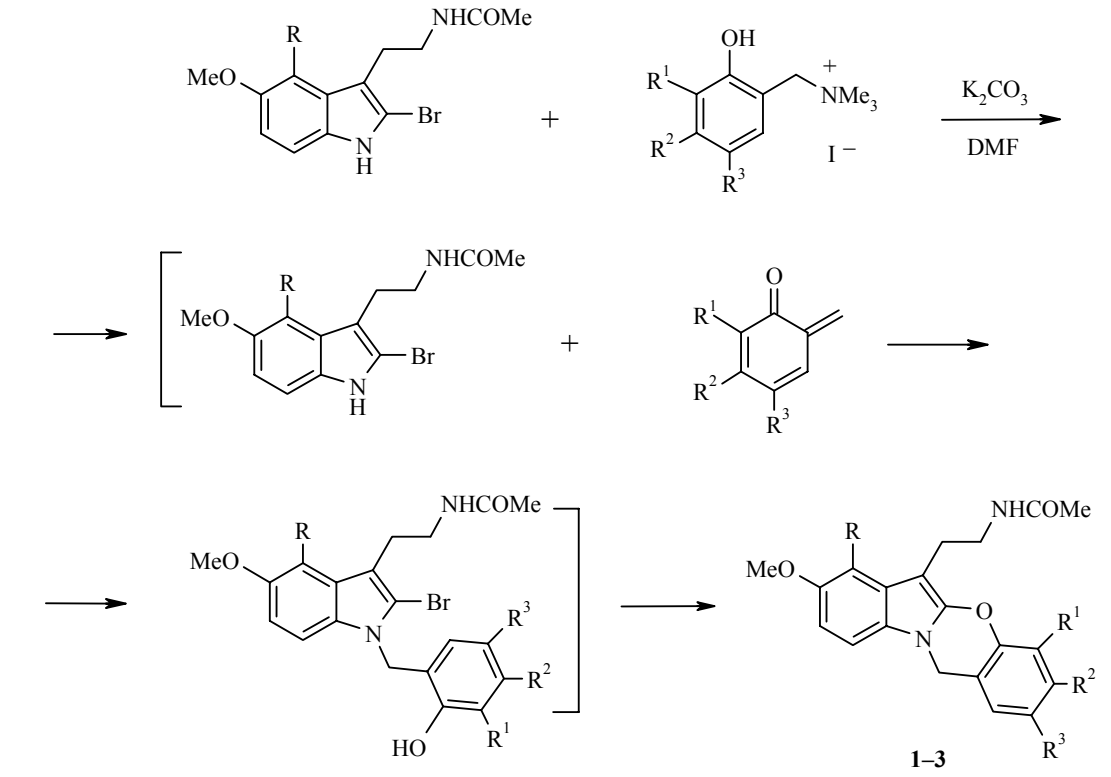
The reaction proceeds *via* the intermediate formation of *o*-methylenequinone [7] which alkylates the bromomelantonin molecule at the nitrogen atom with formation of a substituted 2-(1H-indol-1-ylmethyl)phenol, which underwent further cyclization with evolution of HBr molecules.

The IR spectra of compounds **1-3** contain NH absorption bands in the 3310-3302 region and carbonyl absorptions at 1647-1639 cm^{-1}. In the ^1H NMR spectra the protons of the methylene group are shifted to weak field and are found at 5.05-5.16 ppm, which indicates that alkylation of 2-bromomelatonin occurs at the nitrogen atom [8, 9] and not at the C-3 atom which would lead to the isomeric 10*b*,11-dihydrochromeno-[2,3-*b*]indoles. In the mass spectrum a peaks are present corresponding to the loss of the acetamide molecule from the molecular ion as a result of a MacLafferty rearrangement, and the fragment ion of $[M-CH_2NHCOMe]^+$ resulting from decomposition at the β-bond relative to the nitrogen atom. In addition, there are intense peaks resulting from retro-Diels-Alder decomposition of the oxazines ring.

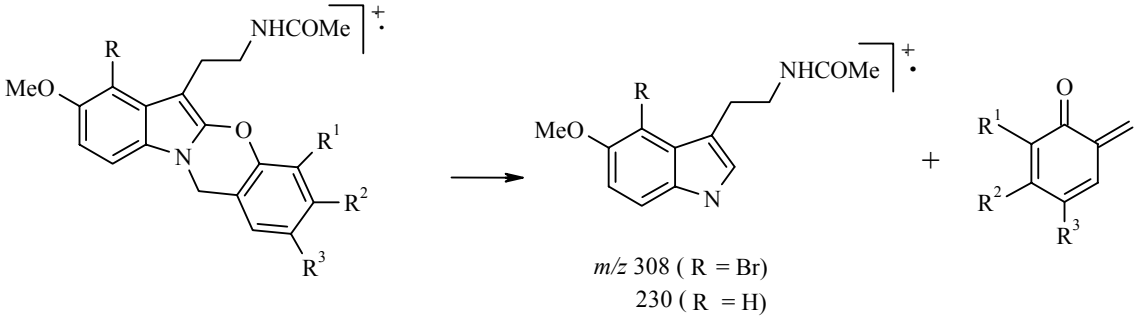
* To whom correspondence should be addressed, e-mail: orgchem@samgtu.ru.

[1]Samara State Technical University, Samara 443100, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, 1050-1053, July, 2009. Original article submitted September 16, 2008.



1 R = R^1 = R^2 = H, R^3 = OMe; **2** R = Br, R^1 = H, R^2 = R^3 = Me,
3 R = Br, R^1 = 1-adamantyl, R^2 = H, R^3 = Me



m/z 308 (R = Br)
230 (R = H)

EXPERIMENTAL

IR spectra of KBr tablets were recorded with a Shimadzu FTIR-8400S spectrometer. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker AM 300 (300 MHz) instrument, and mass spectra were recorded with a Finnigan Trance DSQ chromato-mass spectrometer with direct injection and an ionization energy of 70 eV. Elemental analyses were carried out with a EuroVector EA-300 automatic CHNS analyzer.

2-bromomelatonin was obtained according the method in [10], 2,4-bromomelatonin – in [1]. Initial 2-[(dimethylamino)methyl]phenols iodomethylates were synthesized by aminomethylation of the corresponding phenols under Mannich reaction conditions [1] with subsequent quaternization by methyl iodide.

N-[2-(2,8-Dimethoxy]-12H-indolo[2,1-*b*][1,3]benzoxazin-6-yl)ethyl]acetamide (1). A mixture of 2-bromomelatonin (1.0 g, 3.2 mmol), iodomethylate of 2-[(dimethylamino)methyl]-4-methoxyphenol (1.07 g, 3.3 mmol), and K_2CO_3 (4 g, 29 mmol) in DMF (20 ml) was boiled with stirring in an atmosphere of argon until evolution of trimethylamine ceased (~ 4 h). The mixture was cooled, poured into water, the precipitate was filtered off, washed with water and cold ethanol, and crystallized from DMF to give 0.64 g (54%) of colorless crystals; mp 218-220°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 2932, 2835 (CH_2), 1639 (CO), 1589, 1481, 1435, 1373, 1269 (C–O–C), 1234, 1207, 1165, 1041, 914. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.77 (3H, s, CH_3CO); 2.78 (2H, t, *J* = 7.35, $C\underline{H_2}CH_2N$); 3.20-3.30 (2H, m, $CH_2\underline{CH_2}N$); 3.76 (6H, s, $2CH_3CO$); 5.16 (2H, s, CH_2); 6.71 (1H, d, *J* = 8.1, H arom); 6.90-7.00 (3H, m, H arom); 7.17-7.23 (2H, m, H arom); 7.93 (1H, br. s, NH). Mass spectrum (EI), *m/z* (I_{rel}, %): 366 $[M]^+$ (10), 307 $[M\text{-}CH_3CONH_2]^+$ (15), 294 $[M\text{-}CH_2NHCOCH_3]^+$ (100), 279 $[M\text{-}CH_2NHCOCH_3\text{-}CH_3]^+$ (12), 230 $[M\text{-}C_8H_8O_2]^+$ (48), 188 (25), 187 (15), 182 (45), 181 (27), 91 $[C_7H_7]^+$ (12), 77 $[C_6H_5]^+$ (13), 43 $[CH_3CO]^+$ (44). Found, %: C 68.60; H 5.91; N 7.72. $C_{21}H_{22}N_2O_4$. Calculated, %: C 68.84; H 6.05; N 7.69.

N-[2-(7-Bromo-8-methoxy-2,3-dimethyl-12H-indolo[2,1-*b*][1,3]benzoxazin-6-yl)ethyl]acetamide (2) was obtained analogously to compound **1** from 2,4-dibromomelatonin (1 g, 2.6 mmol), iodomethylate of 2-[(dimethylamino)methyl]-4,5-dimethylphenol (0.87 g, 2.7 mmol), and K_2CO_3 (3.25 g, 24 mmol) as colorless crystals; mp 199-201°C (dec., ethanol), yield 0.49 g (43%). IR spectrum, ν, cm^{-1}: 3302 (NH), 3078 (CH arom), 2927, 2870 (CH_3), 1647 (CO), 1578, 1558, 1508, 1493, 1454, 1431, 1312, 1277, 1242 (C–O–C), 1223, 1173, 1076, 1041, 837, 775. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.75 (3H, s, CH_3CO); 2.17 (3H, s, CH_3); 2.20 (3H, s, CH_3); 3.02 (2H, t, *J* = 7.3, $C\underline{H_2}CH_2N$); 3.25-3.40 (2H, m, $CH_2C\underline{H_2}N$); 3.80 (3H, s, CH_3O); 5.05 (2H, s, CH_2); 6.88 (1H, d, *J* = 8.8, H-9); 6.99 (1H, s, H-4); 7.08 (1H, s, H-1); 7.27 (1H, d, *J* = 8.8, H-10); 7.89 (1H, br. s, NH). Mass spectrum (EI, for isotope ^{79}Br), *m/z* (I_{rel}, %): 442 $[M]^+$ (2), 383 $[M\text{-}CH_3CONH_2]^+$ (3), 370 $[M\text{-}CH_2NHCOCH_3]^+$ (15), 308 $[M\text{-}C_9H_{10}O]^+$ (100), 265 $[M\text{-}C_9H_{10}O\text{-}CH_3CO]^+$ (78), 223 (26), 186 (35), 171 (27), 143 (26), 129 (18), 89 (12), 43 $[CH_3CO]^+$ (42). Found, %: C 60.02; H 5.19; N 6.37. $C_{22}H_{23}BrN_2O_3$. Calculated, %: C 59.60; H 5.23; N 6.30.

N-{2-[4-(1-Adamantyl)-7-bromo-8-methoxy-2-methyl-12H-indolo[2,1-*b*][1,3]benzoxazin-6-yl]ethyl}-acetamide (3) was obtained analogously to compound **1** from 2,4-dibromomelatonin (1 g, 2.6 mmol), iodomethylate of 6-(1-adamantyl)-2-[(dimethylamino)methyl)]-4-methylphenol (1.13 g, 2.6 mmol), and K_2CO_3 (3.25 g, 24 mmol) as colorless crystals; mp 169-171°C (acetic acid), yield 0.91 g (63%). IR spectrum, ν, cm^{-1}: 3306 (NH), 3078 (CH arom), 2905, 2847 (CH Ad), 1639 (CO), 1578, 1547, 1462, 1435, 1369, 1292, 1265, 1250 (C–O–C), 1200, 1150, 1083, 1053, 779. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.74 (9H, br. s, CH_3CO, H Ad); 2.05-2.15 (9H, m, H Ad); 2.29 (3H, s, CH_3); 3.11 (2H, t, *J* = 7.35, $C\underline{H_2}CH_2N$); 3.25-3.35 (2H, m, $CH_2C\underline{H_2}N$); 3.81 (3H, s, CH_3O); 5.14 (2H, s, CH_2); 6.91 (1H, d, *J* = 8.8, H-9); 7.02 (2H, br. s, H-1,3); 7.33 (1H, d, *J* = 8.8, H-10); 7.82 (1H, br. s, NH). Mass spectrum (EI, isotope ^{79}Br), *m/z* (I_{rel}, %): 562 $[M]^+$ (7), 503 $[M\text{-}CH_3CONH_2]^+$ (3), 490 $[M\text{-}CH_2NHCOCH_3]^+$ (100), 412 $[M\text{-}Br]^+$ (47), 308 $[M\text{-}C_{18}H_{22}O]^+$ (4), 195 (4), 165 (6), 141 (7), 135 $[C_{10}H_{15}]^+$ (5), 91 $[C_7H_7]^+$ (7), 72 $[CH_2NHCOCH_3]^+$ (7), 43 $[CH_3CO]^+$ (12). Found, %: C 66.19; H 6.14; N 5.07. $C_{31}H_{35}BrN_2O_3$. Calculated, %: C 66.07; H 6.26; N 4.97.

REFERENCES

1. M. Mor, S. Rivara, C. Silva, F. Bordi, and P. V. Plazzi, *J. Med. Chem.,* **41**, 3831 (1998).
2. L. Huang, E. L. Ellsworth, S. Randhawa, M. A. Stier, Y. Huang, P. Bird, M. Lebedev, K. Wu, R. G. Micetich, J. M. Domagala, R. Singh, and N. L. Colbry, *Tetrahedron. Lett.,* **41**, 4061 (2000).

3. L. M. Gaster, G. F. Joiner, F. D. King, P. A. Wyman, J. M. Sutton, S. Bingham, E. S. Ellis, G. J. Sanger, and K. A. Wardle, *J. Med. Chem.,* **38**, 4760 (1995).
4. M. Fedouloff, F. Hossner, M. Voyle, J. Ranson, J. Powles, G. Riley, and G. Sanger, *Biorg. Med. Chem.,* **9**, 2119 (2001).
5. N. E. Sidorina and V. A. Osyanin, *Khim. Geterotsikl. Soedin.,* 1406 (2005). [*Chem. Heterocycl. Comp.,* **41**, 1201 (2005)].
6. V. A. Osyanin and N. E. Sidorina, *Khim. Geterotsikl. Soedin.,* 1741 (2006). [*Chem. Heterocycl. Comp.,* **42**, 1499 (2006)].
7. Van De R. W. Water and T. R. R. Petus, *Tetrahedron*, **58**, 5367 (2002).
8. G. Decodts, M. Wakselman, and M. Vilkas, *Tetrahedron*, **26**, 3313 (1970).
9. A. Andreani, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, A. Roda, M. Guardigli, S. Traniello, and S. Spisani, *Eur. J. Med. Chem.,* **39**, 785 (2004).
10. S. H. Doss, R. M. Mohareb, G. A. Elmegeed, and N. A. Luoca, *Pharmazie*, **58**, 607 (2003).
11. M. Tramontini, *Synthesis,* 703 (1973).