Use of the *tert*-amino effect in the synthesis of spirocyclic fused α-carbolines

N. M. Vlaskina,[a] K. F. Suzdalev,[a]★ M. N. Babakova,[a] V. V. Mezheritskii,[a] and V. G. Kartsev[b]

[a]Research Institute of Physical and Organic Chemistry, Rostov State University, 194/2 prosp. Stachki, 344090 Rostov-on-Don, Russian Federation. Fax: +7 (863) 243 4667. E-mail: consuz@mail.ru
[b]I-B-Screen Co., P.O. Box 128, 119019 Moscow, Russian Federation. E-mail: screen@ibscreen.chg.ru

The use of the *tert*-amino effect in cyclization of reaction products from 2-(azepan-1-yl)-1-methyl-1*H*-indole-3-carbaldehyde and active methylene compounds afforded spirocyclic fused α-carbolines.

Key words: *tert*-amino effect, active methylene compounds, α-carbolines.

Biologically active compounds of the carboline series occupy a significant place among fused indole derivatives. α-Carbolines are used in the therapy of atherosclerosis;[1] besides, they are fragments of natural alkaloids.[2]

Several methods employed for the synthesis of α-carbolines may be divided into two groups. The first group is based on transformations of indole derivatives, namely, on reactions of 2-aminoindoles with β-dicarbonyl compounds.[3] The second group involves creation of the indole fragment during a reaction.[1,4,5]

The goal of the present work was to develop a new method for the synthesis of spirocyclic fused α-carbolines by means of the *tert*-amino effect. The term "*tert*-amino effect" means cyclization at the α-carbon atom of the dialkylamino group for dialkylarylamines with an unsaturated *ortho*-substituent.[6,7] For instance, the synthesis of spiro derivatives of fused quinolines has been reported recently;[8,9] this approach has also been used to obtain δ-carboline derivatives.[10] However, this method has not been applied hitherto to the synthesis of α-carboline systems.

The starting 2-(azepan-1-yl)-1-methyl-1*H*-indole-3-carbaldehyde (**1**) was prepared by nucleophilic substitution of the Cl atom of indolecarbaldehyde **2** in boiling benzene (Scheme 1). Reactions of compound **1** with 1,3-dimethylbarbituric and Meldrum´s acids in boiling Pr^iOH for 3—4 h gave spirocyclic carbolines **3** and **4** in low yields, which is caused by resinification of the reaction mixture. To isolate intermediates **5** and **6**, we reduced the reaction duration to 15—30 min (see Scheme 1). The low yields of intermediates **5** and **6** are due to low conversion degrees of the starting reagents.

The structures of products **3** and **4** were proved by comparing their ^{1}H and ^{13}C NMR spectra with those of intermediates **5** and **6**. In contrast to compound **5**, product **3** has the chiral center C(17) near the N atom of the seven-membered ring, which complicates the ^{1}H NMR spectrum. The methyl protons of the barbituric fragment in compound **3** are diastereotopic and thus magnetically nonequivalent. The methylene protons in the piperidine fragment appear as two doublets at δ 3.10 and 3.44. The multiplet at δ 3.22—3.37 corresponds to the methylene protons at the N atom of the seven-membered ring. The signal for the proton at the tertiary C atom shared by the seven- and six-membered rings is split due to coupling with two protons of the adjacent CH_2 group and appears as a doublet of doublets at δ 3.81. The missing (compared to the spectrum of compound **5**) signal for the olefinic proton indicates that the double bond transforms into a single one.

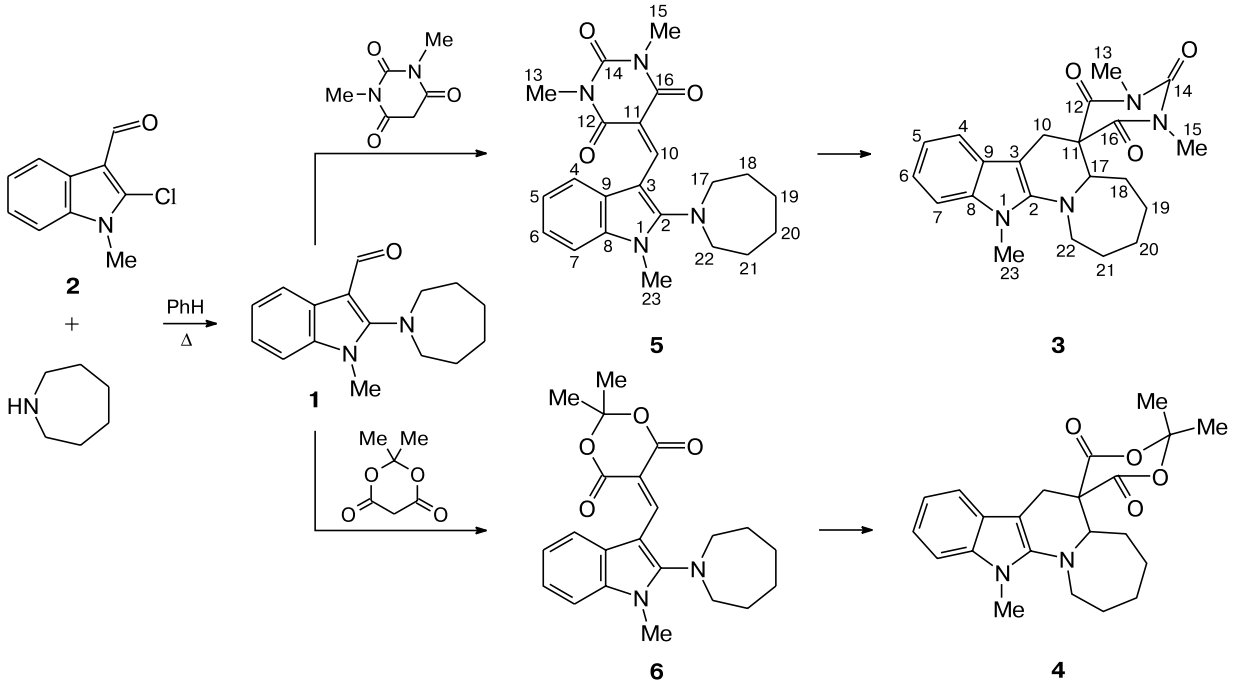
Supporting evidence for structure **3** was obtained from ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum of compound **5** with complete proton decoupling shows 19 signals instead of 22 signals for product **3**. This is explained by equivalence, in pairs, of the C(17) and C(22), C(18) and C(21), and C(19) and C(20) atoms.

The ^{13}C NMR spectrum of compound **3** is more complex than that of compound **5** since all the C atoms in the seven-membered ring have become magnetically nonequivalent upon the cyclization. Note that the C(10) and C(11) atoms in compound **5** are olefinic and their signals appear at δ 147.6 and 105.5; in product **3**, these atoms are sp^3-hybridized and their signals are shifted upfield (δ 29.7 and 51.0, respectively). The signal for the secondary C(17) atom in compound **5** appears at δ 55.9; in compound **3**, this atom becomes tertiary and its signal is shifted downfield (δ 69.0), which indicates the formation of a new C—C bond.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 371—373, February, 2006.

1066-5285/06/5502-0384

Scheme 1



The ^{1}H NMR spectrum of compound **4** resembles that of product **3**. Because of the presence of the chiral center, the CH_2 protons are also magnetically nonequivalent and their chemical shifts are different.

Thus, the use of the *tert*-amino effect in the series of indole derivatives allowed for the first time the synthesis of spirocyclic fused α-carbolines.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer (300 MHz) in $CDCl_3$. Signals in the ^{13}C NMR spectra of compounds **3** and **5** were assigned be comparing data obtained with and without proton decoupling. For compound **3**, signals were additionally assigned by using 2D heteronuclear shift correlation experiment ({^{1}H, ^{13}C} HETCOR). IR spectra were recorded on a Specord IR75 instrument (Nujol). Mass spectra were recorded on a Varian MAT-44 instrument (EI, ionizing energy 70 eV). 2-Chloro-1-methylindole-3-carbaldehyde (**2**) was prepared according to a known procedure.[11]

Commercial Meldrum´s (Acros) and 1,3-dimethylbarbituric acids (Lancaster) were used.

2-(Azepan-1-yl)-1-methyl-1*H*-indole-3-carbaldehyde (1). Azepane (1.34 mL, 0.018 mol) was added to 2-chloro-1-methylindole-3-carbaldehyde (**2**) (1.2 g, 0.006 mol) and the reaction mixture was refluxed in benzene (8 mL) for 3 h. The precipitate of azepane hydrochloride that formed was filtered off. The mother liquor was chromatographed on aluminum oxide (column 30×2 cm) with benzene as an eluent. The first, yellow fraction (R_f 0.2) was collected and concentrated. The oily residue was dissolved in benzene (1 mL) and then light petroleum (5—10 mL, b.p. 40—70 °C) was added. The cream-colored precipitate was filtered off. The yield was 0.4 g (26%), m.p. 80 °C. Found (%): C, 74.81; H, 7.83; N, 10.94. $C_{16}H_{20}N_2O$. Calculated (%): C, 74.96; H, 7.86; N, 10.92. IR, ν/cm^{-1}: 1635 (C=O); 1600, 1580 (C—C arom.). ^{1}H NMR, δ: 1.71—1.92 (m, 8 H, $(CH_2)_4$); 3.41—3.55 (m, 4 H, $(CH_2)_2$); 3.65 (s, 3 H, Me); 7.20—7.35 (m, 3 H, H(5), H(6), H(7)); 8.20—8.30 (m, 1 H, H (4)); 10.20 (s, 1 H, CHO).

9,1´,3´-Trimethylspiro[azepano[1,2-*a*]-α-carboline-3,5´-hexahydropyrimidine]-2´,4´,6´-trione (3). A mixture of aldehyde **1** (0.6 g, 0.002 mol) and 1,3-dimethylbarbituric acid (0.408 g, 0.002 mol) was refluxed in Pr^{i}OH (5 mL) for 4 h. The reaction mixture was chromatographed on aluminum oxide (column 15×2 cm) with chloroform as an eluent. The first, yellow fraction (R_f 0.66) was collected and concentrated. The oily residue was dissolved in benzene (3 mL) and crystallized with addition of light petroleum ether (10 mL, b.p. 40—70 °C) as a cream-colored solid. The yield of compound **3** was 0.020 g (4%), m.p. 212—214 °C. Found (%): C, 66.84; H, 6.72; N, 14.34. $C_{22}H_{26}N_4O_3$. Calculated (%): C, 66.98; H, 6.64; N, 14.21. IR, ν/cm^{-1}: 1740, 1670 (C=O); 1610 (C—C arom.). ^{1}H NMR, δ: 1.17—2.30 (m, 8 H, $(CH_2)_4$); 3.10, 3.44 (both d, 1 H each, CCH_2); 3.22—3.37 (m, 5 H, NCH_2, Me); 3.40, 3.64 (both s, 3 H each, Me); 3.81 (dd, 1 H, CH, J_1 = 4.2 Hz, J_2 = 12.2 Hz); 6.98—7.39 (m, 4 H, H arom.). ^{13}C NMR, δ: 25.5 (C(20)); 28.9 (C(13)); 29.5 (C(18)); 29.7 (C(10), C(19)); 30.5 (C(23)); 32.0 (C(21)); 49.0 (C(22)); 51.0 (C(11)); 69.0 (C(17)); 92.0 (C(3)); 108.0 (C(7)); 116.0 (C(4)); 119.0 (C(6)); 119.4 (C(5)); 127.0 (C(9)); 128.3 (C(15)); 135.2 (C(8)); 144.8 (C(2)); 151.9 (C(16)); 169.0 (C(14)); 172.0 (C(12)). MS, *m/z*: 394 $[M]^+$.

9,2´,2´-Trimethylspiro[azepano[1,2-*a*]-α-carboline-3,5´-[1,3]dioxane]-4´,6´-dione (4) was obtained analogously by refluxing for 3 h. The yield of compound **4** was 0.092 g (11%),

m.p. 218—220 °C, R_f 0.82. Found (%): C, 69.15; H, 6.84; N, 7.43. $C_{22}H_{26}N_2O_4$. Calculated (%): C, 69.09; H, 6.85; N, 7.33. IR, ν/cm^{-1}: 1770, 1730 (C=O); 1620, 1590 (C—C arom.). ^{1}H NMR, δ: 1.22—2.22 (m, 8 H, $(CH_2)_4$); 1.78, 1.80 (both s, 3 H each, Me); 3.21, 3.42 (both d, 1 H each, CCH_2, J = 15.7 Hz); 3.23—3.37, 3.43—3.58 (both m, 1 H each, NCH_2); 3.63 (s, 3 H, Me); 3.85 (dd, 1 H, CH, J_1 = 4.2 Hz, J_2 = 12.5 Hz); 7.10—7.35 (m, 4 H, H arom.). MS, m/z: 382 $[M]^+$.

5-[2-(Azepan-1-yl)-1-methyl-1*H*-indol-3-ylmethylene]-1,3-dimethylhexahydropyrimidine-2,4,6-trione (5). A mixture of aldehyde **1** (0.6 g, 0.002 mol) and 1,3-dimethylbarbituric acid (0.408 g, 0.002 mol) was heated in Pr^{i}OH (4 mL) for 15 min. The resulting red crystals were filtered off and recrystallized from acetonitrile. The yield was 0.152 g (17%), m.p. 208 °C. Found (%): C, 66.84; H, 6.67; N, 14.30. $C_{22}H_{26}N_4O_3$. Calculated (%): C, 66.98; H, 6.64; N, 14.21. IR, ν/cm^{-1}: 1700 (C=O); 1650 (C=O); 1630 (C=C); 1580 (C—C arom.). ^{1}H NMR, δ: 1.70—2.00 (m, 8 H, $(CH_2)_4$); 3.41 (s, 6 H, 2 Me); 3.56—3.67 (m, 4 H, $(CH_2)_2$); 3.7 (s, 3 H, Me); 7.10—7.25 (m, 4 H, H arom.); 8.61 (s, 1 H, =CH). ^{13}C NMR, δ: 27.6 (C(18), C(21)); 28.2 (C(13), C(15)); 30.0 (C(19), C(20)); 32.0 (C(23)); 55.9 (C(17), C(22)); 105.5 (C(11)); 107.0 (C(3)); 110.0 (C(7)); 122.2 (C(4)); 123.0 (C(6)); 123.8 (C(5)); 126.0 (C(9)); 137.5 (C(8)); 147.6 (C(10)); 152.0 (C(2)); 160.8 (C(16)); 162.0 (C(14)); 164.0 (C(12)). MS, m/z: 394 $[M]^+$.

5-[2-(Azepan-1-yl)-1-methyl-1*H*-indol-3-ylmethylene]-2,2-dimethyl[1,3]dioxane-4,6-dione (6). A mixture of aldehyde **1** (0.6 g, 0.002 mol) and Meldrum´s acid (0.288 g, 0.002 mol) was heated in Pr^{i}OH (4 mL) for 30 min. The precipitate was filtered off, dissolved in benzene, and chromatographed on aluminum oxide (column 15×2 cm) with benzene as an eluent. The orange eluate (R_f 0.08) was concentrated. The oily residue was dissolved in benzene (3 mL) and then light petroleum ether (10 mL, b.p. 40—70 °C) was added. The orange precipitate was filtered off. The yield was 0.024 g (3%), m.p. 157—159 °C. Found (%): C, 69.11; H, 6.79; N, 7.24. $C_{22}H_{26}N_2O_4$. Calculated (%): C, 69.09; H, 6.85; N, 7.33. IR, ν/cm^{-1}: 1740, 1680 (C=O); 1600 (C—C arom.). ^{1}H NMR, δ: 2.72—2.95 (m, 14 H, 2 Me, $(CH_2)_4$); 3.60—3.75 (m, 7 H, Me, $(CH_2)_2$); 7.12—7.35 (m, 4 H, H arom.); 8.61 (s, 1 H, =CH). MS, m/z: 382 $[M]^+$.

References

1. L. A. Sorbera, L. Martin, J. S. Silvestre, and J. Castaner, *Drugs Fut.*, 2000, **25**, 1138.
2. P. Molina, P. M. Fresneda, M. A. Sanz, C. Foces-Foces, and M. C. R. de Arellano, *Tetrahedron*, 1998, **54**, 9653.
3. S. V. Simakov, in *Selected Methods for Synthesis and Modification of Heterocycles. The Chemistry of Synthetic Indole Systems*, Ed. V. G. Kartsev, IBS PRESS, Moscow, 2004, Vol. **3**, 260.
4. R. A. Abramovich, D. H. Hey, and R. D. Mulley, *J. Chem. Soc.*, 1954, 4263.
5. P. Nantka-Namirski and J. Kalinowski, *Acta Pol. Pharm.*, 1974, **31**, 137; *Chem. Abstr.*, 1974, **81**, 152112.
6. O. Meth-Cohn and H. Suschitzky, *Adv. Heterocycl. Chem.*, 1972, **14**, 211.
7. O. Meth-Cohn, *Adv. Heterocycl. Chem.*, 1996, **65**, 1.
8. E. V. D´yachenko, T. V. Glukhareva, E. F. Nikolaenko, A. V. Tkachev, and Yu. Yu. Morzherin, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 1191 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 1240].
9. K. A. Krasnov and V. G. Kartsev, *Zh. Org. Khim.*, 2005, **41**, 920 [*Russ. J. Org. Chem.*, 2005, **41**, 901 (Engl. Transl.)].
10. V. G. Kartsev, K. A. Krasnov, R. N. Vydzhak, and S. Ya. Panchishin, *Abstr. 3rd EuroAsian Heterocyclic Meeting "Heterocycles in Organic and Combinatorial Chemistry" (Novosibirsk, 12—17 September, 2004)*, Novosibirsk, 2004, 160.
11. L. Marchetti and G. Tosi, *Ann. Chim.*, 1969, **59**, 712.

Received October 14, 2005;
in revised form January 20, 2006