Synthesis of scopine 3-amino-2-phenylpropionate derivatives*

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The 8-azabicyclo[3.2.1]octane (tropane) fragment is found in some natural alkaloids (atropine, scopolamine, anatoxin, *etc.*).[1—4] Like many other synthetic derivatives of this heterocycle, they exhibit analgetic, hypotensive, anti-Parkinsonian, and methacholinolytic activities and are used in medical practice as chemotherapeutic drugs.[5—10]

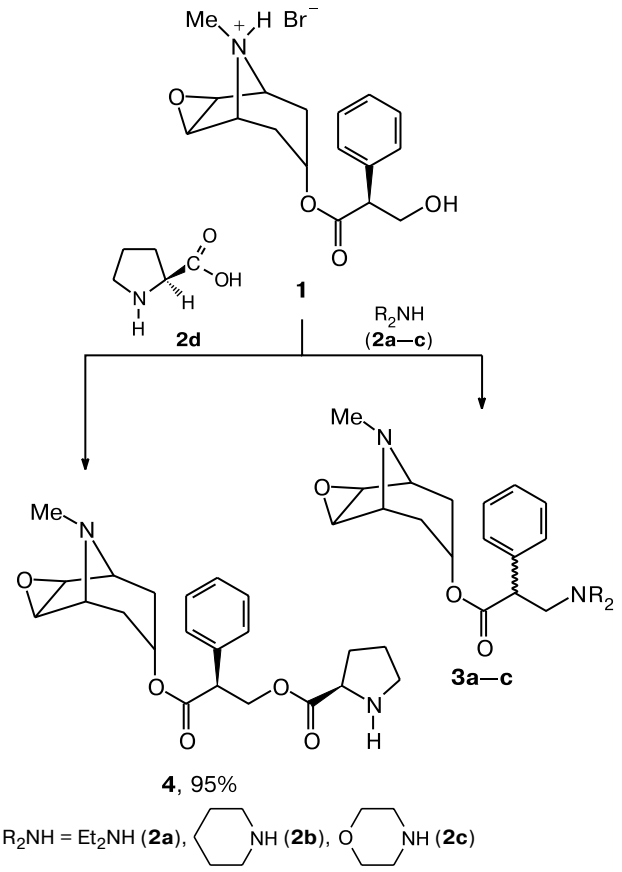
In the present work, we developed a new method for the synthesis of scopine-containing β-amino acid derivatives that may be of interest as physiologically active compounds. The starting materials were scopolamine hydrobromide (**1**) and secondary amines such as diethylamine (**2a**), piperidine (**2b**), and morpholine (**2c**).

Heating of scopolamine hydrobromide **1** with diethylamine **2a** in the molar ratio 1 : 3 at 120 °C gave scopine 3-(*N*,*N*-diethylamino)-2-phenylpropionate (**3a**) in ~10% yield. Reactions of scopolamine hydrobromide **1** with piperidine **2b** and morpholine **2c** were much more efficient: the yields of amino esters **3b** and **3c** were 88 and 70%, respectively. In all cases, racemization of the chiral center in the acid moiety of scopolamine took place. Under these conditions, the epoxide ring of scopolamine did not undergo opening in the presence of the aforementioned amines. In contrast to amines **2a**—**c**, the reaction of *L*-proline (**2d**) with scopolamine hydrobromide occurred as esterification to give optically active scopine 2-phenyl-3-(pyrrolidin-2-ylcarbonyloxy)propionate (**4**) in 95% yield.

When an aqueous solution of amine **2a** or scopolamine rather than its hydrobromide **1** were used, the ester bond of scopolamine underwent very rapid hydrolysis to give scopoline (6-methyl-2-oxa-6-azatricyclo[3.3.1.0^{3,7}]-nonan-4-ol) and tropic (3-hydroxy-2-phenylpropionic) acid.[11] Interestingly, the reaction with isopropylamine yielded a complex mixture of products.

Apparently, the formation of β-amino acid esters **3a**—**c** passes through the formation of scopine 2-phenylprop-2-enoate followed by the Michael addition of amines **2a**—**c** to the activated C=C bond,[12—14] which is evident from racemization of the optically active (−)-S-center of the acid fragment in scopolamine.

Scheme 1



Conditions: 120 °C, 7 h.

In summary, we proposed a route to derivatives of scopine 3-amino-2-phenylpropionate *via* reactions of scopolamine hydrobromide with secondary amines.

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The compositions and structures of compounds **3a—c** and **4** were confirmed by data from TLC (Silufol plates), elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, and IR spectroscopy.

IR spectra were recorded on a Specord M-80 instrument (thin film or Nujol). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz, respectively) in $CDCl_3$ or DMSO-d_6 with Me_4Si as the internal standard.

Synthesis of scopine 3-amino-2-phenylpropionates 3a—c (general procedure). A mixture of scopolamine hydrobromide (1.27 g, 3.3 mmol) and amine **2a—c** (9.9 mmol) was heated at 120 °C for 7 h. The reaction mixture was cooled, dissolved in acetone (10 mL), and filtered. The filtrate was concentrated *in vacuo* to give compounds **3a—c**.

Scopine 3-(*N,N*-diethylamino)-2-phenylpropionate (3a). The yield was 0.12 g (10%), an oil. Found (%): C, 70.25; H, 8.50; N, 7.84. $C_{21}H_{30}N_2O_3$. Calculated (%): C, 70.36; H, 8.44; N, 7.81. IR, ν/cm^{-1}: 710, 850, 1170, 1595, 1750, 3050, 3060, 3070, 3090. ^{1}H NMR ($CDCl_3$), δ: 1.0 (t, 6 H, 2 Me, ^3J = 7.2 Hz); 1.38 (br.d, 1 H, H_{eq}(2), ^2J = 15.3 Hz); 1.93—2.13 (m, 3 H, H_{ax}(2), H_{eq}(4) H_{ax}(4)); 2.45 (s, 3 H, NMe); 2.56 (dd, 1 H, H_a(11), $^2J_{ab}$ = 14 Hz, $^3J_{11a,10}$ = 7.0 Hz); 2.83 (q, 4 H, 2 CH_2, ^3J = 7.2 Hz); 3.00 (d, 1 H, H(7), $^3J_{6,7}$ = 2.7 Hz); 3.25 (m, 3 H, H(1), H(5), H_b(11)); 3.44 (d, 1 H, H(6) $^3J_{6,7}$ = 2.7 Hz); 3.65 (dd, 1 H, H(10), $^3J_{10,11b}$ = 10.8 Hz, $^3J_{10,11a}$ = 5.4 Hz); 4.95 (t, 1 H, H(3), $^3J_{3,2ax(4ax)}$ = 5.3 Hz); 7.20—7.35 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 11.30 (Me); 30.01 and 30.15 (C(2) and C(4)); 41.35 (NMe); 45.61 (CH_2N); 50.80 (C(10)); 53.26 (C(11)); 55.62, 56.02 (C(1), C(5)); 57.32, 57.43 (C(6), C(7)); 66.08 (C(3)); 127.16 (Ph (C_p)); 127.97, 128.56 (Ph (C_o, C_m)); 137.42 (Ph (C_{ipso})); 171.88 (COO).

Scopine 2-phenyl-3-piperidinopropionate (3b). The yield was 1.07 g (88%), an oil. Found (%): C, 71.20; H, 8.21; N, 7.54. $C_{22}H_{30}N_2O_3$. Calculated (%): C, 71. 32; H, 8.16; N, 7.56. IR, ν/cm^{-1}: 710, 840, 1170, 1595, 1750, 3050, 3060, 3070, 3090. ^{1}H NMR ($CDCl_3$), δ: 1.41 (m, 2 H, CH_2); 1.42 (br.d, 1 H, H_{eq}(2), ^2J = 15.3 Hz); 1.53 (m, 4 H, NCH_2CH_2); 1.58 (br.d, 1 H, H_{eq}(4), ^2J = 15.2 Hz); 2.03 (ddd, 1 H, H_{ax}(2), ^2J = 15.3 Hz, $^3J_{1,2ax}$ = 4.1 Hz, $^3J_{3,2ax}$ = 5.5 Hz); 2.10 (ddd, 1 H, H_{ax}(4), ^2J = 15.2 Hz, $^3J_{3,4ax}$ = 5.5 Hz, $^3J_{5,4ax}$ = 4.1 Hz); 2.35 (dt, 2 H_{ax}, 2 CH_2N, ^2J = 11.4 Hz, ^3J = 5.7 Hz); 2.48 (dt, 2 H_{eq}, 2 CH_2N, ^2J = 11.4 Hz, ^3J = 5.7 Hz); 2.49 (s, 3 H, NMe); 2.50 (dd, 1 H, H_a(11), $^2J_{a,b}$ = 12.6 Hz, $^3J_{10,11a}$ = 4.6 Hz); 3.04 (dd, 1 H, H(1), $^3J_{1,2ax}$ = 4.1 Hz, $^3J_{1,2eq}$ = 1.9 Hz); 3.13 (d, 1 H, H(7), $^3J_{6,7}$ = 3.0 Hz); 3.14 (dd, 1 H, H(5), $^3J_{5,4ax}$ = 4.1 Hz, $^3J_{5,4eq}$ = 1.9 Hz); 3.16 (dd, 1 H, H_b(11), $^3J_{10,11b}$ = 10.2 Hz, $^2J_{ab}$ = 2.6 Hz); 3.60 (d, 1 H, H(6), $^3J_{6,7}$ = 3.0 Hz); 3.76 (dd, 1 H, H(10), $^3J_{10,11a}$ = 4.6 Hz, $^3J_{10,11b}$ = 10.2 Hz); 4.98 (t, 1 H, H(3), $^3J_{3,2ax(4ax)}$ = 5.5 Hz); 7.20—7.35 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 24.11 (C(4′)); 25.85 (C(3′), C(5′)); 30.56 (C(2)); 30.84 (C(4)); 41.93 (NMe); 50.23 (C(10)); 54.61 (C(2′),C(6′)); 56.15 (C(1)); 56.39 (C(5)); 57.67 (C(7)); 57.75 (C(6)); 61.67 (C(11)); 66.26 (C(3)); 127.32 (Ph (C_p)); 127.66 and 128.56 (Ph (C_o and C_m)); 135.54 (Ph (C_{ipso})); 171.94 (COO).

Scopine 3-morpholino-2-phenylpropionate (3c). The yield was 0.86 g (70%), an oil. Found (%): C, 67.68; H, 7.55; N, 7.56. $C_{21}H_{28}N_2O_4$. Calculated (%): C, 67.72; H, 7.58; N, 7.52. IR, ν/cm^{-1}: 710, 760, 850, 1170, 1600, 1730, 3060, 3080. ^{1}H NMR ($CDCl_3$), δ: 1.41 (br.d, 1 H, H_{eq}(2), ^2J = 15.4 Hz); 1.60 (br.d, 1 H, H_{eq}(4), ^2J = 15.2 Hz); 2.10 (ddd, 1 H, H_{ax}(2), ^2J = 15.4 Hz, $^3J_{1,2ax}$ = 4.0 Hz, $^3J_{3,2ax}$ = 5.4 Hz); 2.18 (ddd, 1 H, H_{ax}(4), ^2J = 15.2 Hz, $^3J_{3,4ax}$ = 5.5 Hz, $^3J_{5,4ax}$ = 3.9 Hz); 2.43 (dt, 2 H_{ax}, 2 CH_2N, ^2J = 10.5 Hz, ^3J = 5.0 Hz); 2.50 (s, 3 H, MeN); 2.56 (dd, 1 H, H_a(11), $^2J_{a,b}$ = 12.5 Hz, $^3J_{10,11a}$ = 5.0 Hz); 2.57 (dt, 2 H_{eq}, 2 CH_2N, ^2J = 10.5 Hz, ^3J = 5.0 Hz); 3.01 (d, 1 H, H(7), $^3J_{6,7}$ = 3.0 Hz); 3.06 (dd, 1 H, H(1), $^3J_{1,2ax}$ = 4.0 Hz, $^3J_{1,2eq}$ = 2.0 Hz); 3.17 (dd, 1 H, H(5), $^3J_{5,4ax}$ = 3.9 Hz, $^3J_{5,4eq}$ = 1.9 Hz); 3.18 (dd, 1 H, H_b(11), $^2J_{a,b}$ = 12.5 Hz, $^3J_{10,11b}$ = 10.1 Hz); 3.44 (d, 1 H, H(6), $^3J_{6,7}$ = 2.97 Hz); 3.66 (t, 4 H, 2 CH_2O, ^3J = 5.0 Hz); 3.75 (dd, 1 H, H(10), $^3J_{10,11a}$ = 5.0 Hz, $^3J_{10,11b}$ = 10.1 Hz); 4.99 (t, 1 H, H(3), $^3J_{3,2ax}$ = 5.4 Hz, $^3J_{3,4ax}$ = 5.5 Hz); 7.20—7.35 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 30.56 (C(2)); 30.85 (C(4)); 42.13 (NMe); 49.89 (C(10)); 53.67 (C(2′), C(6′)); 55.92 (C(1)); 56.20 (C(5)); 57.85 (C(6)); 57.93 (C(7)); 61.03 (C(11)); 66.33 (C(3)); 66.80(C(3′), C(5′)); 127.54 (Ph (C_p)); 127.62, 128.68 (Ph (C_o, C_m)); 137.03 (Ph (C_{ipso})); 171.53 (COO).

Scopine 2-phenyl-3-(pyrrolidin-2-ylcarbonyloxy)propionate (4). The yield was 1.25 g (95%), an oil, $[\alpha]_{20}^{D}$ -47.3 (*c* 0.69, EtOH). Found (%): C, 66.02; H, 6.98; N, 7.05. $C_{22}H_{28}N_2O_5$. Calculated (%): C, 65.98; H, 7.05; N, 7.00. IR, ν/cm^{-1}: 725, 850, 1175, 1580, 1735, 3080, 3090. ^{1}H NMR (DMSO-d_6), δ: 1.48 (br.d, 1 H, H_{eq}(2), ^2J = 16.1 Hz); 1.62 (br.d, 1 H, H_{eq}(4), ^2J = 15.5 Hz); 1.72 (m, 2 H, H(4′)); 1.87 (m, 1 H, H_a(3′)); 1.97—2.19 (m, 3 H, H_{ax}(2), H_{ax}(4), H_b(3′)); 2.56 (s, 3 H, NMe); 3.01 (dt, 1 H, H_a(5′), ^2J = 11.3 Hz, ^3J = 7.3 Hz); 3.15 (dt, 1 H, H_b(5′), ^2J = 11.3 Hz, ^3J = 6.7 Hz); 3.34 (d, 1 H, H(7), $^3J_{6,7}$ = 3.2 Hz); 3.40 (br.s, 1 H, H(1)); 3.46 (br.s, 1 H, H(5)); 3.60 (dd, 1 H, H_a(11), $^2J_{a,b}$ = 9.9 Hz, $^3J_{10,11a}$ = 5.6 Hz); 3.66 (d, 1 H, H(6), $^3J_{6,7}$ = 3.2 Hz); 3.68 (dd, 1 H, H(10), $^3J_{10,11b}$ = 9.0 Hz, $^3J_{10,11a}$ = 5.6 Hz); 3.78 (dd, 1 H, H(2′), $^3J_{2',3'b}$ = 8.7 Hz, $^3J_{2',3'a}$ = 6.2 Hz); 3.90 (dd, 1 H, H_b(11), $^2J_{a,b}$ = 9.9 Hz, $^3J_{10,11b}$ = 9.0 Hz); 4.80 (t, 1 H, H(3), $^3J_{3,2ax(4ax)}$ = 5.0 Hz); 7.20—7.35 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 25.16 (C(4′)); 25.56 (C(2)); 25.67 (C(4)); 30.42 (C(5′)); 47.00 (C(3′)); 53.76 (C(1)); 54.08 (C(5)); 55.70 (C(10)); 56.20 (C(6)); 59.04 (C(7)); 59.19 (C(6)); 62.50 (C(1′)); 64.39 (C(11)); 64.74 (C(3)); 64.80 (NMe); 128.92 (Ph (C_p)); 129.37, 130.00 (Ph (C_o, C_m)); 137.36 (Ph (C_{ipso})); 172.60 (C(9)); 174.33 (COO).

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