Synthesis of new functionally substituted fullerenopyrrolidines

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New fullerenopyrrolidines were synthesized by the three-component reactions of fullerene C_{60}, *N*-methylglycine, and aromatic aldehydes, *viz.*, *N*,*N*-bis(2-chloroethyl)-4-aminobenzaldehyde, *N*-(2-chloroethyl)-*N*-methyl-4-aminobenzaldehyde, indole-3-carbaldehyde, 4-phenylbenzaldehyde, and anthracene-9-carbaldehyde. The structures of the resulting compounds were established by spectroscopic methods.

Key words: fullerene C_{60}, fullerenopyrrolidines, *N*,*N*-bis(2-chloroethyl)-4-aminobenzaldehyde, *N*-(2-chloroethyl)-*N*-methyl-4-aminobenzaldehyde, indole-3-carbaldehyde, 4-phenylbenzaldehyde, anthracene-9-carbaldehyde.

In the modern chemistry of fullerenes, the development of procedures for the synthesis of new compounds and materials has attracted increasing attention.[1—3] The published data on different aspects of the practical application of fullerenes provide evidence[4] that fullerene C_{60} is one of the most economically profitable starting reagents for the preparation of biologically active compounds. Biological activities of fullerene C_{60} and its derivatives were examined in many studies.[5—7] Photodynamic activity of some derivatives of fullerene C_{60} is of particular interest.[8,9] This property gave impetus to the search for new biologically active compounds based on C_{60}. It should be noted that the synthesis of fullerene derivatives containing groups responsible for biological activity has not been adequately explored. There is reason to hope that the introduction of these groups into the fullerene molecule will allow one to reveal the specific properties of biologically active fullerene derivatives. Previously,[10] we have described the synthesis of fullerenopyrrolidine bearing the sterically hindered phenol fragment, which is often responsible for antioxidant activity.[10]

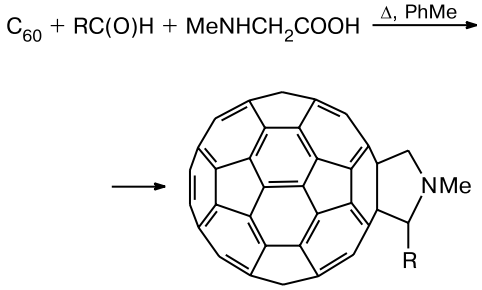
In the present study, we report the synthesis of new fullerenopyrrolidines with functional groups, which can make a specific contribution to the properties of the starting fullerenopyrrolidines.

Results and Discussion

We used the bis(chloroethyl)amino group as one of such functional groups. It is known that this group is responsible for antitumor activity of alkylating drugs, which are used in medicine, in particular, in the treatment of leucosis.[11,12] It is most convenient to synthesize derivatives of fullerene C_{60} containing this group by the [3+2] cycloaddition reaction.[13,14]

Heating a mixture of fullerene C_{60}, sarcosine, and *N*,*N*-bis(2-chloroethyl)-4-aminobenzaldehyde in toluene (Scheme 1) afforded a mixture of a monoadduct and polyadducts. Compound **1** was isolated in 36.2% yield (with respect to consumed fullerene C_{60}) by chromatography on SiO_2.

Scheme 1



1—5

R = $C_6H_4N(CH_2CH_2Cl)_2$ (**1**), $C_6H_4N(Me)CH_2CH_2Cl$ (**2**), 3-indolyl (**3**), 4-PhC_6H_4 (**4**), 9-anthracenyl (**5**)

Under the analogous conditions, the reaction of *N*-2-chloroethyl-*N*-methylaminobenzaldehyde, sarcosine, and C_{60} produced compound **2**. In this compound,

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the chloroethylamino group can exhibit the alkylating properties.

The reaction with the use of indole-3-carbaldehyde as the carbonyl component gave rise to indole-containing compound **3** in 40% yield (with respect to consumed fullerene C_{60}). This compound was synthesized taking into account that indole and its derivatives are involved in biologically active natural and synthetic compounds.[15,16]

As mentioned above, the photophysical properties are of importance for derivatives of fullerene C_{60} to exhibit biological activity. The introduction of polyaromatic fragments into fullerene C_{60} can change the photophysical properties of its derivatives. As part of our continuing studies of the properties of new fullerene derivatives and search for compounds exhibiting photodynamic activity, we synthesized fullerenopyrrolidine **4** containing the diphenyl fragment. This compound was prepared according to a general procedure for the synthesis of fullerenopyrrolidines with the use of 4-phenylbenzaldehyde as the carbonyl fragment. We chose anthracene as another polyaromatic fragment. The reaction of sarcosine, C_{60}, and anthracene-9-carbaldehyde afforded compound **5**, which was isolated by chromatography in 7.5% yield. The low yield of this product is attributable to the possible involvement of the anthracene fragment in the [4+2] cycloaddition giving rise to mono- and diadducts, as was observed in the reactions of C_{60} with anthracene and 9,10-dimethylanthracene.[17]

The structures and purities of compounds **1**—**5** were confirmed by the data from spectroscopic methods, elemental analysis, mass spectrometry, and HPLC.

The UV spectra of compounds **1**—**5** have absorption bands at 258, 268, 328, and 430 nm typical of virtually all fullerenopyrrolidines. It should be noted that the UV spectra of the compounds synthesized in the present study show an absorption band at 714 nm, which is of importance in the examination of the photodynamic biological activity.

The IR spectra of compounds **1**—**5** have absorption bands at 525, 1178, and 1425 cm^{-1} belonging to stretching vibrations of the fullerene core typical of monoadducts of fullerene C_{60} and a series of other absorption bands corresponding to stretching vibrations of the attached fragments.

The structures of the compounds were also confirmed by ^1H and ^{13}C NMR spectroscopy. Thus, the ^1H NMR spectra of compounds **1**—**4** have signals for the protons of the *N*-methyl group (δ 2.78), CH group (~δ 5.25—5.30), and CH_2 groups (at δ 4.2—4.7) of the pyrrolidine fragment. The positions of the signals for the protons at position 5 of the pyrrolidine fragment depend on the nature of this group. The spectrum of compound **1** shows signals for the protons of the N—CH_2 and Cl—CH_2 groups at δ 2.3 and 2.35, respectively, and signals for the protons of the aromatic nucleus at δ 7.16—7.26. The ^1H NMR spectra of compounds **2**—**4** have signals for the H(2) atom of the pyrrolidine fragment and aromatic protons in the regions of δ 5.20—5.30 and 7.10—7.30, respectively.

The compositions of the compounds were established not only by elemental analysis but also by mass spectrometry (EI). As expected, the mass spectra have low-intensity molecular ion peaks of fullerene derivatives (EI; the energy of ionizing electrons was 70 eV) attributable to low volatility of these compounds. The peaks of decomposition products are much more intense among which are the ion peaks $[M - MeNCH_2]^+$, $[C_{60}CH_2]^+$ (*m/z* 734), C_{60}^+ (*m/z* 720), *etc.* observed in the mass spectra of all compounds. The results of elemental analysis, mass spectrometry, and spectroscopic methods as well as the chromatographic homogeneity provide support for the correctness of the structures assigned to the compounds obtained.

Taking into account that some compounds contain pharmacophore groups, we started examination of their biological activities. The results of these experiments will be published elsewhere. However, it can be noted that compound **1** (as a water-soluble complex with polyvinylpyrrolidone) showed moderate antitumor activity at doses of 4—5 mg kg^{-1} against L1210 leukemia and B16 melanoma in BDF-1 mice.

Experimental

Fullerene C_{60} was prepared according to a procedure described previously.[18] The purity (99.9%) was checked by HPLC on a Gilson chromatograph equipped with a UV detector (column with the reversed phase C_{18} (Partisil-5 ODS-3), a 1 : 1 (v/v) toluene—MeCN mixture as the eluent). Chromatographically homogeneous sarcosine was purchased from Reanal (Hungary). The organic solvents were dried and distilled before use. The UV spectra were recorded on a Specord M-40 spectrophotometer. The IR spectra were measured on a Vector-22 (Bruker) spectrometer (KBr pellets). The ^1H and ^{13}C NMR spectra were recorded on Bruker WM-250 (250 and 63 MHz) and Bruker MSL-400 (400 and 100.57 MHz, respectively) spectrometers in $CDCl_3$ with Me_4Si as the internal standard. The mass spectra were measured on a Kratos MS-890 instrument; the energy of ionizing electrons was 70 eV; the temperature of the ionization chamber was 300 °C.

1-[*N*′,*N*′-Bis(2-chloroethyl)-4-aminophenyl]-*N*-methylfullereno-C_{60}-[1,9-*c*]pyrrolidine (1). A solution of fullerene C_{60} (0.216 g, 0.3 mmol), *N*-methylglycine (0.053 g, 0.6 mmol), and 4-bis(2-chloroethyl)aminobenzaldehyde[19] (0.074 g, 0.3 mmol) in toluene (200 mL) was refluxed for 10 h. Chromatography on SiO_2 with continuous monitoring by HPLC (hexane as the eluent) afforded unconsumed fullerene C_{60} in a yield of 0.044 g. Then compound **1** was isolated as a dark-brown powder by elution with a 1 : 1 hexane—toluene mixture, m.p. >300 °C, the yield was 0.08 g (36% with respect to consumed C_{60}). Found (%): N, 2.74; Cl, 7.41. $C_{73}H_{18}N_2Cl_2$. Calculated (%): N, 2.82; Cl, 7.15. MS (EI), *m/z* (I_{rel} (%)): 993 $[M]^+$ (5), 720 $[M - C_{13}H_{28}N_2Cl_2]^+$ (100). UV (THF—$CHCl_3$, 10 : 2),

λ_{max}/nm (ε): 258 (50000), 261 (50000), 268 (44000), 328 (16000), 431 (2000), 460 (1400), 636 (200), 714 (140). IR, ν/cm^{-1}: 526, 551, 734, 821, 1032, 1179, 1214, 1246, 1277, 1331, 1352, 1387, 1427, 1461, 1518, 1613, 1719, 2361, 2774, 2853, 2923. ^{1}H NMR, δ: 2.30 and 2.35 (both s, 2 H each); 2.79 (s, 3 H); 4.43 and 4.70 (both d, 1 H each, J = 9.2 Hz); 5.30 (s, 1 H); 7.16—7.26 (m, 4 H, H arom.). ^{13}C NMR, δ: 39.56; 40.06; 53.37; 66.44; 69.61; 82.77; 90.80; 111.61; 125.47; 127.89; 128.60; 130.44; 135.32; 136.16; 136.42; 139.59; 139.75; 139.79; 141.54; 141.61; 141.68; 142.15; 142.20; 142.26; 143.94; 144.21; 144.28; 144.67; 144.79; 144.95; 145.05; 145.18; 145.31; 145.49; 145.67; 145.86; 146.02; 146.06; 146.29; 153.25; 153.55.

1-[*N*′-(2-Chloroethyl)-*N*′-methyl-4-aminophenyl]-*N*-methylfullereno-C$_{60}$-[1,9-*c*]pyrrolidine (2). Compound **2** was synthesized under the conditions analogous to those used in the synthesis of compound **1** starting from fullerene C_{60} (0.216 g, 0.3 mmol), *N*-methylglycine (0.053 g, 0.6 mmol), and *N*-(2-chloroethyl)-*N*-methyl-4-aminobenzaldehyde (0.119 g, 0.6 mmol), which was synthesized according to a known procedure[19] (m.p. 68—69 °C). The yield of compound **2** was 0.083 g (38.8% with respect to consumed C_{60}). UV (CH_2Cl_2), λ_{max}/nm (ε): 255.4 (95520), 304 (sh) (12400), 323.9 (12270), 431.2 (1318), 696 (450). IR, ν/cm^{-1}: 526, 552, 574, 725, 766, 819, 1029, 1104, 1121, 1177, 1214, 1339, 1351, 131, 1427, 1460, 1520, 1612, 2776, 2851, 2921. ^{1}H NMR, δ: 2.17 (m, 2 H, NCH_2); 2.32 (m, 2 H, CH_2Cl); 2.35 (s, 3 H); 3.49 and 3.75 (both d, 1 H each, J = 7.2 Hz); 5.16 (s, 3 H); 7.18—7.77 (m, 4 H, H arom.). ^{13}C NMR, δ: 38.50; 39.70; 40.25; 54.42; 68.64; 69.81; 77.22; 83.12; 111.83; 124.69; 125.14; 128.03; 128.06; 128.77; 130.23; 135.46; 135.55; 136.39; 136.52; 139.37; 139.74; 139.88; 139.95; 141.31; 141.42; 141.42; 141.58; 141.74; 141.76; 141.79; 141.85; 141.88; 141.89; 141.92; 142.02; 142.05; 142.32; 142.36; 142.43; 142.75; 142.86; 142.89; 144.13; 144.14; 144.42; 144.45; 144.86; 144.95; 144.97; 144.99; 145.02; 145.12; 145.18; 145.21; 145.26; 145.34; 145.52; 145.66; 145.82; 145.86; 145.89; 145.95; 145.99; 146.04; 146.26; 146.36; 146.60; 146.99; 147.02; 147.90; 153.57; 153.62; 153.83; 156.22.

1-(3-Indolyl)-*N*-methylfullereno-C$_{60}$-[1,9-*c*]pyrrolidine (3). Compound **3** was obtained as a dark-brown powder under the conditions analogous to those used in the synthesis of compound **1** starting from fullerene C_{60} (0.216 g, 0.3 mmol), *N*-methylglycine (0.080 g, 0.9 mmol), and indole-3-carbaldehyde (0.087 g, 0.2 mmol) in toluene (200 mL). The yield was 0.087 g (40% with respect to consumed C_{60}), m.p. >360 °C. Found (%): N, 3.01. $C_{71}H_{12}N_2$. Calculated (%): N, 3.14. MS (EI), m/z (I_{rel} (%)): 892 [M]$^+$ (10), 720 [M – $C_{11}H_{12}N_2$]$^+$ (100). UV (THF—$CHCl_3$, 10 : 2), λ_{max}/nm (ε): 257 (41000), 269 (34000), 326 (14000), 430 (1700), 455 (1200), 714 (100). IR, ν/cm^{-1}: 525, 554, 580, 600, 700, 750, 910, 1030, 1096, 1178, 1215, 1330, 1425, 1453, 1490, 1547, 1636, 1718, 2770, 2830, 2852, 2922, 2941, 3050. ^{1}H NMR, δ: 2.78 (s, 3 H); 4.23 and 4.93 (both d, 1 H each, J = 9.3 Hz); 5.24 and 6.60 (both s, 1 H each); 7.11—7.23 (m, 4 H, H arom.); 9.6 (s, 1 H, NH). ^{13}C NMR, δ: 111.46; 113.08; 120.63; 123.13; 124.65; 125.66; 127.60; 127.75; 127.88; 127.99; 128.11; 128.24; 128.29; 128.34; 128.43; 128.53; 129.25; 137.57; 142.34; 142.42; 142.58; 142.81; 143.26; 143.37; 144.63; 144.92; 145.36; 145.45; 145.47; 145.68; 145.74; 145.86; 146.16; 146.29; 146.33; 146.38; 146.42; 146.45; 147.46; 154.28; 156.85.

1-(4-Biphenylyl)-*N*-methylfullereno-C$_{60}$-[1,9-*c*]pyrrolidine (4). Compound **4** was synthesized under the conditions analogous to those used in the synthesis of compound **1** starting from fullerene C_{60} (0.216 g, 0.3 mmol), *N*-methylglycine (0.080 g, 0.9 mmol), and 4-phenylbenzaldehyde[20] (0.109 g, 0.3 mmol). After chromatography on SiO_2 (toluene—MeCN, 10 : 1, as the eluent), compound **4** was obtained in a yield of 0.057 g (41.7% with respect to consumed C_{60}), m.p. >300 °C. Found (%): N, 1.43. $C_{71}H_{12}N_2$. Calculated (%): N, 1.50. MS (EI), m/z (I_{rel} (%)): 929 [M]$^+$ (10), 720 [M – $C_{15}H_{15}N$]$^+$ (100). UV (THF—$CHCl_3$, 10 : 2), λ_{max}/nm (ε): 257 (41000), 269 (34000), 326 (14000), 430 (1700), 455 (1200), 714 (100). IR, ν/cm^{-1}: 525, 554, 580, 600, 700, 750, 910, 1030, 1096, 1178, 1215, 1330, 1425, 1453, 1490, 1547, 1636, 1718, 2770, 2830, 2852, 2922, 2941, 3050. ^{1}H NMR, δ: 2.79 (s, 3 H); 4.43 and 4.70 (both d, 1 H each, J = 9.1 Hz); 5.30 (s, 1 H); 7.16—7.26 (m, 4 H, H arom.). ^{13}C NMR, δ: 40.14; 69.17; 77.41; 83.57; 125.47; 127.89; 128.60; 130.44; 135.32; 136.16; 136.42; 139.59; 139.75; 139.79; 141.54; 141.61; 141.68; 142.15; 142.20; 142.26; 143.94; 144.21; 144.28; 144.67; 144.79; 144.95; 145.05; 145.18; 145.31; 145.49; 145.67; 145.86; 146.02; 146.06; 146.29; 153.25; 153.55.

1-(9-Anthracenyl)-*N*-methylfullereno-C$_{60}$-[1,9-*c*]pyrrolidine (5). Compound **5** was synthesized under the conditions analogous to those used in the synthesis of compound **1** starting from fullerene C_{60} (0.216 g, 0.3 mmol), *N*-methylglycine (0.080 g, 0.9 mmol), and anthracene-9-carbaldehyde (0.124 g, 0.3 mmol) in toluene (200 mL). After chromatography on SiO_2 (toluene—MeCN, 10 : 1, as the eluent), compound **5** was obtained in a yield of 0.017 g (7.5% with respect to consumed C_{60}), m.p. >300 °C. MS (EI), m/z (I_{rel} (%)): 953 [M]$^+$ (10), 720 [M – $C_{17}H_{15}N$]$^+$ (100). UV (THF—$CHCl_3$, 10 : 2), λ_{max}/nm (ε): 256 (41000), 269 (34000), 328 (14000), 355 (sh.), 377.6 (sh.), 401 (1700), 429 (1200), 714 (100). IR, ν/cm^{-1}: 530, 575, 1181, 1096, 1178, 1215, 1335, 1428, 1463, 1580, 1643, 2774, 2836, 2928, 3040.

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