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N-Methylcarbazole-3-carboxylic Acid and Its Amides

N. G. Plekhanova, D. V. Ovchinnikov, and E. N. Glibin

St. Petersburg State Institute of Technology, Moskovskii pr. 26, 198013, St. Petersburg, 198013 Russia

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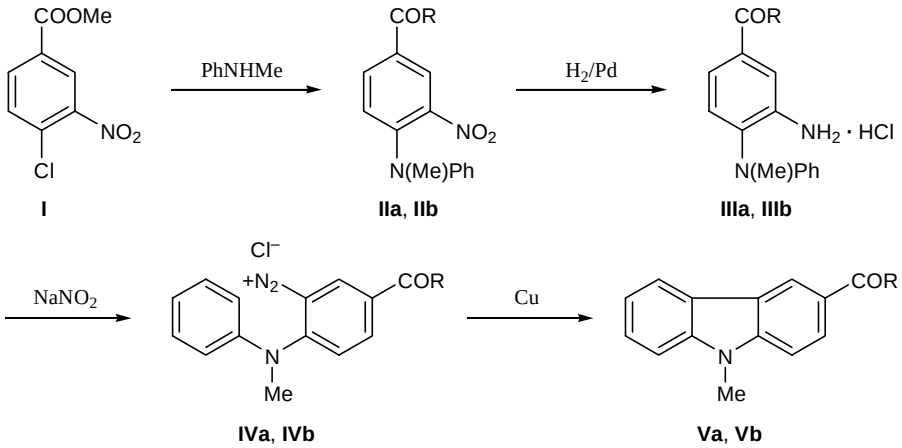
Abstract—*N*-Methylcarbazole-3-carboxylic acid was synthesized from *N*-methyl-2-amino-4-carboxydiphenylamine through the corresponding diazo compound by a modified Pschorr procedure. The acid was converted into *N*-methylcarbazole-3-carbonyl chloride which was treated with amines containing benzo- and aza-crown ether moieties, as well as with 3-(dimethylamino)propylamine, to obtain the respective N-substituted amides.

Heterocyclic compounds of the carbazole series occur in nature and exhibit valuable pharmacological properties [1, 2]. Some carbazole derivatives are capable of forming complexes with DNA [2, 3]. We anticipated that, like Tilorone [4] and xanthenecarboxamides [5], carbazolecarboxamides will form complexes with DNA and that some of these will exhibit antitumor activity. Antitumor agents [6, 7] and DNA-binding compounds [8, 9] were found among actinocin amides having a 3-dimethylaminopropyl moiety or a benzocrown ether fragment in the amide group. Therefore, we expected that *N*-methylcarbazolecarboxamides possessing analogous fragments in the amide group will also be interesting from the viewpoint of antitumor activity.

We have synthesized methyl 4-methyl(phenyl)amino-3-nitrobenzoate **IIa** and the respective acid **IIb** in satisfactory yields by nucleophilic substitution of the chlorine atom in methyl 4-chloro-3-nitrobenzoate (**I**) [10]. The replacement process is facilitated by the presence of two strong electron-acceptor substituents. We have found that hydrolysis of ester group is preceded by formation of diphenylamine. Nitro compounds **IIa** and **IIb** were reduced to the corresponding amines **IIIa** and **IIIb** by catalytic hydrogenation in the presence of 5% Pd/C. Amines **IIIa** and **IIIb** were treated with sodium nitrite to obtain diazo compounds **IVa** and **IVb** which were then converted into carbazole derivatives **Va** and **Vb** via high-temperature intramolecular cyclization in the presence of copper powder (Scheme 1). The yields of both ester **Va** and carboxylic acid **Vb** were fairly high (72 and 70%, respectively). Intermediate products **IIIa**, **IIIb** and **IVa**, **IVb** were not isolated because of their instability.

By treatment of acid **Vb** with thionyl chloride we obtained chloride **VI** which (without isolation) was brought into reaction with amines. As a result, *N*-methylcarbazol-3-carboxamides **VII**–**XV** were

Scheme 1.



I **IIa**, **IIb** **IIIa**, **IIIb**

IVa, **IVb** **Va**, **Vb**

R = OMe (**a**), OH (**b**).

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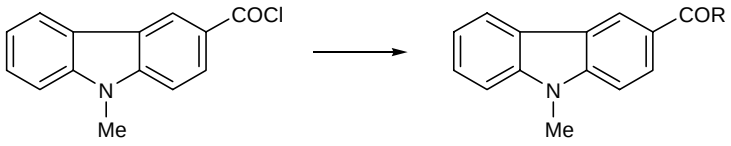
Scheme 2.



VI **VII–XV**

VII, R = $NHCH_2CH_2CH_2NMe_2$; **VIII**, R = NH-4'-benzo-15-crown-5; **IX**, R = NH-4'-benzo-18-crown-6; **X**, R = $NHCH_2CONH$-4'-benzo-15-crown-5; **XI**, R = $NHCH_2CONH$-4'-benzo-18-crown-6; **XII**, R = $NHCH_2CH_2CONH$-4'-benzo-15-crown-5; **XIII**, R = $NHCH_2CH_2CONH$-4'-benzo-18-crown-6; **XIV**, R = 1-aza-15-crown-5; **XV**, R = 1-aza-18-crown-6.

obtained (Scheme 2). While studying the synthesis of actinocin amides, we previously showed that the most convenient procedure for the preparation of ω-amino acid amides involves the corresponding azides as intermediate products [11, 12]. In the present work we have found that ω-amino acid amides can be obtained in satisfactory yields by a simpler procedure, via activation of the amino acid by mixed anhydrides using ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate [13]. The subsequent hydrogenation of amides **XVI**–**XIX** over Pd/C gave glycine and β-alanine amides **XX**–**XXIII** (Scheme 3), and treatment of the latter with *N*-methylcarbazole-3-carbonyl chloride (**VI**) afforded compounds **X**–**XIII**.

Scheme 3.

$ZNH(CH_2)_nCOOH + HR \longrightarrow ZNH(CH_2)_nCOR$

XVI–XIX

$\longrightarrow H_2N(CH_2)_nCOR$

XX–XXIII

XVI, **XX**, R = $NHCH_2CONH$-4'-benzo-15-crown-5; **XVII**, **XXI**, R = $NHCH_2CONH$-4'-benzo-18-crown-6; **XVIII**, X**XII**, R = $NHCH_2CH_2CONH$-4'-benzo-15-crown-5; **XIX**, **XXIII**, R = $NHCH_2CH_2CONH$-4'-benzo-18-crown-6; Z = $OCOCH_2Ph$.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker instrument at 300 MHz in $CDCl_3$ using HMDS as reference. The melting points were determined on an NMK Koefler apparatus. TLC analysis was performed on Silufol UV-254 (360) plates using the following solvent systems: chloroform–methanol–25% aqueous ammonia, 20:2:1 (A); chloroform–methanol–acetic acid, 48:1:1.5 (B); benzene (C); ethyl acetate (D); chloroform–methanol, 10:1 (E), 5:1 (E'); ethyl acetate–hexane, 1:1 (F).

Methyl 4-methyl(phenyl)amino-3-nitrobenzoate (IIa) and 4-methyl(phenyl)amino-3-nitrobenzoic acid (IIb). A mixture of 3.23 g (15 mmol) of methyl 4-chloro-3-nitrobenzoic acid (**I**) [10], 2.96 g (15 mmol) of barium carbonate, and 8.2 g (75 mmol) of *N*-methylaniline was stirred for 4–5 h at 140–150°C (until initial compound **I** disappeared completely; TLC, system C). The mixture was cooled and treated with 200 ml of diethyl ether. The extract was washed with 1 N hydrochloric acid, 200 ml of a 3% aqueous solution of $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated, and the residue was recrystallized from methanol to obtain 2.49 g (58%) of ester **IIa**, mp 102–104°C; the product was chromatographically pure (systems A–C). Found, %: C 62.77, 62.69; H 4.86, 4.98. $C_{15}H_{14}N_2O_4$. Calculated, %: C 62.93; H 4.93.

The solution obtained by washing of the extract with 3% aqueous $NaHCO_3$ was washed with 50 ml of diethyl ether and acidified with concentrated hydrochloric acid to pH ~1–2. The orange precipitate of compound **IIb** was filtered off, washed with water, dried, and recrystallized from methanol. Yield 0.57 g (14%), mp 194–196°C. The product was chromatographically pure (systems A–C). Found, %: C 61.56, 61.83; H 4.39, 4.35. $C_{14}H_{12}N_2O_4$. Calculated, %: C 61.76; H 4.41.

Methyl 3-amino-4-[methyl(phenyl)amino]benzoate hydrochloride (IIIa). Compound **IIa**, 1 g, was reduced with hydrogen at room temperature under atmospheric pressure in the presence of 0.15 g of 5% Pd/C in 50 ml of anhydrous methanol until the initial nitro compound disappeared completely from the reaction mixture (TLC, systems B and C). The catalyst was filtered off, and the filtrate was acidified with a saturated solution of hydrogen chloride in ethanol and evaporated. The residue was treated with dry benzene, the mixture was evaporated, the residue was ground with dry diethyl ether, and the precipitate

was filtered off. Yield 0.93 g (91%); the product was chromatographically pure (systems A–C).

3-Amino-4-[methyl(phenyl)amino]benzoic acid (IIIb) was synthesized as described above for compound **IIIa** from 0.9 g of acid **IIb**. The progress of the reaction was monitored by TLC (system A). Yield 0.65 g (71%); the product was chromatographically pure (systems A–C).

Methyl *N*-methylcarbazole-3-carboxylate (Va). Hydrochloride **IIIa**, 1 g (3.42 mmol), was dissolved in 40 ml of hydrochloric acid (1:9), the solution was cooled to 0°C, a solution of 0.26 g (3.76 mmol) of $NaNO_2$ in 1 ml of water was added under stirring, and the mixture was stirred for 10 min. Copper powder, 1 g, was then added, and the mixture was stirred for 30 min at room temperature, heated to 60–70°C, and stirred at that temperature until the diazonium compound completely disappeared (test with 2-naphthol). The mixture was treated with 200 ml of diethyl ether, the extract was washed in succession with water, a 3% aqueous solution of $NaHCO_3$, and water again, dried over Na_2SO_4, and evaporated, and the residue was recrystallized from methanol. Yield 0.59 g (72%), mp 130–132°C (from methanol); the product was chromatographically pure (systems A–C). Found, %: C 74.74, 74.66; H 5.76, 5.71. $C_{15}H_{13}NO_2$. Calculated, %: C 75.30; H 5.48.

***N*-Methylcarbazole-3-carboxylic acid (Vb).** *a*. The procedure was analogous to that utilized in the synthesis of ester **Va**; 0.5 g of acid **IIIb** and 0.14 g of $NaNO_2$ were used. The only difference was that the extract containing compound **Vb** was washed only with water (washing with a solution of $NaHCO_3$ was excluded). Yield 0.27 g (70%), mp 256–258°C (from acetone); the product was chromatographically pure (systems A–C). Found, %: C 75.01, 75.03; H 5.02, 4.94. $C_{14}H_{11}NO_2$. Calculated, %: C 74.65; H 4.92.

b. A mixture of 0.5 g of compound **Va** and 25 ml of a saturated solution of NaOH in methanol was heated for 30 min under reflux. The mixture was diluted with 20 ml of water, treated with diethyl ether (2×10 ml), and acidified with hydrochloric acid to pH 1–2, and the precipitate was filtered off, washed with water, and dried. Yield 0.42 g (90%), mp 256–258°C. The product was chromatographically identical to a sample obtained as described in *a*, and no depression of the melting point was observed on mixing with the latter.

***N*-(3-Dimethylaminopropyl)-9-methylcarbazole-3-carboxamide (VII)**. Acid **Vb**, 0.26 g, was dissolved in 15 ml of dry benzene, 0.25 ml of thionyl chloride was added, and the mixture was heated for 30 min under reflux. The mixture was evaporated, dry benzene was added to the residue, and the solvent was removed on a rotary evaporator; this procedure was repeated three times. Acid chloride **VI** thus obtained was dissolved in 10 ml of dry benzene, 0.57 ml of 3-dimethylaminopropylamine was added to the solution, and the mixture was stirred for 2 h at room temperature and was left to stand for 15 h. The benzene solution was washed with a 3% aqueous solution of $NaHCO_3$ (2×10 ml) and with water and dried over Na_2SO_4. The solvent was distilled off to obtain 31 g (85%) of compound **VII**, mp 121–122°C (from benzene–hexane); the product was chromatographically pure (systems A–C). ^{1}H NMR spectrum, δ, ppm: 2.21 s and 2.26 s [6H, $N(CH_3)_2$]; 1.92 m, 2.43 m, and 3.53 m (6H, $3CH_2$); 3.88 s (1H, NCH_3); 6.81–7.58 m (4H, H_{arom}); 8.01 d and 8.12 d (2H, H_{arom}); 8.86 s (1H, H_{arom}). Found, %: C 73.54, 73.44; H 7.54, 7.60. $C_{19}H_{23}N_3O$. Calculated, %: C 73.76; H 7.49.

***N*-(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)-9-methylcarbazole-3-carboxamide (VIII).** A solution of 4'-aminobenzo-15-crown-5 (obtained by hydrogenation of 0.328 g of 4'-nitrobenzo-15-crown-5 [14]) and 0.14 ml of triethylamine were added to a solution of acid chloride **VI** (prepared from 0.225 g of acid **Vb**) in 6 ml of dry benzene. The mixture was stirred for 2 h at room temperature and was left to stand for 15 h. The precipitate was filtered off and washed with benzene. Yield 0.34 g (70%), mp 213–215°C (from acetone). The product was chromatographically pure (systems A–C). ^{1}H NMR spectrum, δ, ppm: 3.45–4.31 m (23H, OCH_2CH_2O, NCH_3), 6.76–7.54 m (6H, H_{arom}), 8.01 d and 8.13 d (2H, H_{arom}), 8.61 s and 8.82 s (2H, H_{arom}). Found, %: C 68.43, 68.54; H 6.14, 6.25. $C_{28}H_{30}N_2O_6$. Calculated, %: C 68.56; H 6.16.

***N*-(2,3,5,6,8,9,11,12,14,15-Decahydro-1,4,7,10,-13,16-benzohexaoxacyclooctadecin-18-yl)-9-methylcarbazole-3-carboxamide (IX)** was synthesized as desribed above for compound **VIII** from 0.225 g of compound **Vb** and 0.375 g of 4'-nitrobenzo-18-crown-6 [14]. Yield 0.374 g (70%), mp 204–206°C (from acetone); The product was chromatographically pure (systems A–C). ^{1}H NMR spectrum, δ, ppm: 3.45–4.31 m (23H, OCH_2CH_2O, NCH_3), 6.76–7.54 m (6H, H_{arom}), 8.01 d and 8.13 d (2H, H_{arom}), 8.61 s and 8.82 s (2H, H_{arom}). Found, %: C 67.45, 67.52; H 6.90, 6.76. $C_{30}H_{34}N_2O_7$. Calculated, %: C 67.40; H 6.41.

Compounds **X**–**XV** were synthesized in a similar way. Their yields, systems for TLC, melting points,

solvents for crystallization, ^{1}H NMR spectra, and elemental analyses are listed below.

***N*-(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)(9-methylcarbazole-3-carbonylamino)acetamide (X).** Yield 48%; TLC: system E'; mp 208–210°C (from methanol); ^{1}H NMR spectrum, δ, ppm: 3.4–4.3 m (19H, OCH_2CH_2O, NCH_3), 4.42 m (2H, $NHCH_2CO$), 6.83–7.68 m (6H, H_{arom}), 8.05 d and 8.12 d (2H, H_{arom}), 8.65 s and 8.84 s (2H, H_{arom}). Found, %: C 65.61, 65.64; H 6.03, 6.08. $C_{30}H_{33}N_3O_7$. Calculated, %: C 65.80; H 6.07.

***N*-(2,3,5,6,8,9,11,12,14,15-Decahydro-1,4,7,10,-13,16-benzohexaoxacyclooctadecin-18-yl)(9-methylcarbazole-3-ylcarbonylamino)acetamide (XI).** Yield 67%; TLC: system E; mp 118–120°C (from ethyl acetate–methanol, 5:3). ^{1}H NMR spectrum, δ, ppm: 3.6–4.1 m (23H, OCH_2CH_2O, NCH_3), 4.41 m (2H, NHC**H**$_2$CO), 6.81–7.56 m (6H, H_{arom}); 8.02 d and 8.14 d (2H, H_{arom}), 8.63 s and 8.82 s (2H, H_{arom}). Found, %: C 65.25, 65.32; H 6.36, 6.41. $C_{32}H_{37}N_3O_8$. Calculated, %: C 64.96; H 6.30.

***N*-(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)-3-(9-methylcarbazole-3-carbonylamino)propionamide (XII).** Yield 28%; TLC: system E'; mp 178–180°C (from ethyl acetate–methanol). ^{1}H NMR spectrum, δ, ppm: 3.5–4.05 m (19H, OCH_2CH_2O, NCH_3), 4.3 m (4H, NHC**H**$_2$C**H**$_2$CO), 6.80–7.58 m (6H, H_{arom}), 8.04 d and 8.11 d (2H, H_{arom}), 8.65 s and 8.79 s (2H, H_{arom}). Found, %: C 66.52, 66.57; H 6.36, 6.38. $C_{31}H_{35}N_3O_7$. Calculated, %: C 66.30; H 6.28.

***N*-(2,3,5,6,8,9,11,12,14,15-Decahydro-1,4,7,10,-13,16-benzohexaoxacyclooctadecin-18-yl)-3-(9-methylcarbazole-3-ylcarbonylamino)propionamide (XIII).** Yield 26%; TLC: system E; mp 138–140°C (from ethyl acetate–methanol). ^{1}H NMR spectrum, δ, ppm: 3.62–4.14 m (23H, OCH_2CH_2O, NCH_3), 4.27 m (NHC**H**$_2$C**H**$_2$CO), 6.76–7.62 m (6H, H_{arom}), 8.05 d and 8.17 d (2H, H_{arom}), 8.67 s and 8.82 s (2H, H_{arom}). Found, %: C 65.61, 65.52; H 6.63, 6.70. $C_{33}H_{39}N_3O_8$. Calculated, %: C 65.44; H 6.49.

***N*,*N*-(3,6,9,12-Tetraoxatetradecane-1,14-diyl)-9-methylcarbazole-3-carboxamide (XIV).** Yield 72%; TLC: systems A, D; mp 115–117°C (from ethyl acetate–methanol). ^{1}H NMR spectrum, δ, ppm: 3.34–3.82 m (23H, OCH_2CH_2O, NCH_3), 6.80–7.58 m (4H, H_{arom}), 8.05 d and 8.13 d (2H, H_{arom}), 8.82 s (1H, H_{arom}). Found, %: C 67.26, 67.18; H 7.12, 7.14. $C_{26}H_{34}N_2O_6$. Calculated, %: C 67.58; H 7.08.

***N*,*N*-(3,6,9,12,15-Pentaoxaheptadecane-1,17-diyl)-9-methylcarbazole-3-carboxamide (XV).** Yield 50%; TLC: systems A, D; mp 84–86°C (from ethyl acetate–methanol). ^{1}H NMR spectrum, δ, ppm: 3.32–3.85 m (27H, OCH_2CH_2O, NCH_3), 6.82–7.65 m (4H, H_{arom}), 8.03 d and 8.12 d (2H, H_{arom}), 8.85 s (1H, H_{arom}). Found, %: C 65.92, 65.98; H 7.37, 7.35. $C_{26}H_{34}N_2O_6$. Calculated, %: C 66.36; H 7.28.

4'-[ω-(Benzyloxycarbonylamino)alkylcarbonylamino]benzocrown ethers XVI–XIX (*general procedure***).** To a suspension of 1 mmol of *N*-benzyloxycarbonyl amino acid in 5 ml of anhydrous tetrahydrofuran we added under stirring in a dry inert atmosphere 0.3 g (1.2 mmol) of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate and then a solution of 4'-aminobenzocrown ether in a few milliliters of anhydrous THF. The mixture was stirred at room temperature until the initial aminobenzocrown ether disappeared (TLC), the solvent was removed under reduced pressure on a rotary evaporator, and the residue was recrystallized from ethyl acetate.

***N*-(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)(benzyloxycarbonylamino)acetamide (XVI).** Yield 82%; TLC: systems E', F; mp 136–138°C (from ethyl acetate–acetone). Found, %: C 60.43, 60.47; H 6.41, 6.43. $C_{24}H_{30}N_2O_8$. Calculated, %: C 60.75; H 6.37.

***N*-(2,3,5,6,8,9,11,12,14,15-Decahydro-1,4,7,10,-13,16-benzohexaoxacyclooctadecin-18-yl)(benzyloxycarbonylamino)acetamide (XVII).** Yield 89%; TLC: systems E', F; mp 153–156°C (from ethyl acetate–acetone). Found, %: C 59.91, 60.03; H 6.69, 6.67. $C_{26}H_{34}N_2O_9$. Calculated, %: C 60.22; H 6.61.

***N*-(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)-3-(benzyloxycarbonylamino)propionamide (XVIII).** Yield 77%; TLC: systems E', F; mp 125–127°C (from ethyl acetate–acetone). Found, %: C 61.21, 61.24; H 6.65, 6.70. $C_{25}H_{32}N_2O_8$. Calculated, %: C 61.46; H 6.60.

***N*-(2,3,5,6,8,9,11,12,14,15-Decahydro-1,4,7,10,-13,16-benzohexaoxacyclooctadecin-18-yl)-3-(benzyloxycarbonylamino)propionamide (XIX).** Yield 91%; TLC: systems E', F; mp 141–142°C (from ethyl acetate–acetone). Found, %: C 60.71, 60.74; H 6.86, 6.89. $C_{27}H_{36}N_2O_9$. Calculated, %: C 60.89; H 6.81.

Crown-containing amino acid amides XX–XXIII were synthesized by catalytic hydrogenation of compounds **XVI**–**XIX** under atmospheric pressure in methanol over 5% Pd/C. The progress of the reaction

was monitored by TLC using system E'. The solvent was removed under reduced pressure on a rotary evaporator, and compounds **XX–XXIII** were brought into reaction with chloride **VI** without isolation and purification. The procedure was the same as in the synthesis of compound **VIII**. The properties of products **X**–**XIII** are given above.

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