Synthesis and Central Nervous System Stimulant Activity of 5,8-Methanoquinazolines Fused with 1,2,4-Triazole, Tetrazole and 1,2,4-Triazine

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Received December 31, 1997

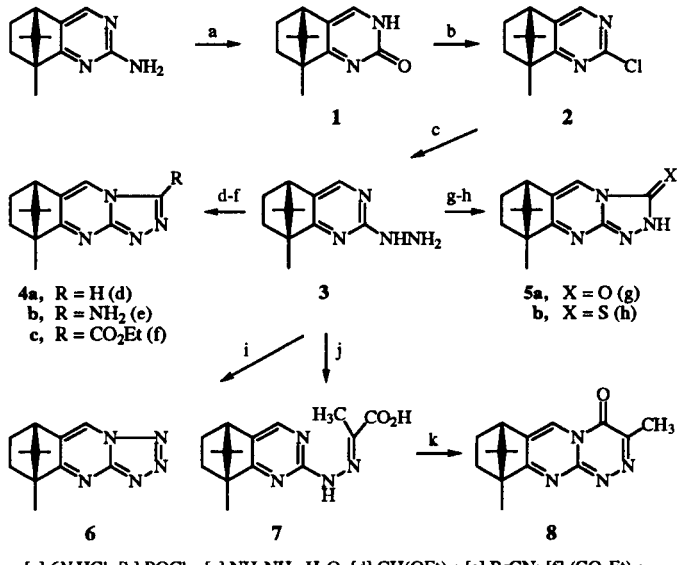
5,8-Methanoquinazolines fused with 1,2,4-triazole **4-5**, tetrazole **6**, and 1,2,4-triazine **8** were prepared starting from 2-hydrazino-5,8-methanoquinazoline **3**. Compound **3** and **6** showed the most potent central nervous system (CNS) stimulant activities.

J. Heterocyclic Chem., **35**, 325 (1998).

In a previous paper we reported the synthesis of novel 5,8-methanoquinazolines fused with imidazole, thiadiazole, pyrimidine and 1,3,5-triazine [1]. Most compounds of this group exhibited central nervous system (CNS) stimulant activity. In continuation of our studies on the structure and activity relationship, we report now the synthesis of 5,8-methanoquinazolines fused with 1,2,4-triazole, tetrazole and 1,2,4-triazine starting from 2-hydrazino-5,8-methanoquinazoline **3**.

Compound **3** was prepared as shown in Scheme 1. (5*S*,8*R*)-2-Amino-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline [1] was hydrolyzed in hydrochloric acid to provide quantitatively 5,8-methanoquinazolin-2-one **1** which subsequently underwent chlorination with phosphorus oxychloride to yield the chloro derivative **2**. Hydrazinolysis of **2** with hydrazine hydrate proceeded readily to give the hydrazino compound **3** in 79% overall yields. The ^{1}H nmr spectrum of **3** showed hydrazino protons at δ 3.50 ppm (NH_2) and δ 6.24 ppm (NH). Ring closure of **3** with triethyl orthoformate gave 1,2,4-triazolo[3,4-*b*]quinazoline **4a**. The structure of **4a** was established by ^{1}H nmr spectrum in which a triazole proton appeared at δ 8.65 ppm. Treatment of **3** with cyanogen bromide in methanol also gave the 3-amino compound **4b**. The presence of this amino group was determined by ir and ^{1}H nmr spectra. 3-Ethoxycarbonyl analogue **4c** was obtained after a prolonged heating of **3** with diethyl oxalate. The ethoxycarbonyl group of **4c** was chracterized by ^{1}H nmr spectrum. Compound **3**, on heating with 1,1'-carbonyldiimidazole in toluene, gave 1,2,4-triazino-[3,4-*b*]quinazolin-3-one **5a**, which was confirmed to exist as a keto form by ir and ^{1}H nmr spectra. Similar ring closure of 3 with carbon disulfide proceeded in pyridine to provide **5b**. The structure of **5b** was confirmed to be thione form as well as **5a** on the basis of the spectral data. Tetrazolo[5,1-*b*]quinazoline **6** was readily obtained in good yield when **3** was treated with sodium nitrite in hydrochloric acid at room temperature. The ir spectrum of **6** showed no band around 2150 cm^{-1} which excluded the azido (N_3) structure in the solid state. A compound in which a six-membered ring is annelated to the quinazoline ring, was prepared *via* a hydrazone intermediate **7** as follows; condensation of **3** with pyruvic acid, followed by cyclization of **7** in boiling acetic acid led to the formation of 1,2,4-triazino[3,4-*b*]quinazoline **8**.

Scheme 1



[a] 6*N* HCl; [b] $POCl_3$; [c] $NH_2NH_2 \cdot H_2O$; [d] $CH(OEt)_3$; [e] BrCN; [f] $(CO_2Et)_2$; [g] Im_2CO; [h] CS_2; [i] 5% $NaNO_2$; [j] $CH_3COCOCO_2H$; [k] CH_3CO_2H

The CNS stimulant activity of synthesized compounds **1-8** was evaluated using mice (ddy, strain, male 25-30 g). The compounds were dissolved in dimethyl sulfoxide and administerd intraperitonealy in a dose of 100 mg/Kg. Compounds **1, 3, 4b, 5b** and **6** possessed the satisfactory activity. Among them, **3** and **6** had the most potent activity,

which was comparable to pentylentetrazole. We recently reported that (5*S*,8*R*)-3-hydrazino-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazine and (6*S*,9*R*)-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methanotetrazolo[1,5-*b*][1,2,4]benzotriazine, structural isomers of **3** and **6**, showed CNS stimulant activity comparable to pentylenetetrazole [2]. It is of great interest in view of the structural similarity that the CNS stimulant activity is maintained even if the 1,2,4-benzotriazine ring is replaced by the quinazoline ring.

EXPERIMENTAL

Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were obtained on a JASCO IRA-2 spectrometer. The ^{1}H nmr spectra were recorded with a JEOL EX-270 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-DX 300 spectrometer.

(5*S*,8*R*)-8,9,9-Trimethyl-2,3,5,6,7,8-hexahydro-5,8-methanoquinazolin-2-one **1**.

A solution of 2 g (9.85 mmoles) of (5*S*,8*R*)-2-amino-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline [1] in 30 ml of 6*N* hydrochloric acid was refluxed for 27 hours and evaporated to dryness. The residue was washed with 5% sodium bicarbonate solution and extracted with chloroform. The chloroform was distilled from the extract to give a white powder. Recrystallization from ethyl acetate gave colorless crystals, mp 232°, yield 1.92 g (96%); ^{1}H nmr (deuteriochloroform): δ 7.37 (s, 1H, 4-H), 12.6 (br s, 1H, NH); ms: m/z 204 (M^+).

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.49; H, 7.81; N, 13.77.

(5*S*,8*R*)-2-Chloro-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline **2**.

A solution of 1.5 g (7.35 mmoles) of **1** in 15 ml of phosphorus oxychloride was refluxed for 30 minutes and evaporated to dryness. The residue was dissolved in a mixture of 60 ml of 1,4-dioxane and 30 ml of 20% potassium hydroxide solution. The mixture was refluxed for 2 hours and extracted with chloroform. The choroform was distilled from the extract to give a white powder. Recrystallization from ethyl acetate gave colorless crystals, mp 96-97°, yield 1.5 g (93%); ^{1}H nmr (deuteriochloroform): δ 8.27 (s, 4H, 4-H); ms: m/z 222 (M^+), 224 (M^++2).

Anal. Calcd. for $C_{12}H_{15}ClN_2$: C, 64.71; H, 6.79; N, 12.58. Found: C, 64.90; H, 6.62; N, 12.49.

(5*S*,8*R*)-2-Hydrazino-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline **3**.

A mixture of 1.4 g (6.26 mmoles) of **2** and 15 ml of hydrazine hydrate in 15 ml of dry pyridine was refluxed for 4 hours and evaporated to dryness. The residue was washed with 3% potassium carbonate solution and extracted with chloroform. The choroform was distilled from the extract to give a white solid. Recrystallization from hexane gave colorless crystals, mp 85°, yield 1.2 g (89%); ^{1}H nmr (deuteriochloroform): δ 3.50 (br s, 2H, NH_2), 6.24 (s, 1H, NH), 7.95 (s, 1H, 4-H); ms: m/z 218 (M^+).

Anal. Calcd. for $C_{12}H_{18}N_4$: C, 66.02; H, 8.31; N, 25.67. Found: C, 66.17; H, 8.39; N, 25.59.

(6*S*,9*R*)-9,11,11-Trimethyl-6,7,8,9-tetrahydro-6,9-methano-[1,2,4]triazino[3,4-*b*]quinazoline **4a**.

A suspension of 0.03 g (0.14 mmole) of **3** and 0.4 ml of triethyl orthoformate was stirred at 60° for 4 hours. The precipitate was filtered and recrystallized from ethyl acetate to give colorless crystals, mp 180°, yield 0.011 g (35%); ^{1}H nmr (deuteriochloroform): δ 8.04 (s, 1H, 5-H), 8.65 (s, 1H, 3-H); ms: m/z 228 (M^+).

Anal. Calcd. for $C_{13}H_{16}N4$: C, 68.39; H, 7.06; N, 24.54. Found: C, 68.50; H, 7.20; N, 24.60.

(6*S*,9*R*)-3-Amino-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methano[1,2,4]triazolo[3,4-*b*]quinazoline **4b**.

A mixture of 0.04 g (0.18 mmole) of **3** and 0.078 g (0.74 mmole) of cyanogen bromide in 4 ml of 75% methanol was stirred at room temperature for 23 hours and evaporated to dryness. The residue was dissolved in 3 ml of water and made alkaline with 5% sodium bicarbonate solution to precipitate a white solid which was collected. The filtrate was extracted with chloroform-ethanol (10:1) and solvents were distilled from the extract to give a white solid. The combined white solid was recrystallized from ethanol to give colorless crystals, mp 279°, yield 0.03 g (64%); ir (potassium bromide): 3350, 3200 (NH_2) cm^{-1}; ^{1}H nmr (deuteriochloroform-methanol-d_4 = 10:1): δ 7.86 (s, 1H, 5-H); ms: m/z 243 (M^+).

Anal. Calcd. for $C_{13}H_{17}N_5$: C, 64.17; H, 70.43; N, 28.78. Found: C, 64.29; H, 70.49; N, 28.90.

Ethyl (6*S*,9*R*)-9,11,11-Trimethyl-6,7,8,9-tetrahydro-6,9-methano[1,2,4]triazolo[3,4-*b*]quinazoline-3-carboxylate **4c**.

A mixture of 0.04 g (0.18 mmole) of **3** and 0.027 g (0.18 mmole) of diethyl oxalate in 4 ml of absolute ethanol was refluxed for 19 hours and evaporated to dryness. The residue was recrystallized from ethyl acetate to give yellow crystals, mp 269°, yield 0.033 g (60%); ^{1}H nmr (deuteriochloroform): δ 1.50 (t, 3H, J = 7 Hz, CH_2CH_3), 4.55 (q, 2H, J = 7 Hz, CH_2CH_3), 8.97 (s, 1H, 5-H); ms: m/z 300 (M^+).

Anal. Calcd. for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.79; H, 6.90; N, 18.60.

(6*S*,9*R*)-9,11,11-Trimethyl-2,3,6,7,8,9-hexahydro-6,9-methano-[1,2,4]triazolo[3,4-*b*]quinazolin-3-one **5a**.

A mixture of 0.04 g (0.18 mmole) of **3** and 0.06 g (0.18 mmole) of 1,1'-carbonyldiimidazole in 2 ml of toluene was refluxed for 1 hour and evaporated to dryness. The residue was recrystallized from ethyl acetate to give colorless crystals, mp 257°, yield 0.03 g (67%); ir (potassium bromide): 3130 (NH), 1730 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.67 (s, 1H, 5-H), 10.46 (br s, 1H, NH); ms: m/z 244 (M^+).

Anal. Calcd. for $C_{13}H_{16}N_4O$: C, 63.91; H, 6.60; N, 22.93. Found: C, 63.99; H, 6.70; N, 22.85.

(6*S*,9*R*)-9,11,11-Trimethyl-2,3,6,7,8,9-hexahydro-6,9-methano-[1,2,4]triazolo[3,4-*b*]quinazoline-3-thione **5b**.

A solution of 0.04 g (0.18 mmole) of **3** in 1.5 ml of carbon disulfide was refluxed for 13.5 hours and evaporated to dryness. The residue was recrystallized from ethyl acetate-ether (1:1) to give yellow crystals, mp 298°, yield 0.021 g (44%); ir (potassium bromide): 3115 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.21 (s, 1H, 5-H), 12.0 (br s, 1H, NH); ms: m/z 260 (M^+).

Anal. Calcd. for $C_{13}H_{16}N_4S$: C, 59.97; H, 6.19; N, 21.52. Found: C, 59.88; H, 6.11; N, 21.70.

(6*S*,9*R*)-9,11,11-Trimethyl-6,7,8,9-tetrahydro-6,9-methanotetrazolo[5,1-*b*]quinazoline **6**.

To an ice-cold solution of 5 mg (0.023 mmole) of **3** in 0.5 ml of 5% hydrochloric acid solution was added a solution of 0.5 ml of 5% sodium nitrite solution during 10 minutes. The reaction mixture was stirred for 1 hour at room temperature, neutralized with 5% sodium bicarbonate solution and extracted with chloroform. The chloroform was distilled from the extract to give a white solid. Recrystallization from ether gave colorless crystals, mp 155°, yield 5 mg (95%); ^{1}H nmr (deuteriochloroform): δ 8.60 (s, 1H, 5-H); ms: m/z 229 (M^+), 201 (M^+-N_2).

Anal. Calcd. for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.54. Found: C, 62.98; H, 6.52; N, 30.42.

2-Oxopropanoic Acid [(5*S*,8*R*)-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazolin-2-yl]hydrazone **7**.

A mixture of 0.1 g (0.5 mmole) of **3** and 0.041 g (0.47 mmole) of pyruvic acid in 4 ml of absolute ethanol was refluxed for 2 hours and evaporated to dryness. The residue was dissolved in 3 ml of 10% sodium bicarbonate solution and filtered. The filtrate was acidified with 10% hydrochloric acid and extracted with chloroform. The chloroform was distilled from the extract to give a white solid. Recrystallization from ethyl acetate gave colorless plates, mp 242°, yield 0.12 g (89%); ^{1}H nmr (deuteriochloroform): δ 2.18 (s, 1H, =CCH_3), 8.22 (s, 1H, 4-H); ms: m/z 244 (M^+-CO_2).

Anal. Calcd. for $C_{15}H_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.42; H, 7.03; N, 19.49.

(7*S*,10*R*)-3,10,12,12-Tetramethyl-7,8,9,10-tetrahydro-7,10-methano[1,2,4]triazino[3,4-*b*]quinazolin-3-one **8**.

A solution of 0.09 g (0.31 mmole) of **7** in 3 ml of acetic acid was refluxed for 30 hours and evaporated to dryness. The residue was neutralized with 10% sodium bicarbonate solution and extracted with chloroform. The chloroform was distilled from the extract to give a white solid. Recrystallization from ethanol gave colorless needles, mp >300°, yield 0.05 g (59%); ^{1}H nmr (deuteriochloroform): δ 2.47 (s, 1H, 3-CH_3), 7.90 (s, 1H, 6-H); ms: m/z 270 (M^+).

Anal. Calcd. for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.48; H, 6.59; N, 20.69.

Acknowledgement.

The authors thank the Ministry of Education, Science and Culture for support of this work with a Grant-in-Aid for Scientific Research. Thanks are also due to the staffs of Analytical Center of this Faculty for elemental analyses and spectral measurement.

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