# Synthesis and Central Nervous System Stimulant Activity of Camphor-1,2,4-benzotriazines Fused with Five and Six-membered Heterocycles

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Novel camphor-1,2,4-triazines fused with imidazole **2-3**, thiadiazole **4**, 1,2,4-triazole **7**, pyrimidine **9-13** and 1,3,5-triazine **14**, were synthesized starting from (5*R*,8*S*)-3-amino-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazine **1**. Evaluation of central nervous system stimulant activity demonstrated that the presence of a N-N group at C-3 position of 1,2,4-benzotriazine will be essential for the activity.

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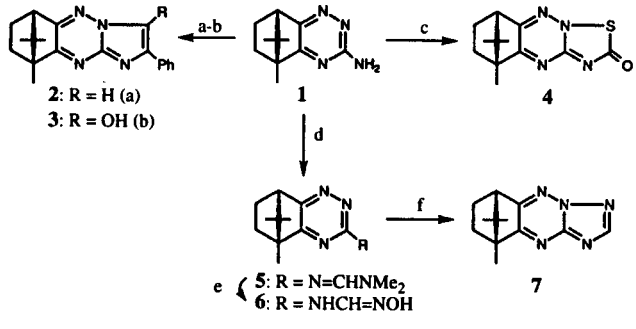
In a previous paper [1], we reported the synthesis and central nervous system (CNS) stimulant activities of camphor-1,2,4-triazines fused with 1,2,4-triazole, tetrazole and 1,2,4-triazines. As a result of the investigation on structure and activity relationship, we found that the presence of a N-N group at C-3 position of 1,2,4-triazine ring might be essential for CNS stimulant activity. As a continuing program aimed at structure and activity relationship, we have prepared novel camphor-1,2,4-triazines **2-14** having a N-C group at C-3 position of 1,2,4-triazine ring, starting from (5*R*,8*S*)-3-amino-5,9,9-trimethyl-5,6,-7,8-tetrahydro-5,8-methano-1,2,4-benzotriazine **1** which is a versatile starting compound for the construction of cyclocondensed heterocyclic ring systems.

Synthesis of camphor-1,2,4-triazines **2-4** and **7** fused with five-membered heterocycles is summarized in Scheme 1. Compound **1**, prepared by modifing the reported procedure [2], was condensed with 2-bromoacetophenone to give tetracyclic 2-phenyl-6,9-methanoimidazo[1,2-*b*][1,2,4]benzotriazine **2**. Formation of an imidazole ring was ascertained by the $^1$H nmr spectrum which showed new signal attributable to imidazole proton at δ 7.44 ppm. Similar cyclization with phenyl glyoxal monohydrate proceeded in the presence of hydrochloric acid to give 2-phenyl-3-hydroxy-6,9-methanoimidazo[1,2-*b*]-[1,2,4]benzotriazine **3**. Construction of a thiadiazole ring was carried out by treatment of **1** with chlorocarbonylsulfenyl chloride to yield 2-oxo-5,8-methanothiadiazolo-[2,3-*b*][1,2,4]benzotriazine **4** in 83% yield. 6,9-Methano-1,2,4-triazolo[2,3-*b*][1,2,4]benzotriazine **7** was prepared in three steps from compound **1**. Compound **1** was converted to the corresponding formamidine **5**, which was subsequently treated with hydroxylamine hydrochloride to give formamide oxime **6**. Cyclization to **7** was achieved by heating **6** in polyphosphoric acid at 120°. A triazole proton was appeared at δ 8.47 ppm in $^1$H nmr spectrum, confirming the structure **7**.

The compounds in which a six-membered ring is annelated to camphor-1,2,4-triazine ring were prepared as

Scheme 1

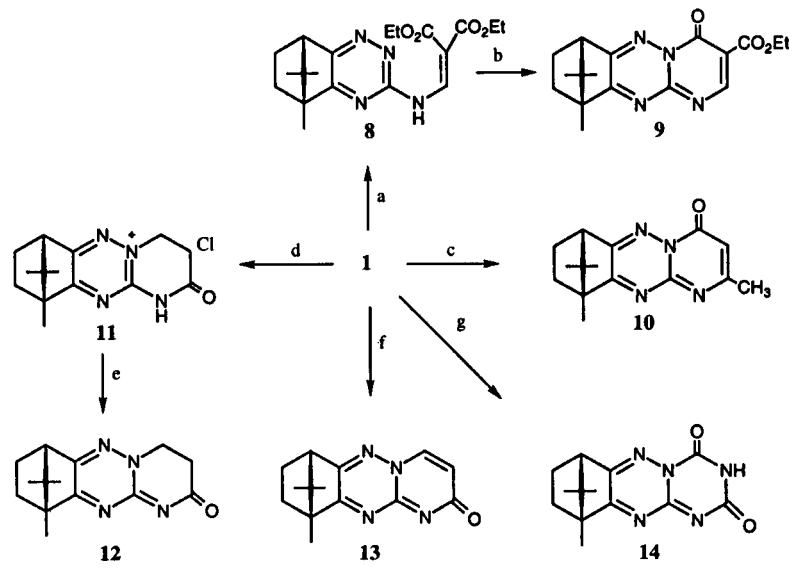



a, $C_6H_5COCH_2Br$; b, $C_6H_5COCHO$; c, ClCOSCl; d, $Me_2NCH(OMe)_2$; e, $NH_2OH$•HCl; f, PPA

shown in Scheme 2. Condensation of **1** with diethyl ethoxymethylenemalonate under thermal condition yielded the intermediate; diethyl(5,8-methano-1,2,4-benzotriazin-3-yl)aminomethylenemalonate **8** which, on heating at elevated temperature in Dowtherm A, readily underwent cyclization to provide ethyl 4-oxo-7,10-methanopyrimido[1,2-*b*][1,2,4]benzotriazine-3-carboxylate **9**. A new signal due to the pyrimidine proton was clearly appeared at δ 9.00 ppm in the $^1$H nmr spectrum. The structural analogous **10** was also obtained from reaction of **1** with ethyl acetoacetate. Treatment of **1** with 3-chloropropionyl chloride in the presence of triethylamine gave cyclic 2-oxo-7,10-methanopyrimido[1,2-*b*][1,2,4]benzotriazinium chloride **11**, which was converted to the free base **12** on treatment with an aqueous solution of potassium carbonate. Prolonged heating of **1** with methyl propiolate in ethanol provided pyrimido[1,2-*b*][1,2,4]benzotriazin-2-one **13**. In the $^1$H nmr spectrum, two olefinic protons appeared as doublets at δ 6.44 ppm and δ 7.98 ppm, respectively.

Bifunctional electrophilic reagent *N*-(chlorocarbonyl)-isocyanate was reacted with **1** followed by treatment with

Scheme 2




a, $EtOCH{=}C(CO_2Et)_2$; b, Dowtherm A; c, $CH_3COCH_2CO_2Et$; d, $ClCH_2CH_2COCl$; e, 10% $K_2CO_3$; f, methyl propiolate; g, ClCONCO, $Et_3N$

triethylamine gave [1,3,5]triazino[1,2-*b*][1,2,4]benzotriazine-2,4(3*H*)-dione **14**. The $^1H$ nmr spectrum of **14** displayed a deuterium oxide exchangeable proton at δ 8.16 ppm, consistent with a NH proton of 1,3,5-triazine ring.

The CNS stimulant activity of synthesized compounds **1-14** was evaluated using mice (ddy, strain, male, 25-30 g). The compounds were suspended in physiological saline and administered orally in a dose of 100 mg/Kg. Contrary to our expectations, none of these compounds showed any satisfactory CNS stimulant activity. Administration in a dose of up to 250 mg/Kg however was ineffective on activity. These results demonstrate that the presence of a N-N group at C-3 position of 1,2,4-benzotriazine is most probably essential for the stimulant activity.

In conclusion, we have prepared novel camphor-1,2,4-triazines fused with imidazole, thiadiazole, 1,2,4-triazole, pyrimidine and 1,3,5-triazine, and found that replacement of the N-N group by a N-C group at the C-3 position of the 1,2,4-triazine ring resulted in disappearance of CNS stimulant activity.

## EXPERIMENTAL

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared spectra were measured with a JASCO IRA-2 spectrometer. Mass spectra were measured with a JEOLJMS-DX 300 spectrometer. The $^1H$ nmr and $^{13}C$ nmr spectra were recorded with a JEOL EX-270 spectrometer using tetramethylsilane as an internal standard.

(5*R*,8*S*)-3-Amino-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazine **1**.

A suspension of camphorquinone (20 g, 0.12 mole) and aminoguanidine bicarbonate (14 g, 0.1 mole) in ethanol (300 ml) was stirred under reflux for 24 hours. The clear solution was evaporated *in vacuo*. The residue was recrystallized from methanol to give colorless needles, mp 262-264° (265° [2]), yield 14.5 g (69%); ir (potassium bromide): 3340 and 3200 ($NH_2$), 1635 (C=N) $cm^{-1}$; $^1H$ nmr (deuteriochloroform-methanol-$d_4$): δ 3.06 (1H, d, J = 4 Hz, 8-H), 5.50 (2H, br s, $NH_2$); $^{13}C$ nmr (deuteriochloroform-methanol-$d_4$): δ 9.02 (11-Me), 18.28 (10-Me), 20.03 (5-Me), 50.39 (C-8), 157.96 (C-4a or C-8a), 161.81 (C-4a or C-8a), 172.87 (C-3); ms: m/z 204 ($M^+$).

*Anal.* Calcd. for $C_{11}H_{16}N_4$: C, 64.68; H, 7.90; N, 27.43. Found: C, 64.67; H, 7.91; N, 27.49.

(6*S*,9*R*)-2-Phenyl-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methanoimidazo[1,2-*b*][1,2,4]benzotriazine **2**.

To a suspension of **1** (0.5 g, 2.5 mmoles) in absolute ethanol (10 ml) was added a solution of 2-bromoacetophenone (0.5 g, 2.5 mmoles) in absolute ethanol (5 ml). The mixture was stirred at room temperature for 1 hour and then under reflux for 10 hours. After evaporation *in vacuo*, the residue was chromatographed on silica gel. Elution with chloroform gave a dark green solid. Recrystallization from chloroform-ether gave green yellowish needles, mp 240-241°, yield 0.56 g (75%); $^1H$ nmr (deuteriochloroform): δ 3.01 (1H, d, J = 4 Hz, 6-H), 7.44 (1H, s, 3-H); ms: m/z 304 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{20}N_4$: C, 74.97; H, 6.62; N, 18.41. Found: C, 75.06; H, 6.48; N, 18.61.

(6*S*,9*R*)-2-Phenyl-3-hydroxy-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methanoimidazo[1,2-*b*][1,2,4]benzotriazine **3**.

A mixture of **1** (0.4 g, 2 mmoles), phenylglyoxal monohydrate (0.26 g, 2 mmoles), 35% hydrochloric acid (0.2 ml) and ethanol

(2 ml) was stirred at room temperature for 2 days and evaporated *in vacuo*. The dark red residue was washed with 5% sodium bicarbonate and extracted with chloroform. Removal of extract gave a dark red solid. Recrystallization from methanol-ether gave dark red needles, mp 255-257°, yield 0.47 g (75%); ir (potassium bromide): 3450 (OH) $cm^{-1}$; $^1H$ nmr (deuteriochloroform-methanol-$d_4$): δ 7.15 (3H, m, Ar), 7.95 (2H, m, Ar); ms: m/z 320 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.46; H, 6.20; N, 17.31.

(5*R*,8*S*)-5,11,11-Trimethyl-5,6,7,8-tetrahydro-5,8-methano-2*H*-thiadiazolo[2,3-*b*][1,2,4]benzotriazin-2-one **4**.

To a stirred suspension of **1** (0.3 g, 1.5 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise a solution of chlorocarbonyl chloride (0.29 g, 2.2 mmoles) in dry tetrahydrofuran (5 ml) under nitrogen. The mixture was stirred at room temperature for 25 hours and evaporated *in vacuo*. The residue was chromatographed on silica gel (chloroform) to give a yellowish solid. Recrystallization from chloroform-methanol gave green yellowish needles, mp 218-220°, yield 0.32 g (83%); ir (potassium bromide): 1705 (C=O) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.07 (1H, d, J = 4 Hz, 8-H); $^{13}C$ nmr (deuteriochloroform): δ 175.5 (C=O); ms: m/z 262 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{14}N_4OS$: C, 54.94; H, 5.38; N, 21.36. Found: C, 55.12; H, 5.33; N, 21.54.

*N*,*N*-Dimethyl-*N*'-[(5*R*,8*S*)-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazin-3-yl]formamidine **5**.

A mixture of **1** (0.2 g, 1 mmole) and *N*,*N*-dimethylformamide dimethylacetal (0.3 ml) in toluene (20 ml) was heated under reflux for 20 minutes. The solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (chloroform) to give an analytically pure sample as a colorless oil, yield 0.24 g (94%); $^1H$ nmr (deuteriochloroform): δ 3.18 (6H, s, $N(Me)_2$), 8.67 (1H, s, N=CH); ms: m/z 259 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{21}N_5$: C, 64.83; H, 8.16; N, 27.00. Found: C, 65.11; H, 8.40; N, 27.12.

*N*-[(5*R*,8*S*)-5,9,9-Trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazin-3-yl]formamide Oxime **6**.

A mixture of **5** (0.24 g, 0.93 mmole) and equimolar amount of hydroxylamine hydrochloride in absolute methanol (5 ml) was stirred at room temperature for 20 minutes. The solvent was evaporated *in vacuo*. The residue was recrystallized from methanol to give colorless plates, mp 209-210°, yield 0.22 g (96%); $^1H$ nmr (deuteriochloroform): δ 7.97 (1H, d, J = 6 Hz, NHC*H*), 8.31 (1H, d, J = 6 Hz, N*H*CH); ms: m/z 247 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{17}N_5O$: C, 58.28; H, 6.93; N, 28.32. Found: C, 58.36; H, 6.88; N, 28.21.

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

A mixture of **6** (0.2 g, 0.8 mmole) and polyphosphoric acid (1 ml) was stirred at 120° for 1 hour under nitrogen. After cooling, water (10 ml) was added, neutralized with 5% sodium bicarbonate and extracted with chloroform. The extract was evaporated *in vacuo*. The residue was recrystallized from hexane to give colorless plates, mp 163-165°, yield 0.17 g (92%); $^1H$ nmr (deuteriochloroform): δ 8.47 (1H, s, 2-H); ms: m/z 229 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.54. Found: C, 62.65; H, 6.69; N, 30.37.

Diethyl *N*-[(5*R*,8*S*)-5,9,9-Trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazin-3-yl]aminomethylenemalonate **8**.

A mixture of **1** (0.2 g, 1 mmole) and diethyl ethoxymethylenemalonate (0.22 g, 1 mmole) in dimethylformamide (10 ml) was refluxed for 14 hours under nitrogen. The solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (chloroform) to give a white solid. Recrystallization from hexane gave colorless needles, mp 101-103°, yield 0.24 g (65%); ir (potassium bromide): 3260 (NH), 1720 ($CO_2Et$) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 9.15 (1H, d, J = 13.2 Hz, NHC*H*=), 10.98 (1H, d, J = 13.2 Hz, N*H*CH=, deuterium oxide exchangeable); ms: m/z 374 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{26}N_4O_4$; C, 60.95; H, 7.00; N, 14.96. Found: C, 60.84; H, 7.08; N, 15.09.

Ethyl (7*S*,10*R*)-10,12,12-Trimethyl-4-oxo-7,8,9,10-tetrahydro-7,10-methano-4*H*-pyrimido[1,2-*b*][1,2,4]benzotriazine-3-carboxylate **9**.

A solution of **8** (0.07 g, 0.2 mmole) in Dowtherm A (2 ml) was stirred at 180-190° for 2 days. After cooling, the mixture was diluted with hexane (15 ml) and allowed to stand to precipitate a white solid. Recrystallization from hexane gave a light yellow crystalline powder, mp 165-167°, yield 0.049 g (80%); ir (potassium bromide): 1760 ($CO_2Et$) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.48 (3H, t, J = 8 Hz, $CH_2CH_3$), 4.43 (2H, q, J = 8 Hz, $CH_2CH_3$), 9.00 (1H, s, 2-H); ms: m/z 328 ($M^+$).

*Anal.* Calcd. for $C_{17}H_{20}N_4O_3$: C, 72.18; H, 6.14; N, 17.06. Found: C, 72.03; H, 6.06; N, 17.13.

(7*S*,10*R*)-2,10,12,12-Tetramethyl-7,8,9,10-tetrahydro-7,10-methano-4*H*-pyrimido[1,2-*b*][1,2,4]benzotriazin-4-one **10**.

A mixture of **1** (0.2 g, 1 mmole) and ethyl acetoacetate (0.26 g, 2 mmoles) in acetic acid (2 ml) was refluxed for 8 hours. The solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (chloroform-methanol = 100:3) to give a light yellow solid. Recrystallization from chloroform-ether gave light yellow needles, mp 280-281°, yield 0.2 g (75%); ir (potassium bromide): 1705 (C=O) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.24 (1H, s, 2-Me), 6.49 (1H, s, 3-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, 66.85; H, 6.57; N, 20.61.

(7*S*,10*R*)-10,12,12-Trimethyl-2-oxo-1,2,3,4,7,8,9,10-octahydro-7,10-methanopyrimido[1,2-*b*][1,2,4]benzotriazinium Chloride **11**.

To a stirred suspension of **1** (0.5 g, 2.5 mmoles) and triethylamine (0.3 g, 3 mmoles) in dry chloroform (15 ml) was added dropwise a solution of 3-chloropropionyl chloride (0.38 g, 3 mmoles) in dry chloroform (5 ml). The mixture was stirred at room temperature for 12 hours and then under reflux for 3 hours. After cooling, the white precipitates were collected and recrystallized from ethanol-ether to give a white amorphous powder, mp 240-243°, yield 0.53 g (73%); $^1H$ nmr (deuteriochloroformdimethyl sulfoxide-$d_6$): δ 3.23 (2H, t, J = 8 Hz, $COCH_2CH_2$), 4.81 (2H, t, J = 8 Hz, $COCH_2CH_2$); ms: m/z 258 ($M^+$-HCl).

*Anal.* Calcd. for $C_{14}H_{19}ClN_4O$: C, 57.04; H, 6.50; N, 19.01. Found: C, 57.21; H, 6.70; N, 19.19.

(7*S*,10*R*)-10,12,12-Trimethyl-3,4,7,8,9,10-hexahydro-7,10-methanopyrimido[1,2-*b*][1,2,4]benzotriazin-2-one **12**.

A solution of **11** (0.5 g, 1.7 mmoles) in water (10 ml) was mixed with 10% potassium carbonate (20 ml) and extracted with

chloroform. The extract was evaporated *in vacuo*. The residue was recrystallized from ethanol-ether to give light yellow needles, mp 185-187°, yield 0.4 g (96%); ir (potassium bromide): 1660 (C=O) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 2.81 (2H, t, J = 8 Hz, $COCH_2CH_2$), 4.33 (2H, t, J = 8 Hz, $COCH_2CH_2$); ms: m/z 258 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.22; H, 7.18; N, 21.50.

(7*S*,10*R*)-10,12,12-Trimethyl-7,8,9,10-tetrahydro-7,10-methanopyrimido[1,2-*b*][1,2,4]benzotriazin-2-one **13**.

To a suspension of **1** (0.5 g, 2.5 mmoles) in ethanol (5 ml) was added dropwise a solution of methyl propiolate (0.2 g, 2.5 mmoles) in ethanol (5 ml). The mixture was refluxed for 2 days under nitrogen. The solvent was evaporated *in vacuo*. The residue was recrystallized from ethanol-ether to give light yellow needles, mp 240°, yield 0.48 g (68%); ir (potassium bromide): 1640 (C=O) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 6.44 (1H, d, J = 7.2 Hz, 3-H), 7.98 (1H, d, J = 7.2 Hz, 4-H); ms: m/z 256 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.49; H, 6.08; N, 21.99.

(7*S*,10*R*)-10,12,12-Trimethyl-7,8,9,10-tetrahydro-7,10-methano-[1,3,5]triazino[1,2-*b*][1,2,4]benzotriazine-2,4(3*H*)dione **14**.

To a stirred suspension of **1** (0.3 g, 1.5 mmoles) in dry dichloromethane (10 ml) was added dropwise at 0° a solution of chlorocarbonyl isocyanate (0.16 g, 1.5 mmoles) in dry dichloromethane (5 ml) under nitrogen. After stirring for 30 minutes at room temperature, triethylamine (0.25 ml) was added to the mixture. The mixture was stirred for an additional 1 hour and evaporated *in vacuo*. The residue was chromatographed on silica gel (chloroform) to give a light yellow powder. Recrystallization from methanol-ether gave light yellow needles, mp 148-150°, yield 0.34 g (85%); ir (potassium bromide): 1725 (C=O) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 8.16 (1H, br s, NH); ms: m/z 273 ($M^+$), 230 ($M^+$-CONH).

*Anal.* Calcd. for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.01; H, 5.38; N, 25.55.

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## REFERENCES AND NOTES

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