SYNTHESIS AND CENTRAL NERVOUS SYSTEM STIMULANT ACTIVITY OF CAMPHOR-1,2,4-TRIAZINES FUSED WITH 1,2,4-TRIAZOLE, TETRAZOLE AND 1,2,4-TRIAZINE†

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Abstract-Camphor-1,2,4-triazines fused with 1,2,4-triazole(**3-9**), tetrazole(**10**) and 1,2,4-triazine(**11**), were synthesized starting with (5*R*, 8*S*)-3-hydrazino-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazine(**2**). Compounds(**2,3** and**10**) showed central nervous system (CNS) stimulant activities.

We have been engaged in the synthesis and the pharmacological evaluation of novel nitrogen containing polyheterocycles fused with *d*-camphor. In the course of our study, we have previously prepared (5*S*,8*R*)-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,3-benzotriazine and elucidated its prominent central nervous system (CNS) stimulant activity.[1] This finding prompted us to investigate the relationship between structure and CNS stimulant activity of isomeric 5,8-methano-1,2,4-benzotriazines(**3-11**) fused with triazole, tetrazole and triazine. Since the heterocyclic hydrazines have been proved to be versatile starting product for the construction of the condensed heterocycles as we reported,[2] we are interested in the chemistry of (5*S*,8*R*)-3-hydrazino-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazine(**2**) which can undergo cyclization reaction with appropriate reagents leading to the formation of novel hetrocyclic ring systems. We wish to report here on synthesis and CNS stimulant activity of novel camphor-1,2,4-triazine derivatives.

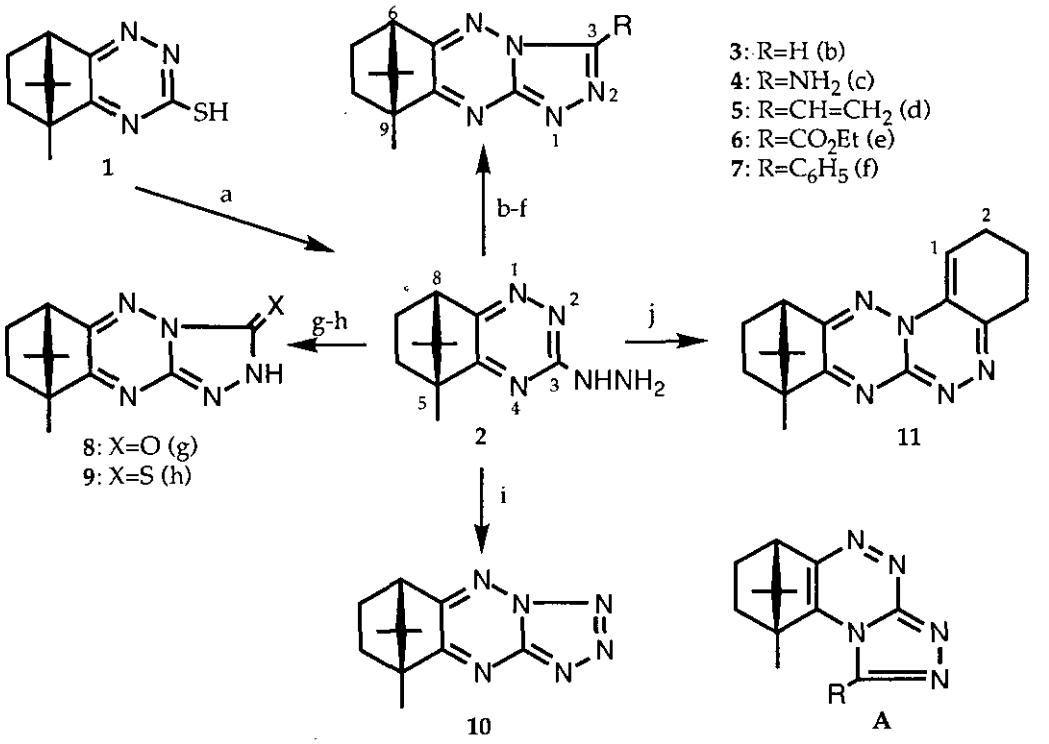
Compound (**2**)[3] was readily prepared by hydrazinolysis of known (5*S*,8*R*)-3-merucapt-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazine(**1**)[4] in excellent yield. ^{1}H Nmr spectrum of **2** showed hydrazino protons at δ 3.78 ppm(NH_2) and δ 6.54 ppm (NH). Synthesis of condensed camphor-1,2,4-benzotriazines(**3-11**) is summarized in Scheme 1. Ring closure of **2** with triethyl orthoformate under acidic conditions proceeded to provide (6*S*,9*R*)-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methano-1,2,4-triazolo[4,3-*b*][1,2,4]benzotriazine(**3**).[5] ^{1}H Nmr spectrum of **3** showed a triazole proton at δ 8.81 ppm, confirming structure . Treatment of **2** with cyanogen bromide gave (6*S*,9*R*)-3-amino-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methano-1,2,4-triazolo[4,3-*b*][1,2,4]-

triazine(**4**).[6] The presence of newly formed amino group was ascertained by ir and ^{1}H nmr spectra. When compound (**2**) was treated with acryloyl chloride, (6*S*,9*R*)-3-ethenyl-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methano-1,2,4-triazolo[4,3-*b*][1,2,4]triazine(**5**)[7] was obtained. A prolonged heating of **2** with diethyl oxalate in ethanol yielded (6*S*,9*R*)-3-ethoxycarbonyl-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methano-1,2,4-triazolo[4,3-*b*][1,2,4]benzotriazine(**6**)[8] after silica gel chromatography, although it is reported that 1-hydrazinophthalazine(hydralazine) is annelated to the phthalazine ring to give 6-membered 2*H*-1,2,4-triazino[3,4-*a*]phthaladine-3,4-dione by refluxing in excess diethyl oxalate.[9] The ethoxycarbonyl group of **6** was characterized by ^{1}H nmr spectrum. (5*R*,8*S*)-3-Benzylidenehydrazino-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazine, prepared from **2** and benzaldehyde, was oxidized with lead tetraacetate to give (6*S*,9*R*)-3-phenyl-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methano-1,2,4-triazolo[4,3-*b*][1,2,4]benzotriazine(**7**).[10] Compound (**2**), on refluxing with 1,1-carbonyldiimidazole in toluene, gave (6*S*,9*R*)-9,11,11-trimethyl-2,3,6,7,8,9-hexahydro-6,9-methano-1,2,4-triazolo[4,3-*b*][1,2,4]benzotriazine-3-one(**8**),[11] which was confirmed to exist as a keto form by ir and ^{1}H nmr spectra Similar ring closure of **2** with carbon disulfide in pyridine proceeded readily to provide (6*S*,9*R*)-9,11,11-trimethyl-2,3,6,7,8,9-hexahydro-6,9-methano-1,2,4-triazolo[4,3-*b*][1,2,4]benzotriazine-3-thione(**9**).[12] Compound (**9**) was confirmed to be thione structure as well as **8** on the basis of the spectral data. (6*S*,9*R*)-9,11,11-Trimethyl-6,7,8,9-tetrahydro-6,9-methano-tetrazolo[1,5-*b*][1,2,4]benzotriazine(**10**)[13] was easily obtained from **2** by the reaction with sodium nitrite in hydrochloric acid. The ir spectrum of **10** 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 1,2,4-benzotriazine system, was formed as follows. Compound (**2**)was refluxed with 1,2-cyclohexanedione in ethanol to give (8*R*,11*S*)-8,14,14-trimethyl-3,4,8,9,10,11-hexahydro-8,11-methano-2*H*-1,2,4-benzotriazino[4,3-*b*][1,2,4]benzotriazine(**11**).[14] Its structure was confirmed by ^{1}H nmr and mass spectra. While we confirmed the chemical structures of **3-11** to be the linearly fused camphor-1,2,4-triazines, the possibility of the isomeric angularly fused camphor-1,2,4-triazines as shown (**A**) in Scheme 1, should be considered. The angular structure, however, was excluded from the following evidences. No NOEs were observed between bridgehead 9-CH_3 and triazole proton in ^{1}H nmr spectrum of **3**. The remarkable chemical shift differences were not observed between 9-CH_3 of **3** and those of **6** and **8**, confirming that 9-CH_3 s of **6** and **8** are not deshielded by carbonyl groups. Construction of the corresponding angular structures of **4-7** and **11** by Dreiding model failed due to strong steric hindrance between 9-CH_3 and substituents of 1,2,4-triazine and cyclohexene ring.

The CNS stimulant activity of synthesized compounds (**1-11**) was evaluated using mice (ddy, strain, male 25-35 g). The compounds were suspended in physiological saline and administered orally in a dose of 100 mg/ kg. Compound (**2**) showed the most potent activity comparable to camphor-1,2,3-triazine.[1] Compound (**3**) and (**10**) also showed activity, potency of which were the same as that of pentylenetetrazole and, howevere, less than 50% of **2**. Introduction of substituents on 1,2,4-triazole ring of **3** resulted in disappearence of activity. From these findings, it was concluded that the presence of a N-N group at C-3 position of 1,2,4-benzotriazine is essential for CNS stimulant activity.

In conclusion, we have prepared novel camphor 1,2,4-benzotriazines fused with 1,2,4-triazole, tetrazole and 1,2,4-triazine and found that some of the condensed camphor-1,2,4-triazines are potent CNS stimulants.



Scheme 1: Reagents and Conditions: a, hydrazine hydrate, pyridine, reflux, 1.5 h, 92%; b, $CH(OEt)_3$, one drop of conc. HCl, room temperature, 0.5 h, 68%; c, BrCN, 75% MeOH, room temperature, 40 h, 90%; d, CH_2=CHCOCl, THF, room temperature, 2 h, 79%; e, $(CO_2Et)_2$, EtOH, reflux, 30 h, 88%; f, C_6H_5CHO, *p*-TsOH, EtOH, reflux, 4 h and $Pb(OAc)_4$, CH_2Cl_2, room temperature, 24 h, 79%; g, Im_2CO, toluene, reflux, 1 h, 89%; h, CS_2, pyridine, reflux, 6 h, 91%; i, 50% $NaNO_2$, 5% HCl, 0°C, 1 h, 93%; j, 1,2-cyclohexanedione, EtOH, reflux, 24 h, 86%.

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REFERENCES AND NOTES

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2. S. Nagai, N. Kato, T. Ueda, N. Oda, and J. Sakakibara, *Heterocycles*, 1986, **24**, 907.
3. **2**.light orange crystalline powders, mp 89-92°C (Et_2O). $[\alpha]_D^{22}$ +51.2 ° (*c*=0.52, $CHCl_3$). Ir($CHCl_3$)cm^{-1}: 3440 and 3340 ($NHNH_2$),1616(C=N).^{1}H Nmr($CDCl_3$) δ: 0.58(3H, s, syn 9-CH_3), 1.09(3H, s, anti 9-CH_3), 1.17(3H, s, 5-CH_3), 3.78(2H, br s, NH_2), 6.54(1H, br s, NH). Elms(m /z): 219(M^+). Anal. Calcd for $C_{11}H_{17}N_5$: C, 60.25; H, 7.81; N, 31.94. Found: C, 60.08; H, 7.67; N, 32.15.

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5. **3**. colorless plates, mp 154-155°C(hexane). $[\alpha]_D^{22}$ +12.3 °(*c*=0.2, $CHCl_3$).^{1}H Nmr($CDCl_3$)δ: 0.76(3H, s, syn 11-CH_3), 1.16(3H, s, anti 11-CH_3), 1.38(3H, s, 9-CH_3), 8.81(1H, s, triazole-H). Elms(m/z): 229(M^+). Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.54. Found: C, 62.69; H, 6.38; N, 30.49.

6. **4** . yellow needles, mp 232-234°C(EtOAc). $[\alpha]_D^{22}$ +16.3°(*c*=0.1, $CHCl_3$). Ir(KBr)cm^{-1}: 3350 and 3280(NH_2). ^{1}H Nmr($CDCl_3$)δ: 0.76(3H, s, syn 11-CH_3), 1.14(3H, s, anti 11-CH_3), 1.34(3H, s, 9-CH_3), 5.76(2H, br s, NH_2). Elms(m/z): 244(M^+). Anal. Calcd for $C_{12}H_{16}N_6$: C, 59.00; H, 6.60; N, 34.40. Found: C, 59.18; H, 6.45; N, 34.18.

7. **5**. colorless prisms, mp 220-222°C(Et_2O). $[\alpha]_D^{22}$ +41.9 °(*c*=0.24, $CHCl_3$). ^{1}H Nmr($CDCl_3$)δ: 0.77(3H, s, syn 11-CH_3), 1.16(3H, s, anti 11-CH_3), 1.38(3H, s, 9-CH_3), 5.77, 6.69 and 7.08(3H, ethenyl protons). Elms(m/z): 255(M^+). Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.92; H, 6.65; N, 27.19.

8. **6**. colorless prisms, mp 177-178°C(EtOAc-hexane). $[\alpha]_D^{22}$ +57°(*c*=0.28, $CHCl_3$).^{1}H Nmr($CDCl_3$)δ: 0.74(3H, s, syn 11-CH_3), 1.16(3H, s, anti 11-CH_3), 1.38(3H, s, 9-CH_3). 1.50(3H, t, *J*=7.2 Hz, CH_3), 4.58(2H, q, *J*=7.2 Hz, CH_2). Elms(m/z): 301(M^+). Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.36; N, 23.24. Found: C, 60.01; H, 6.41; N, 23.18.

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10. **7**. light yellow prisms, mp 181-182°C(Et_2O). $[\alpha]_D^{22}$+96.7°(*c*=0.26, $CHCl_3$). ^{1}H Nmr($CDCl_3$)δ: 0.77(3H, s, syn 11-CH_3), 1.16(3H, s, anti 11-CH3), 1.39(3H, s, 9-CH_3). 7.49-7.60(3H, m, phenyl protons), 8.37-8.44(2H, m, phenyl protons). Elms(m/z): 305(M^+). Anal. Calcd for $C_{18}H_{19}N_5$: C, 70.80; H, 6.27; N, 22.93. Found: C, 70.76; H, 6.19; N, 22.75.

11 **8**. yellow prisms, mp 234-235°C(Et_2O). $[\alpha]_D^{22}$-1.6°(*c*=0.24, $CHCl_3$). Ir(KBr):cm^{-1}: 3130(NH), 1730(C=O). ^{1}H Nmr($CDCl_3$)δ: 0.83(3H, s, syn 11-CH_3), 1.14(3H, s, anti 11-CH_3), 1.32(3H, s, 9-CH_3),10.93(1H, br s, NH). Elms(m/z): 245(M^+). Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.58; H, 6.15; N, 28.70

12. **9**. light orange crystalline powders, mp 270-273°C(Et_2O). $[\alpha]_D^{22}$ +39.6° (*c*=0.26, $CHCl_3$). Ir(KBr)cm^{-1}: 3110(NH). ^{1}H Nmr($CDCl_3$)δ: 0.78(3H, s, syn 11-CH_3), 1.14(3H, s, anti 11-CH3), 1.34(3H, s, 9-CH3), 13.09(lH, s, NH). Elms(m/z): 261(M^+). Anal. Calcd for $C_{12}H_{15}N_5S$: C, 55.15; H, 5.79; N, 26.80. Found: C, 55.10; H, 5.69; N, 26.82.

13. **10**. colorless plates, mp 188-190°C(decomp)(Et_2O). $[\alpha]_D^{22}$ +29.6°(*c*=0.2, $CHCl_3$). ^{1}H Nmr($CDCl_3$)δ: 0.76(3H, s, syn 11-CH_3), 1.20(3H, s, anti 11-CH_3), 1.44(3H, s, 9-CH_3). Elms(m/z): 230(M^+), 174(M^+-N_4). Anal. Calcd for $C_{11}H_{14}N_6$: C, 57.38; H, 6.13; N, 36.50. Found: C, 57.32; H, 6.08; N, 36.48.

14. **11**. light brown amorphous powders, mp 149-152°C(decomp)(EtOAc-hexane). $[\alpha]_D^{22}$+4.5°(*c*=0.96, $CHCl_3$).^{1}H Nmr($CDCl_3$)δ: 0.81(3H, s, syn 14-CH_3), 1.08(3H, s, anti 14-CH_3), 1.21(3H, s, 8-CH_3), 5.71(1H, t, *J*=6 Hz, 1-H). Elms(m/z): 295(M^+). Anal. Calcd for $C_{17}H_{21}N_5$: C, 69.12; H, 7.17; N, 23.71. Found: C, 69.37; H, 7.14; N, 23.65.

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