Synthesis and Central Nervous System Stimulant Activity of Camphor-1,2,3-triazine fused with Diphenylcyclopropenone and Camphor-1,2,3-triazine *N*-Oxides

Shin-ichi Nagai* and Taisei Ueda

Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori Mizuho-ku, Nagoya 467-8603

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Reactions of camphor-1,2,3-triazine **1** with diphenylcyclopropenone **2** gave two cycloadducts; 6,9-methanopyrazolo[1,2-*b*][1,2,3]benzotriazinones **3-4**. Oxidation of **1** with 3-chloroperbenzoic acid gave 1-oxide **5** as the major compound along with a trace of 1,2-dioxide **6**.

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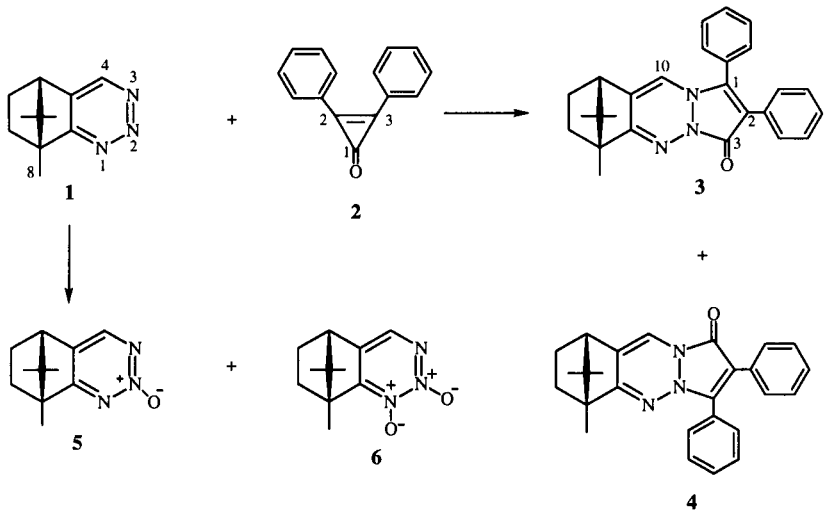
Since our finding that camphor-1,2,3-triazine **1** displayed a ten fold increase in central nervous system stimulant (CNS) activity [1], we have been engaged in the synthesis of isomeric camphor-pyrimidines and camphor-1,2,4-triazines fused with five and six-membered heterocycles and have shown that most of these compounds showed CNS stimulant activity [2-6]. In continuation of our studies on the structure and activity relationship, we now report the cycloaddition of **1** with diphenylcyclopropenone (DPCP) **2** and oxidation of **1** with 3-chloroperbenzoic acid.

The reaction of **1** and **2** in boiling benzene proceeded readily to give two isomeric 1:1 adducts **3** and **4** in 65% and 26% yields respectively. Evidence for the structural assignment of regioisomeric **3** and **4** was obtained from the spectral data. The ir spectra of **3** and **4** showed the tertialy amidic carbonyl absorptions at 1635 and 1638 cm^{-1}. A characteristic *peri* effect of triazine 10-H by the carbonyl group was observed in the ^1H nmr spectrum of **4** which showed the downfield shift (-0.53 ppm) compared with 10-H of **3**. This mode of addition occurred across the N=N bond; it is not exceptional and has previously been observed with 1,2,3-benzotriazine [7]. Adduct **3** could arise by initial nucleophillic attack of the triazine N-2 on C-1 or N-3 on C-2 of DPCP followed by cleavage of the 1,2-bond of DPCP to form the pyrazole ring; formation of **4** could similarly involve attack of N-3 on C-1 or N-2 on C-2.

N-Oxidation of **1** with 3-chloroperbenzoic acid was carried out in refluxing dichloromethane to give 2-oxide **5** in 95% yield and a trace of 1,2-dioxide **6**. The yield of **6** remained unchanged although **5** was oxidized under the same conditions. Further Attempts to improve the yield of **6** under a variety oxidative conditions however failed. In the ^1H nmr spectrum of **5**, no remarkable downfield shifts of both 8-CH_3 and 4-H were observed, suggesting that neither N-1 nor N-3 was oxidized. Boulton and co-workers have previously investigated the site of *N*-oxidation of 1,2,3-benzotriazines using mass spectral data and concluded that the mass spectra of the 2-oxides show fragments corresponding to loss of 30 (M^+-NO) while the isomeric 3-oxides show fragments corresponding to loss of 28 (M^+-N_2) [8]. On the basis of these findings, compound **5** was confirmed to be the 2-oxide because the mass spectrum of **5** showed the characteristic M^+-NO fragment

Figure 1



at 175 m/z. In contrast, compound **6** was assigned the 1,2-dioxide structure based on fragments corresponding to initial loss of 2-N oxygen (16) followed by loss of 2-N and 3-N nitrogens (28). Further structural support for **6** comes from the downfield shift of 8-CH_3 and the lack of a marked downfield shift of 4-H which should be observed in ^1H nmr spectrum if the 3-N was oxidized. Compound **6** is, to the best of our knowledge, the first reported example of 1,2,3-triazine dioxide although the yield was a trace.

The CNS stimulant activity of synthesized compounds besides **6** was evaluated using mice (ddy, strain, male 25-30 g). The compounds were dissolved in dimethyl sulfoxide and administered intraperitonealy in a dose of 50 mg/Kg. Compound **5** was injected into three mice. Immediately after administration, all animals showed tremors and twitches, and then clonic and tonic convulsions developed. All animals died with tonic extensions within two minutes after administration. The activity of **5** was comparable to pentylenetetrazole. Contrary to the expectations, camphor-1,2,3-triazines **3** and **4** fused with DPCP did not show any satisfactory CNS stimulant activity. Administration in a dose of up to 250 mg/Kg however was ineffective on activity. These results strongly suggest that the presence of the conjugated N=N double bond in the 1,2,3-triazine ring is essential for CNS stimulant activity.

In conclusion, we have prepared camphor-1,2,3-triazines **3-4** fused with pyrazole, 2-oxide **5** and 1,2-dioxide **6**. Compound **5** showed strong CNS stimulant activity.

EXPERIMENTAL

Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. The ir spectra were obtained on a JASCO IRA-2 spectrometer. The ^1H nmr spectra were recorded with a JEOL EX-270 and JEOL JMN-LA 400 spectrometers using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-DX 300 spectrometer.

(6*R*,9*S*)-6,12,12-Trimethyl-1,2-diphenyl-6,7,8,9-tetrahydro-6,9-methanopyrazolo[1,2-*b*]benzo[*d*][1,2,3]triazin-3-one (**3**) and (6*R*,9*S*)-6,12,12-Trimethyl-2,3-diphenyl-6,7,8,9-tetrahydro-6,9-methanopyrazolo[1,2-*b*]benzo[*d*][1,2,3]triazin-1-one (**4**).

A mixture of **1** (0.05 g, 0.26 mmole) and DPCP (0.055 g, 0.27 mmole) in dry benzene (10 ml) was vigorously refluxed for 6 hours and evaporated to dryness. The residue was chromatographed on silica gel with chloroform as an eluate.

The first compound to be eluted was recrystallized from hexane to give **3** as orange plates, mp 278-280°, yield 0.034 g (65.1%); ir (potassium bromide): 1635 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.92 (s, 3H, anti 12-CH_3), 1.08 (s, 3H, *syn* 12-CH_3), 1.58 (s, 3 H, 6-CH_3), 7.15 (s, 1H, 10-H), 7.17-7.47 (m, 10H, phenyl protons); ms: m/z 395 (M^+), 380 (M^+-CH_3), 352 (M^+-CH_3-CO).

Anal. Calcd. for $C_{26}H_{25}N_3O$: C, 78.96; H, 6.37; N, 10.62. Found: C, 79.02; H, 6.22; N, 10.56.

Further elution gave a yellow powder. Recrystallization from hexane gave **4** as yellow needles, mp 236-238°, yield 0.014 g (26.8%); ir (potassium bromide): 1638 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.86 (s, 3H, anti 12-CH_3), 1.07 (s, 3H, *syn* 12-CH_3), 1.03 (s, 3H, 6-CH_3), 7.68 (s, 1H, 10-H), 7.16-7.49 (m, 10H, phenyl protons); ms: m/z 395 (M^+), 380 (M^+-CH_3), 352 (M^+-CH_3-CO).

Anal. Calcd. for $C_{26}H_{25}N_3O$: C, 78.96; H, 6.37; N, 10.62. Found: C, 78.82; H, 6.51; N, 10.60.

(5*S*,8*R*)-8,9,9-Trimethyl-5,6,7,8-tetrahydro-5,8-methanobenzo[*d*][1,2,3]triazine 2-Oxide (**5**) and 1,2-Dioxide (**6**).

A mixture of **1** (0.07 g, 0.37 mmole) and 3-chloroperbenzoic acid (0.14 g, 0.81 mmole) in dry dichloromethane (20 ml) was refluxed for 1.5 hours. After cooling, the mixture was washed with 5% sodium carbonate solution. The organic layer was distilled and the residue was chromatographed on a silica gel column (chloroform). The first compound to be eluted was the 2-oxide **5**. Recrystallization from hexane-ether gave colorless needles, mp 144-146°, yield 0.072 g (95%); ^1H nmr (deuteriochroloform): δ 0.71 (s, 3H, anti 9-CH_3), 1.05 (s, 3H, *syn* 9-CH_3), 1.29 (s, 3H, 8-CH_3), 8.23 (s, 1H, 4-H); ms: m/z 205 (M^+), 175 (M^+-NO), 147 (M^+-NO-N_2).

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.49; H, 7.19; N, 20.67.

Further elution gave a trace of **6** as light yellow powders, mp 135-137°, yield 0.5 mg; ^1H nmr (deuteriochloroform): δ 0.68 (s, 3H, anti 9-CH_3), 1.07 (s, 3H, *syn* 9-CH_3), 1.41 (s, 3H, 8-CH_3), 7.94 (s, 1H, 4-H); ms: m/z 221 (M^+), 205 (M^+-O), 177 (M^+-O-N_2).

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.49; H, 7.11; N, 19.21.

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