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Unusual Bicyclic Endoperoxides Containing Pyridazine Ring : Reaction of Unsaturated Bicyclic Endoperoxides with Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate†[1]

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Abstract: Unsaturated bicyclic endoperoxides were reacted with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate. The Diels-Alder addition products **6-10** were isolated and characterized. The primary formed addition products gave the corresponding 1,4-dihydropyridazine derivatives upon extrusion of nitrogen. Pyridazine endoperoxides were synthesized by oxidation of the corresponding 1,4-dihydropyridazine derivatives with PIFA.

Metabolism of polycyclic aromatic hydrocarbons to dihydrodiols and diol epoxides is an important event in the activation of these molecules to ultimate mutagens and carcinogens[2]. It has been searched that some of the analogous aza aromatic compounds show carcinogenity[3]. Kitahara et al.[4] prepared K-region oxides of several aza aromatics and observed mutagenicity levels in *S. Typhimurium TA 100* insufficient. In the case of the larger polycyclic aromatic hydrocompounds, aza substitution can either enhance or diminish biological activity depending on the position of substitution[5].

Quinoline is also considered to have significant mutagenic and carcinogenic activity. The other analogous[6] aza aromatics which include a number of known carcinogens, have received scant attention. In connection with these earlier observation we intended to synthesize some aromatic endoperoxides containing pyridazine ring which are potential precursors for the aromatic diols and eventually epoxides.

Aromatic compounds show practically no reactivity toward singlet oxygen. However, introduction of electron donating substituents into suitable positions causes singlet oxygen addition[7]. In this paper, we introduce for the first time a new synthetic methodology leading to phthalazine-type bicyclic endoperoxides where we reacted suitable unsaturated bicyclic endoperoxides with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate. The Diels-Alder reactions of tetrazine represents most extensively studied examples of inverse electron demand Diels-Alder reactions[8].

2,3-Dioxabicyclo[2.2.2]oct-5-ene **1**[9] reacted with tetrazine **2** in dry methylene chloride to give adduct **5** formed upon nitrogen extrusion from the initial formed tricyclo-adduct **3**. Oxidation of 1,4-dihydropyridazine **5** with phenyliodo-bis(trifluoroacetate) (PIFA) afforded aromatized coumpound **6** in 83% overall yield (Scheme 1).

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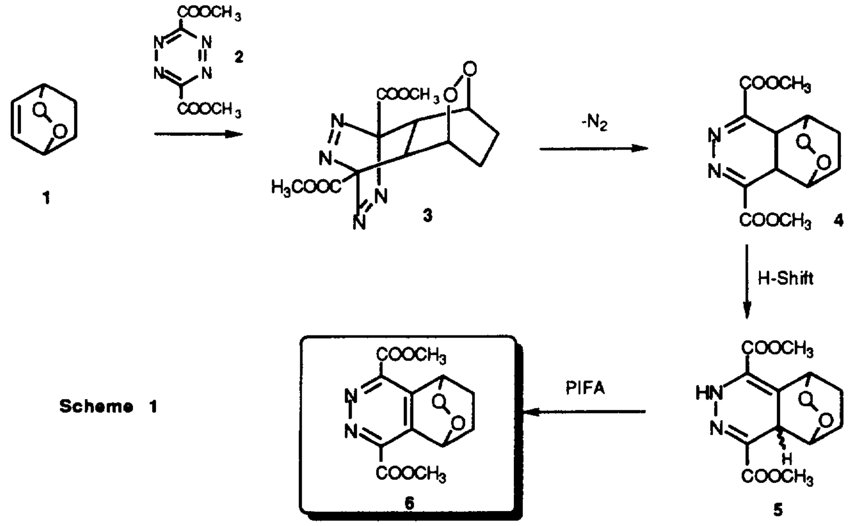
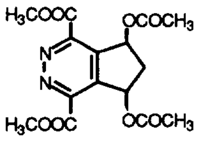
†*Dedicated to Professor Harald Günther on the occasion of his 60th birthday.*



Scheme 1

The structure of the adduct **6** is mainly assigned on the basis of spectral data. The elemental analysis, the mass spectrum [m/e 280 (M$^+$)], and the IR spectrum supported the structure and preservation of peroxide linkage. Furthermore, ^{1}H NMR and ^{13}C NMR spectra (Table 1) agreed with the structure of **6**. Especially 6 lines ^{13}C NMR spectrum indicates the presence of symmetrical structure.

In an analogous manner we have synthesized the following compounds **7**-**10** starting from the appropriate unsaturated bicyclic endoperoxides[10]. In all cases we have been able to isolate the corresponding intermediates; 1,4-dihydropyridazine endoperoxides which have been converted to aromatic compounds **6**-**10**.



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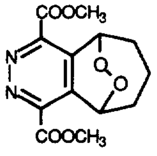

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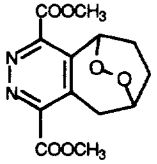

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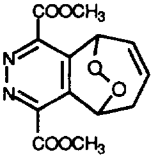

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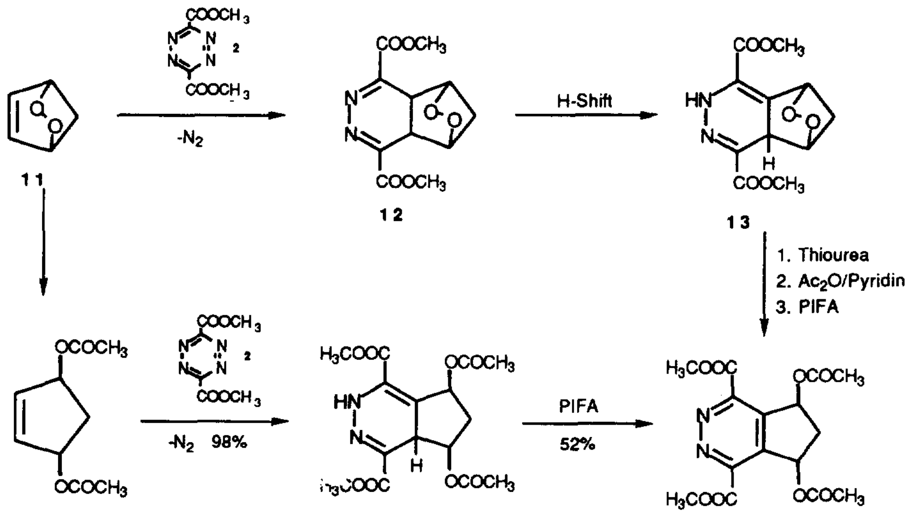
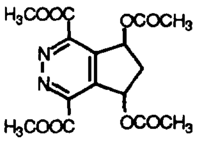
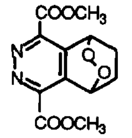
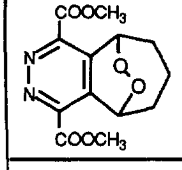
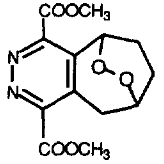
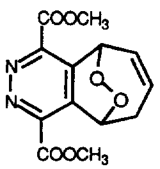
Synthesis of **7** was readily accomplished by two different approaches (Scheme 2). For the first approach we reacted formed cyclopentadiene-endoperoxide **11**[11,9b] with tetrazine **2** at low temperature to give **12**. Selective reduction of the peroxide linkage in **13** with thiourea followed by oxidation with PIFA resulted in the formation of **7** in 15% overall yield. In the second approach, we started from cis-1,3-diacetoxy-cyclopent-2-ene[9b]. Addition of **14** to tetrazine **2** gave 1,4-dihydropyridazine derivative **15** in 98% yield. Oxidation of **15** afforded **7** which was identical with the compound obtained from the first sequence.

The chemistry and biological tests of these interesting peroxides are currently under investigations and will be reported later.



14 **Scheme 2** 15 7

Table 1	Selected Physical Data of Endoroxides 6-10
	m.p. 170-171 °C yellow crystals (overall yield 57%) from CH_2Cl_2/ether; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.60 (dd, 7.7, 2.8 Hz, 2H), 4.05 (s, 6H), 3.06 (A part of AB-system, dt, 15.7, 7.7 Hz, 1H), 2.09 (B part of AB-system, dt, 15.7, 2.8 Hz, 1H), 2.06 (bs, CH_3, 6H) ; ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 171.29 (CO), 165.06 (CO), 152.57 (C), 145.63 (C), 77.84 (OCH), 55.50 (OCH_3), 41.32 (CH2), 22.50 (CH_3). Mass spectrum m/z 352 (M^+,48), 321 (7), 279 (33), 250 (61), 237 (45), 220 (100), 207 (20), 192 (81).
	m.p. 133-134°C pale yellow crystals (overall yield 83 %) from $CHCl_3$/ether; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.15 (m, 2H), 4.11 (s, 6H), 2.67 (A part of AA'XX'-system, 2H) 1.66 (X part of AA'XX'-system, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.41 (CO), 146.72 (C), 139.17 (C), 69.71 (OCH), 54.11 (OCH_3), 21.03 (CH_2). Mass spectrum m/z 280 (M^+, 88), 264 (13), 249 (100), 233 (35), 222 (100), 190 (65), 175 (38), 163 (65).
	m.p. 141-142°C yellow crystals (overall yield 57%) from CH_2Cl_2/ether; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 6.05 (m, 2H), 4,09 (s, 6H), 2.30 (m, 4H), 1.75-1.16 (m, 1H), 0.78-0.59 (m, 1H) ; ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.35 (CO), 148.01 (C), 137.00 (C), 76.70 (OCH), 54.12 (OCH_3), 31.98 (CH_2), 19.10 (CH_2). Mass spectrum m/z 294 (M^+, 8) 280 (4), 262 (100), 247 (23), 232, (52), 204 (35).
	m.p. 135-136°C pale yellow crystals (overall yield 37%) from $CHCl_3$/ether; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 5.79 (m, 1H), 4.84-4.77 (m, 1H) 4.06 (s, 3H), 4.05 (s, 3H), 3.60 (A part of AB-system, d, 19.7 Hz, 1H), 3.57 (B part of AB-system, dd, 19.7 Hz, 5.2 Hz, 1H) 2.80-2.61 (m, 1H), 2.40-2.21 (m, 2H), 1.60-1.43 (m,1H) ; ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 166.93 (CO), 166.71 (CO), 156.09 (C), 151.85 (C), 144.90 (C), 141.03 (C), 79.22 (OCH), 76.71 (OCH), 55.59 (OCH_3), 55.41 (OCH_3), 40.56 (CH_2), 25.27 (CH_2), 22.61 (CH_2). Mass spectrum m/z 294 (M^+, 35) 279 (18), 263 (69), 237 (88), 206 (100).

	m.p. 155-156°C pale yellow crystals (overall yield 34%) from $CHCl_3$/ether; ^1H-NMR (200 MHz, $CDCl_3$) δ = 6.36-6.27 (m, 3H), 5.80 (dt, B part of AB-system, 10.2, 3.6 Hz, 1H), 4.10 (s, 6H), 3.30 (A part of AB-system, bd, 20.0 Hz, 1H), 2.68 (B part of AB-system, bd, 20.0 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 165.80 (2 CO), 149.97 (C), 147.38 (C), 141.68 (C), 137.19 (C), 134.26 (CH), 130.01 (CH), 76.56 (OCH), 74.26 (OCH), 55.69 (2 OCH_3), 37.39 (CH_2).

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