carboxylic acid methyl ester 1,1-dioxide (1) for this work was prepared by the literature method. Its tautomer (2) was oxidized to 3 by silver(I) oxide. The oxidation proceeded at room temperature, and solvent purity was important to the reaction. Compounds 3 were converted to 3-methoxy-2H-4-oxo-1,2-benzothiazine-3- carboxylic acid methyl ester 1,1-dioxide (4a-c) in methanol, 3-ethoxy compound 4d in ethanol and 3-propoxy compound 4e in propanol. The unsymme- trical dimer (5) formed through the intermolecular dehydration between the 4-hydroxyl group of the enol form and the 3-hydroxyl group of the oxidized keto form are generated during the proloned reaction time. The reaction mechanism of the formation of the 3-alkoxy compound (4a-e) and the dimer (5) involves the dehydration between two alcohols.

[PD1-14] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Efficient Macrocyclization for Making Cyclic Peptide

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We can see that there are many spotlights on peptide drugs by examining the recent trend in drug development. For example, drugs like cyclosporin shows striking activity as an autoimmune suppressor. Especially, cyclic peptides stands out among all other peptides as a good drug. That is why we are trying to develop more effective cyclization process.
There are three ways to cyclize certain sequences of amino acids such as Gly-Met-Ile-Phe-Gly. First is head-to-tail cyclization method, linking between N-terminal and C-terminal. Second method utilizes amino acid side chain such as thiol functional group in Cys, making a thioether bond. The last one includes an application of resin-substituted amino acids in solid phase reaction. Among the three methods, solid phase reaction showed the greatest yield.

[PD1-15] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Studies on the Stereoselective Synthesis of Oxazine using a Pd-catalyzed Intramolecular Cyclization

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Palladium(0)-catalyzed intramolecular cyclization of benzamide via p-allylpalladium complex is useful for the synthesis of highly functionalized compounds, particularly when chirality transfer is involved. Therefore, we investigated a new method for oxazine formation reaction catalyzed by palladium(0).
The transformation of acyclic homoallyl benzamide to vinyl oxazine was intensively studied. The stereochemistry of major product was determined to be trans by using NOE experiment.

[PD1-16] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

5,8-QUINAZOLINEDIONES AS POTENT INHIBITORS OF ENDOTHELIUM-DEPENDENT VASORELAXATION

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6-phenylamino-5,8-quinolinedione (LY83583) as a quinone inhibits nitric oxide synthase (NOS). LY83583 is an inhibitor of endothelial NO-dependent vasorelaxation and lowers intracellular cGMP in several tissues and inhibits NOS activity. 6-(Substituted-phenyl)amino-5,8-quinolinediones inhibited the ACh-induced vasorelaxation of PE-precontracted rat aorta with the intact endothelium. The presence of nitrogen on the quinones was important for the inhibitory activities and the 5,8-quinolinediones with a 6-(fluorinated-phenyl)amino group, inhibited strongly the vasorelaxation. From this information, 6/7-arylamino-5,8-quinazolinediones as bioisosteres of 5,8-quinolinediones were prepared and evaluated their biological activities. The most of 5,8-quinolinediones tested inhibited the vasorelaxation of rat aorta with the endothelium

[PD1-17] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Synthesis of Novel D- and L-3'-Deoxy-3'-C-hydroxymethyl Nucleosides with exocyclic methylene as potential Ribonucleotide Reductase Inhibitor

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Ribonucleotide reductase catalyzes the conversion of ribonucleotides to the 2'-deoxyribonucleotides and has been regarded as attractive target for the development of antitumor agents. Among compounds reported, 2'-deoxy-2'-vinyl-substituted nucleoside has been known to act as ribonucleotide reductase inhibitor and its cyclopropyl analogue also appear to act as the same mechanism. Since for the structure-Activity relationship study we were interested in designing and synthesizing the corresponding 3'-homologated derivative of the above nucleoside. And L-nucleosides sometimes show better biological activity profile than the corresponding D-isomer, we synthesized D- and L-3'-deoxy-3'-C-hydroxymethyl nucleosides with exocyclic methylene at 2'-position of the sugar ring. The final D- and L-nucleosides were synthesized from D- and L-xylose via 3-homologated ribosyl acetate as the key intermediate, respectively. Synthesis and antiviral activities will be in detail presented in the meeting.

[PD1-18] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Syntheses and Inhibition Activity of Nitric Oxide Synthase by Yakuchinone Derivatives

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L-Arginine-derived nitric oxide (NO) is an intracellular mediator produced in mammalian cells by two types of nitric oxide synthase, constitutive-NOS(c-NOS) and inducible NOS(i-NOS). I-NOS is Ca2+-independent and is induced by lipopolysaccharides (LPS) or proinflammatory cytokines such as TNF- , IL-1 and IFN-ɣ. The NO produced in large amounts by the i-NOS is responsible for vasodilation and hypotension observed in septic shock and inflammation. In order to prepare i-NOS inhibitor, several yakuchinone derivatives were synthetized and their inhibitory activity of NO production in LPS-activated macrophages were evaluated. The amounts of NO produced by i-NOS was determined by using Griess reagent in the form of NO2-,and the IC50 values were determined as the concentations required for inhibiting the production of NO by 50%.