hemorrhage.[1] It is also claimed to have a remarkable central stimulant effect,[1] a transient hypertensive effect[1,2] and positive inotropic and chronotropic effects.[3] Phytochemical studies on the fruits of this plant have shown the presence of numerous compounds, including the alkaloids rutaecarpine, evodiamine, wuchuyine, hydroxyevodiamine (rhesinine), dehydroevodiamine, evocarpine, 1- methyl- 2 -pentadecyl-4 (1H)-quinolone, 1-methyl- 2- tridecyl- 4 (1H)- quinolone (dihydroevocarpine), 1-methyl-2-undecyl-4 (1H)-quinolone, dihydrorutaecarpine, and 14-formyldihydrorutaecarpine.[4] The non-alkaloid constituents of the fruits include rutaevin, limonin (evodin), evodol, evodinone, evogin, and gushuyic, and other fatty acids.[5] Several compounds from *Evodia rutaecarpa* have been demonstrated to have pharmacological activities. For example, dehydroevodiamine has hypotensive, bradycardiac, vasodilating, and antiarrhythmic effects.[6,7] Evodiamine, a compound that is reduced to form dehydroevodiamine, can exert a positive inotropic effect on the isolated left artria of guinea pigs and an antianoxic action in KCN-induced anoxia in mice.[8] Vasodilation by evodiamine and the cardiovascular effects of dehydroevodiamine have been reported previously.[6,7] Recently, Chiou et al.[9] further reported that rutaecarpine causes vasodilation of isolated rat mesenteric arteries via an endothelial NO-dependent manner. Furthermore, we also found that rutaecarpine inhibition of the aggregation of human platelets is mediated through the inhibition of phospholipase C.[10] In this article, we review the cardiovascular pharmacological effects of rutaecarpine on the basis of *in vitro* and *in vivo* studies, including pharmacological and pharmacokinetic studies.

CHEMISTRY

Rutaecarpine (7,8-dihydro-13H-indolo [2′3′:3,4] pyrido [2,1-b] quinazolin-5-one), an alkaloid isolated from the fruit of *Evodia rutaecarpa*, has been reported to be synthesized by condensation of iminoketene with amides[11] as shown in Fig. 1. Condensation of N-formyltryptamine (A) with sulfinamide anhydride (B) was carried out in a mixture of dry benzene and chloroform at room temperature for 2 h to give 3-indolylethylquinazolin-4-one (C) with a 63% yield. This product was heated with concentrated hydrochloric acid in acetic acid at 110 °C for 16 h to produce rutaecarpine (D).[11] Rutaecarpine, consisting of colorless needles (melting point 259-260°C) with the molecular formula $C_{18}H_{13}N_3O$ and a molecular weight of 287.3, is soluble in alcohol, benzene, chloroform, and ether; however, it is particularly insoluble in water.

PHARMACOKINETIC STUDIES

Pharmacokinetic studies of rutaecarpine were reported by Ko et al.[12] The curves of concentration in plasma versus time after intravenous administration of rutaecarpine (2 mg/kg) in mice revealed that the curves generally exhibit a biexponential decline with administration.[12] The pharmacokinetic parameters of rutaecarpine in rats after administration of an intravenous bolus (2 mg/kg) dose are as follows (mean ± S.E.M.; n = 6): the half-life ($t_{1/2}$), 29.29 ± 4.25 (min); clear rate (CL), 63.46 ± 5.39 $mL \cdot min^{-1}kg^{-1}$; volume, 655.15 ± 43.93 mL/kg; and the area under the curve (AUC),

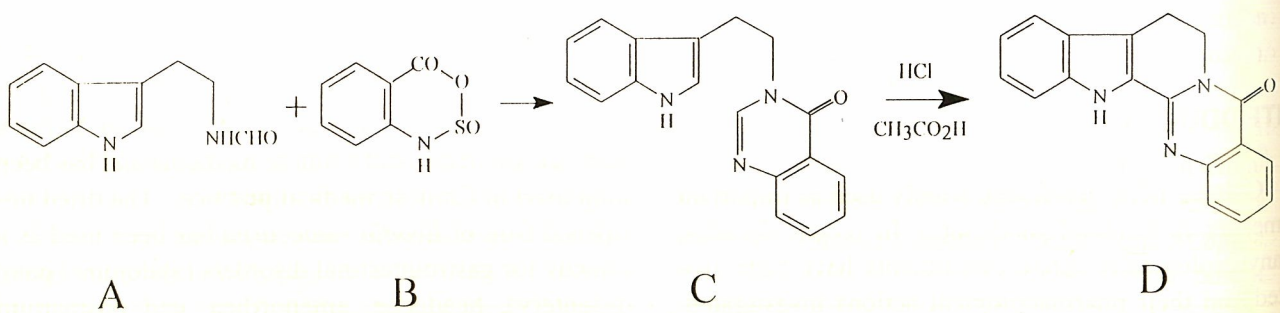

Fig. 1. Chemical synthesis of rutaecarpine.