

A NEW STEREOSELECTIVE SYNTHESIS OF EMETINE AND RELATED ALKALOIDS

Tetsuji Kametani, Masataka Ihara, Yukio Suzuki,

Hirofumi Terasawa, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Reaction of a 3,4-dihydro-1-methylisoquinoline with several α,β -unsaturated esters provides one-step synthesis of benzo[a]quinolizine derivatives. Applying this method, (\pm)-emetine (1) and (\pm)-dihydroprotoemetine (2) have been synthesised.

Heating 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (3) with crotonic anhydride gave 3,4,6,7-tetrahydro-9,10-dimethoxy-4-methylbenzo[a]quinolizin-2-one along with 2-crotonyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline and N-(2-acetyl-4,5-dimethoxyphenethyl)crotonamide. Reaction of 3 with diethyl α,γ -diethoxycarbonylglutaconate in ethanol, followed by silica gel chromatography, afforded 3-ethoxycarbonyl-6,7-dihydro-9,10-dimethoxybenzo[a]quinolizin-4-one (4). On the other hand, reduction of the crude product of the above reaction with sodium borohydride yielded 3-ethoxycarbonyl-2-diethoxycarbonylmethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[a]quinolizin-4-one (5). Hydrolysis of 4 and 5 with ethanolic potassium hydroxide solution furnished the same acid.

Condensation of 3 with dimethyl 3-methoxyallylidene malonate gave 2,3,6,7-tetrahydro-9,10-dimethoxy-3-methoxycarbonyl-2-(β,β -dimethoxyethyl)benzo[a]quinolizin-4-one, which reacted with ethyl iodide in the presence of sodium hydride to yield the 3-ethyl compound (6). Hydrolysis of 6, followed by decarboxylation gave mainly the *cis*-isomer, which was, after catalytic reduction, epimerised to *trans*-isomer, (\pm)-3 α -ethyl-1,2 α ,3 β ,6,7,11 α -hexahydro-9,10-dimethoxy-2 β -(β,β -dimethoxyethyl)benzo[a]quinolizin-4-one (7). Catalytic reduction of 6, followed by hydrolysis and decarboxylation gave selectively the *trans*-isomer (7).

The acetal (7) was converted to (\pm)-dihydroprotoemetine (2) via an aldehyde, which had already been transformed to emetine (1).