STUDIES ON THE SYNTHESIS OF MEDIUM-SIZED AZALACTONES

Shigeyuki Yoshifuji, Ken-ichi Tanaka, Yukimi Takai, and Yoshio Arata
School of Pharmacy, Hokuriku University, Kanagawa-machi, Kanazawa 920-11, Japan

A new and general synthetic method for medium-sized azalactone has been studied. The mercuric acetate-EDTA oxidation of 1-(3-hydroxypropyl)piperidine, 1-(2-hydroxyethyl)-piperidine, 1-(3-hydroxypropyl)pyrrolidine, and 1-(2-hydroxyethyl)-hexahydro-2*H*-azepine gave the corresponding lactams, which on treatment with aqueous perchloric acid followed by dehydration by heating in toluene readily afforded 3,4,6,7,8,9-hexahydro-2*H*-pyrido[2,1-*b*][1,3]-oxazinium perchlorate(1a), 2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridinium perchlorate(1b), 2,3,4,6,7,8-hexahydropyrrolo[2,1-*b*][1,3]oxazinium perchlorate(1c), and 2,3,6,7,8,9-hexahydro-5*H*-oxazolo[3,2-*a*]-azepinium perchlorate(1d), respectively. Reaction of 1a-d with sodium ethoxide in ethanol followed by quaternization with methyl iodide produced 10-ethoxy-5-methylperhydropyrido-[2,1-*b*][1,3]oxazinium iodide(2a), 9-ethoxy-4-methylperhydrooxazolo[3,2-*a*]pyridinium iodide(2b), 9-ethoxy-5-methylperhydropyrrolo[2,1-*b*][1,3]oxazinium iodide(2c), and 10-ethoxy-4-methylperhydrooxazolo-[3,2-*a*]azepinium iodide(2d), respectively. Furthermore, 10-*p*-methoxybenzyloxy-5-methylperhydro-pyrido[2,1-*b*][1,3]oxazinium perchlorate(3a) and 9-*p*-methoxybenzyloxy-4-methylperhydrooxazolo[3,2-*a*]-pyridinium perchlorate(3b) were prepared from 1a and 1b by the similar method using sodium *p*-methoxybenzyloxide in anisalcohol in place of sodium ethoxide in ethanol.

Heating of methiodides(2a-d) in a solution of sodium ethoxide in ethanol gave 2,2-diethoxy-7-methyloctahydro-2*H*-1,7-oxazecine(4a), 2,2-diethoxy-7-methyloctahydro-1,7-oxazonine(4b), 2,2-diethoxy-6-methyloctahydro-1,6-oxazonine(4c), and 2,2-diethoxy-8-methyloctahydro-2*H*-1,8-oxazecine(4d), respectively. Conversion of 4a-d into the expected medium-sized azalactones was carried out in 0.3N oxalic acid solution to give 7-methyloctahydro-2*H*-1,7-oxazecin-2-one(5a), 7-methyloctahydro-1,7-oxazonin-2-one(5b), 6-methyloctahydro-1,6-oxazonin-2-one(5c), and 8-methyloctahydro-2*H*-1,8-oxazecin-2-one(5d) in low yields, together with the corresponding ring-open products. Hydrolysis of 2a and 2d in boiling 0.3N oxalic acid afforded 5a and 5d in 68% and 8%(from 1d) yield, respectively. Alternatively, hydrogenolysis(Pd-C/H_2) of 3a and 3b led to the desired lactones,5a and 5b in 97% and 98% yield, respectively.

On the basis of IR and NMR spectral data of azalactons(5a-d) and their salts, it was found that no transannular interraction between N and C=O was observed in 5a-d.