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SYNTHESES OF NINE- AND TEN-MEMBERED AMINO LACTONES FROM 1-AZABICYCLIC IMMONIUM ETHER PERCHLORATES

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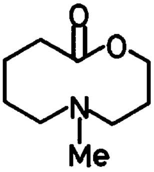
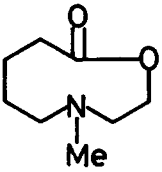
In connection with previous studies[1)] on the syntheses of medium-sized ring amines from 1-azabicycloalkane derivatives, we wish to report the conversion of 1-azabicyclic immonium ether perchlorates(IVa and IVb) into nine- and ten-membered amino lactones(Ia and Ib).

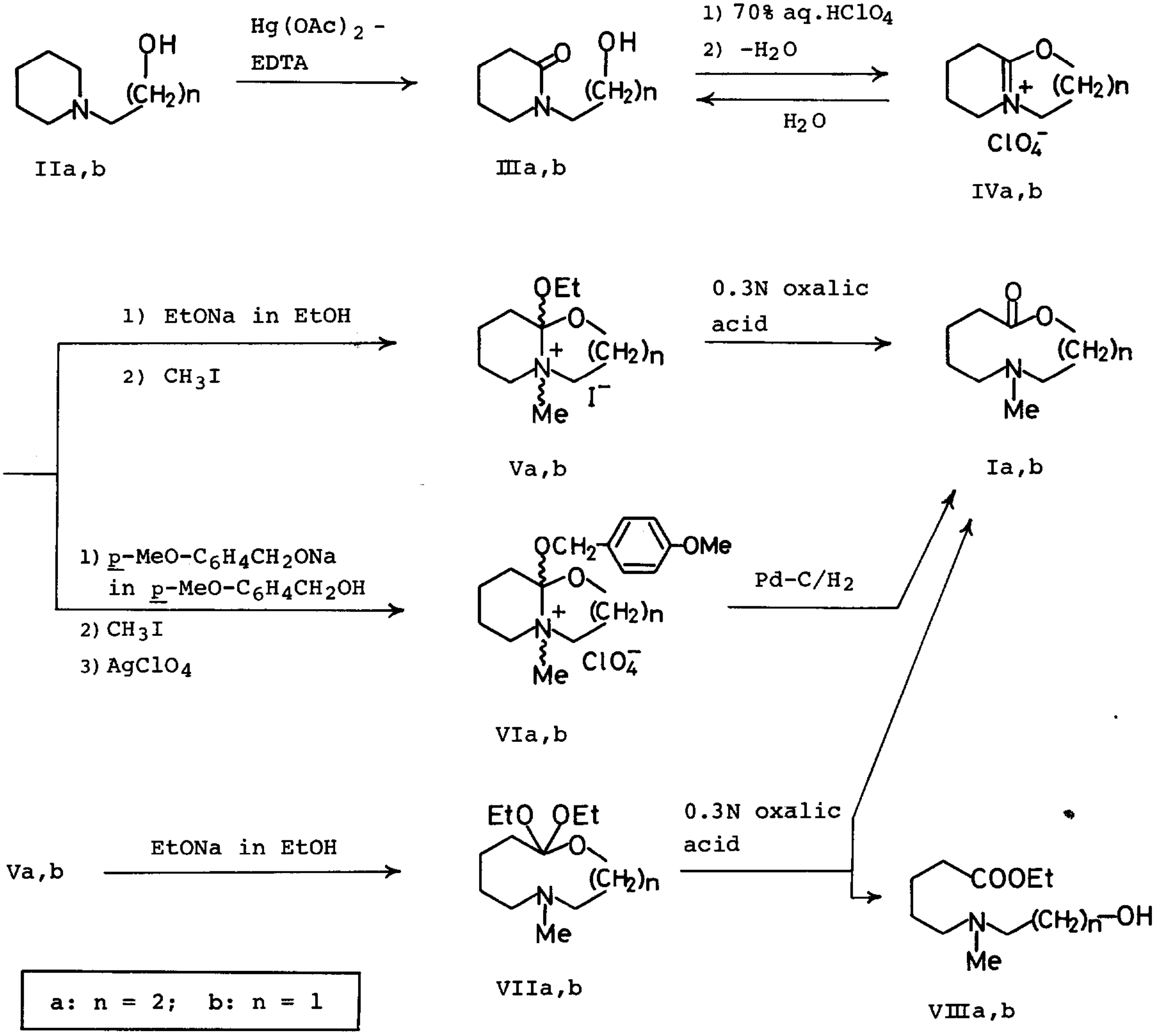


Ia



Ib

Heating of 1-(3-hydroxypropyl)piperidine(IIa) and 1-(2-hydroxyethyl)piperidine(IIb) with a combination[2)] of mercuric acetate and sodium salt of (ethylenedinitrilo)tetraacetic acid(EDTA) in aqueous acetic acid gave the corresponding 2-piperidones, IIIa and IIIb in 74% and 78% yield, respectively, which, on treatment with aqueous perchloric acid followed by dehydration by heating, readily afforded the respective bicyclic amidium perchlorates, IVa[3)] [96% yield; mp 185-186°; IR (nujol) ν max: 1674 cm^{-1}(iminium)] and IVb[98% yield; mp 110-112°; IR(nujol) ν max: 1682 cm^{-1}(iminium)]. When treated with water, IVa and IVb were easily hydrolyzed to revert to IIIa and IIIb, respectively. On the other hand, treatment of IVa and IVb with sodium ethoxide in ethanol followed by quarternization with methyl iodide afforded the ethoxy N-methiodides, Va[81% yield; H-NMR($CDCl_3$) δ: 3.15 and 3.32

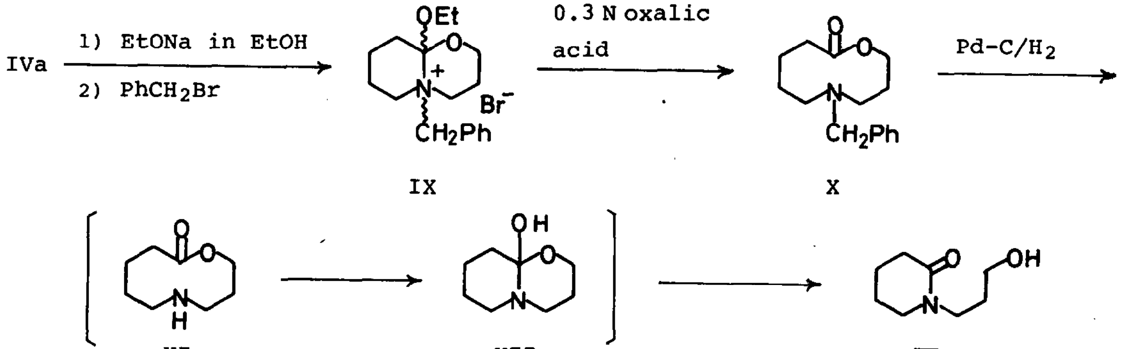


(total 3H, N-CH_3, presumably, a mixture of two stereoisomers)] and Vb[75% yield; mp 182-183°; H-NMR($CDCl_3$) δ: 3.40(3H, N-CH_3)], respectively. Treatment of IVa and IVb with sodium p-methoxybenzyloxide in p-methoxybenzyl alcohol followed by quarternization with methyl iodide gave the p-methoxybenzyloxy N-methiodides, which were further treated with aqueous silver perchlorate to afford the methoperchlorates, VIa[77% yield; H-NMR($CDCl_3$) δ: 3.12 and 3.30(total 3H, N-CH_3, presumably, a mixture of two stereoisomers)] and VIb[80% yield; mp 109-110°; H-NMR ($CDCl_3$) δ: 3.28(3H, N-CH_3)], respectively.

Hereupon, attempts were made to produce the nine- and ten-membered amino lactones(Ia and Ib) from the ethoxy N-methiodides(Va and Vb) and the p-methoxybenzyloxy N-methoperchlorates(VIa and VIb). Heating of methiodide Va in 0.3 N oxalic acid(reflux, 90 min) afforded the corresponding ten-membered lactone(Ia) [bp 145°/12 mmHg(bath temp.); mass m/e 171(M^+); C-NMR($CDCl_3$) δ: 173.6 ppm(C=O); perchlorate: mp 176-177°] in 68% yield. The similar hydrolysis of Vb scarely yielded the expected lactone. Debenzylation of the p-methoxybenzyloxy N-methoperchlorates, VIa and VIb by hydrogenolysis(Pd-C/H_2, 90% aq. EtOH, 1 atm, 20°) led to the corresponding medium-sized amino lactones, Ia(97% yield) and Ib[98% yield; bp 130°/11 mmHg(bath temp.); mass m/e 157(M^+); C-NMR($CDCl_3$) δ: 174.9 ppm (C=O); picrate: mp 164-165°], respectively. On the other hand, heating(70°, 30 min) of the ethoxy N-methiodides, Va and Vb in a solution of sodium ethoxide in ethanol gave the medium-sized ring ortho esters, VIIa[88% yield; bp 135°/12 mmHg (bath temp.); mass m/e 245(M^+); H-NMR($CDCl_3$) δ: 1.20(6H, t, $OCH_2C\underline{H}_3 \times 2$) and 3.52 (4H, q, $OC\underline{H}_2CH_3 \times 2$)] and VIIb[90% yield; bp 130°/12 mmHg(bath temp.); mass m/e 231(M^+); H-NMR($CDCl_3$) δ: 1.21(6H, t, $OCH_2C\underline{H}_3 \times 2$) and 3.51(4H, q, $OC\underline{H}_2CH_3 \times 2$)], respectively. Conversion of VIIa and VIIb into the expected lactones(Ia and Ib) was carried out in 0.3 N oxalic acid(room temp., 15 min) to give Ia and Ib in poor yields, together with the corresponding ring-open products(VIIIa and VIIIb), respectively.

The infrared spectra of the medium-sized amino lactones(Ia and Ib) in carbon tetrachloride(0.2 M solution) showed the ester carbonyl bands at 1734 cm^{-1} and 1740 cm^{-1}, respectively and those of their salts showed the ester carbonyl bands strongly [perchlorate of Ia: 1729 cm^{-1}(nujol); picrate of Ib: 1750 cm^{-1} (nujol)], too. Therefore, no N--C=O transannular interaction[4)] was observed in both amino lactones(Ia and Ib).

By the way, the ethoxy N-benzyl bromide(IX)[77% yield; mp 151-152°] obtained by the reaction of IVa with sodium ethoxide in ethanol followed by quarternization with benzyl bromide was heated in aqueous oxalic acid(reflux, 90 min) to give the ten-membered N-benzyl lactone(X)[bp 140°/3 mmHg(bath temp.); mass m/e 247(M^+); IR(CCl_4) ν max: 1735 cm^{-1}(C=O); C-NMR($CDCl_3$) δ: 174.2 ppm(C=O); perchlorate: mp 152-153°; IR(nujol) ν max: 1733 cm^{-1}(C=O)] in 56% yield. Hydrogenolysis of the perchlorate of X (Pd-C/H_2, EtOH, 1 atm. 20°) afforded the lactam alcohol(IIIa) in a quantitative yield, but not the debenzylated lactone(XI). A mechanism of the conversion of X to IIIa might be postulated as follows: the N-benzyl lactone(X) was precedently hydrogenolyzed to afford the debenzylated product(XI) which resulted in IIIa *via* the formation of the transannular cyclization-type intermediate(XII).



IX X

XI XII IIIa

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