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2-AZABICYCLO[3.3.1]NON-1-ENE SYSTEMS AS REACTION INTERMEDIATES

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Previously, we reported the formation of 2-azabicyclo[3.3.1]non-1-ene system, an unusually stable anti-Bredt's-rule imine[1]. We describe here the synthesis of 1-acetoxy-3-oxo-2-aza-bicyclo[3.3.1]nonane and some substitution reactions at C_1-position, including 3-oxo-2-aza-bicyclo[3.3.1]non-1-ene systems as reaction intermediates.

The amino-ester(III) was obtained from the known methyl 3-oxocyclohexyl acetate(I)[2] according to the following procedures: 1) treatment with methoxyamine hydrochloride-sodium acetate, 2) hydrolysis with methanolic potassium hydroxide to afford II, 3) reduction with sodium and ethanol followed by esterification with methanol-hydrogen chloride (see the scheme 1).

Treatment of III with methanolic sodium methoxide(1 equivalent) in a sealed tube under N_2 atomosphere at 220° for 3 hr gave a cyclization product(IV)[m.p. 85-86°; m/e 139.0988; $\nu_{max}^{CHCl_3}$ 3400 and 1650 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.58(1H, m) and 8.03 ppm(1H,br., N<u>H</u>)] in 50-60% yield.

When treated with lead tetraacetate in anhydrous benzene in a sealed tube at 120° overnight, IV afforded an acetoxy-lactam(V)[m.p. 134-137°; m/e 197.1035; $\nu_{max}^{CHCl_3}$ 3360, 1730, 1656 and 1245 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.05(3H, s) and 7.20 ppm(1H, br., N<u>H</u>)] in 30% yield through a plausible intermediate(VII)*(see the scheme 2).

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* The formation of the intermediate(VI) was confirmed by the following finding: when treated with lead tetraacetate in anhydrous benzene under reflux overnight followed by addition of large amounts of water saturated with sodium chloride, the lactam(IV) gave the N-chloride(VIII) [m/e 175, 173; $\nu_{max}^{CHCl_3}$ 1662 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.88 ppm(1H, m, C<u>H</u>-NCl-CO-)] in high yield.

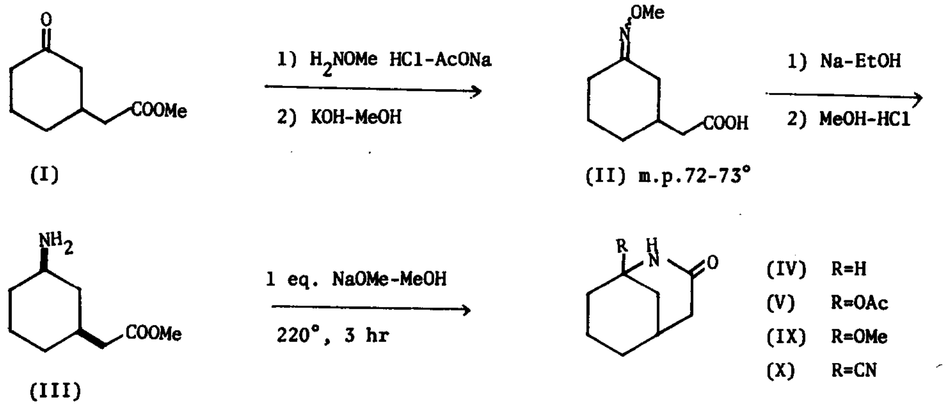
On treatment with sodium borohydride in glyme (or ethanol) at room temperature overnight, V was reconverted into the starting material(IV) in almost quantitative yield, indicating that no rearrangement of the carbon skeleton took place in the course of oxidation.

Furthermore, some substitution reactions at C_1-position were carried out. When treated with methanol-hydrogen chloride at room temperature for 3 hr (or sodium methoxide in methanol at 0° for 5 hr), V gave a methoxy-derivative(IX)[m.p. 104-107°; m/e 169; $\nu_{max}^{CHCl_3}$ 3360 and 1655 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.31(3H, s) and 5.7 ppm(1H, br., N$\underline{H}$)] in high yield.

Similarily, V reacted with potassium cyanide in aqueous tetrahydrofuran at room temperature overnight to give a cyano-derivative(X)[m.p. 134-137°; m/e 164.0976; $\nu_{max}^{CHCl_3}$ 3380, 2280 and 1664 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 6.7 ppm(1H, br., N$\underline{H}$)] in high yield.

In the above cases, the imino intermediate, 3-oxo-2-azabicyclo[3.3.1]non-1-ene(VII)*, is also regarded as a reaction one (see the scheme 2).

scheme 1



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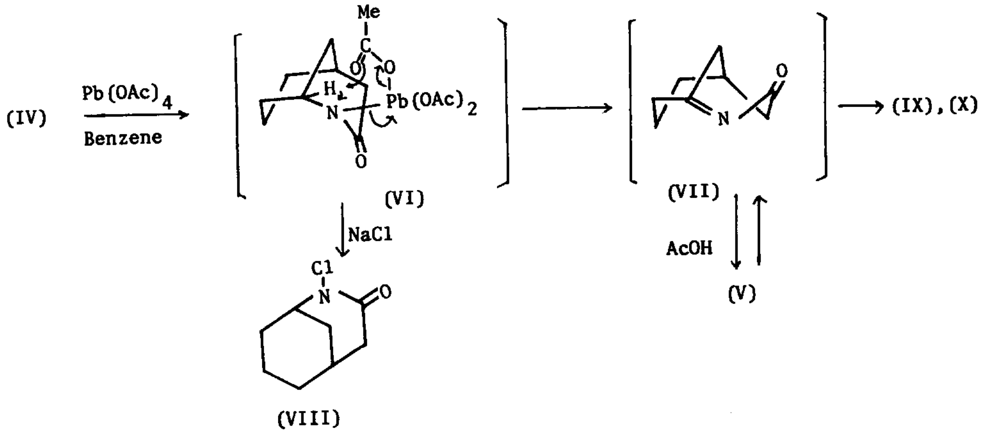
* Recently, the synthesis and chemistry of the anti-Bredt's-rule olefin bicyclo[3.3.1]non-1-ene have been reported in detail3). All the attempts so far trapping the intermediate(VII) did not give good result.

scheme 2



The reaction of 3-oxo-2-azabicyclo[3.2.1]octane(XI)[4] with lead tetraacetate was further carried out according to the above-mentioned procedure.

N-Acetyl-lactam(XII)[m/e 167; $\nu_{max}^{CHCl_3}$ 1690 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 2.39(3H, s) and 4.73 ppm(1H, m)] and N-formyl-lactam(XIII)[m/e 125(M$^+$-28)*; $\nu_{max}^{CHCl_3}$ 1715 and 1685 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.82(1H, m) and 10.02 ppm(1H, s)] were isolated as main products, and the expected acetoxy-lactam(XIV)[m/e 183; $\nu_{max}^{CHCl_3}$ 3420, 1740, 1660 and 1220 cm^{-1}; $\delta_{TMS}^{CCl_4}$ 2.05(3H, s) and 6.90 ppm(1H, br., N<u>H</u>)] was also isolated in poor yield(2%). This reaction may proceed through the plausible intermediate (XV), which has been confirmed by the formation of the N-chloride(XVI)[m/e 161 and 159; $\nu_{max}^{CHCl_3}$ 1665 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.11 ppm(1H, m)]. In particular, the isolation of XIV suggests the formation of 3-oxo-2-azabicyclo[3.2.1]oct-1-ene(XVII)** as an intermediate(see the scheme 3). The detail studies are now in progress.

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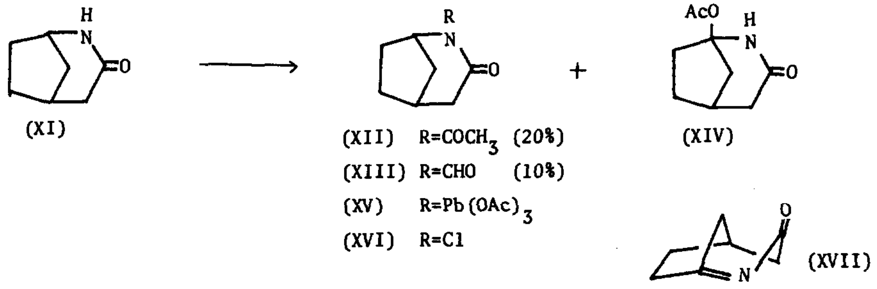
* Molecular ion peak(m/e 153) was not observed.

** The above experiment indicates that the formation of the bridge-head double bond seems to be very difficult in the case of 3-oxo-2-azabicyclo[3.2.1]octane(XI), as compared with that of 3-oxo-2-azabicyclo[3.3.1]nonane(IV). Recently, the formation of 2-azabicyclo[3.2.1]oct-1-ene has been reported as a reaction intermediate[5].

scheme 3



(XI)

(XII) R=$COCH_3$ (20%)
(XIII) R=CHO (10%)
(XV) R=$Pb(OAc)_3$
(XVI) R=Cl

(XIV)

(XVII)

Melting points are uncorrected. All compounds gave satisfactory physical data.

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