SELECTIVE N-ALKYLATION OF ENAMINONE ANIONS LEADING TO 3-N-AZIRIDYL-, -AZETIDYL-, AND -PYRROLIDYLCYCLOHEX-2-EN-1-ONES

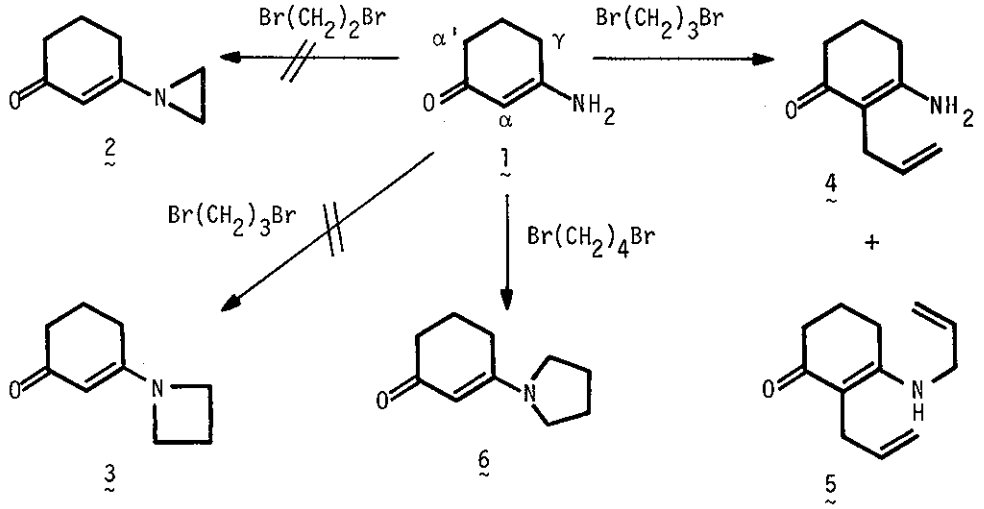
Hideo Iida, Yoshifumi Yuasa, and Chihiro Kibayashi
Tokyo College of Pharmacy
Horinouchi, Hachioji, Tokyo 192-03, Japan

Double N-alkylation of 3-aminocyclohex-2-en-1-one (1) with 1,4-dibromobutane in the presence of sodium hydride gave 3-N-pyrrolidylcyclohex-2-en-1-one (6). The formation of the N-aziridyl and -azetidyl analogues (2 and 3) of 6 was achieved by internal N-alkylation of the N-ω-haloalkyl derivatives of 1 with appropriate strong bases.

On electrophilic alkylation of primary or secondary enaminone anions, they are capable of leading to a wide variety of products such as N-, O-, and C-alkylated derivatives including those produced by α-, α'-, and γ-alkylation. The reaction conditions which determine where alkylation takes place may be associated with the nature of the enaminone and the selection of the alkylating agent, the basic catalyst, and the solvent. Although potentially useful, only a few cases involving N-alkylation of enaminone

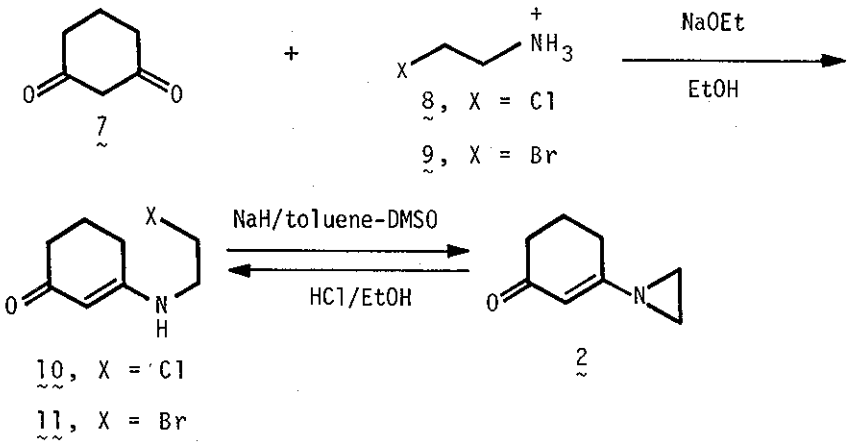
anions have been reported.[1] We now wish to report a new cyclization to three- to five-membered heterocyclic compounds utilizing internal and double N-alkylation of enaminone anions.

Our initial attempts to obtain the aziridine derivative 2 were unsuccessful, because treatment of 3-aminocyclohex-2-en-1-one (1)[2] with 1,2-dibromoethane in the presence of sodium hydride resulted in no reaction. In a next attempt to obtain the azetidine derivative 3, when 1 was heated with 1,3-dibromopropane in toluene–dimethyl sulfoxide (DMSO) in the presence of sodium hydride at 100 °C for 3 h, the C-alkylation and C,N-dialkylation proceeded to give 4 [mp 112.5–114 °C; IR ($CHCl_3$) 3490 and 3390 (NH), 1625 (C=O), 1605 (C=C), 1580 cm^{-1} (conj C=C); NMR ($CDCl_3$) δ 3.07 (d, 2 H, J = 6 Hz, $C\underline{H}_2CH{=}CH_2$), 4.65 (bs, 2 H, NH), 4.79–5.15 (m, 2 H, $CH{=}C\underline{H}_2$), 5.43–6.06 (m, 1 H, $C\underline{H}{=}CH_2$)] and 5 [oil; IR ($CHCl_3$) 3380 (NH), 1625 (C=O), 1610 (C=C), 1565 cm^{-1} (conj C=C); NMR ($CDCl_3$) δ 3.12 (d, 2 H, J = 6 Hz, $CC\underline{H}_2CH{=}CH_2$), 3.71–3.92 (m, 2 H,



$NC\underline{H}_2CH=CH_2$), 4.87–5.30 (m, 4 H, 2 $CH=C\underline{H}_2$), 5.42–6.17 (m, 2 H, 2 $C\underline{H}=CH_2$)], respectively. Upon similar treatment of 1 with 1,4-dibromobutane, the double N-alkylation occurred regioselectively to yield 3-N-pyrrolidylcyclohex-2-en-1-one (6)[3] in 44% yield.

The synthesis of the aziridine and azetidine derivatives was successfully achieved by utilizing the internal N-alkylation of the N-ω-haloalkylated enaminones instead of the reaction of the enaminone with the ω-dihaloalkanes. Thus cyclohexane-1,3-dione (7) was heated with 2-chloroethylamine hydrochloride (8) in boiling ethanol in the presence of sodium ethoxide for 20 h to give 3-(2-chloroethyl)aminocyclohex-2-en-1-one (10) in 34% yield [mp 120–121.5 °C; IR ($CHCl_3$) 3390 (NH), 1605 (C=O), 1575 cm^{-1} (C=C); NMR ($CDCl_3$) δ 5.02 (s, 1 H, vinylic H), 5.54 (bs, 1 H, NH)]. Similar treatment of 7 with 2-bromoethylamine hydrobromide (9) gave the bromo analogue of 10 in 32% yield [mp 127–129.5 °C; IR ($CHCl_3$) 3400 (NH), 1605 (C=O), 1580 cm^{-1} (C=C); NMR ($CDCl_3$) δ 5.10 (s, 1 H, vinylic H), 5.87 (bs, 1 H, NH)]. Subsequent treatment of 10



7

8, X = Cl

9, X = Br

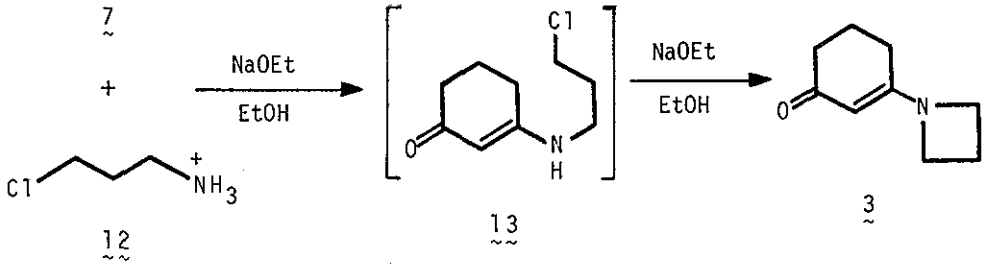
10, X = Cl

11, X = Br

2

with sodium hydride in toluene–DMSO at 100 °C for 1 h afforded 3-N-aziridylcyclohex-2-en-1-one (2) in 66% yield [oil; bp 78 °C (0.14 mm); IR ($CHCl_3$) 1640 (C=O), 1595 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.08 (s, 4 H, 2 CH_2 of the aziridine ring), 5.45 (s, 1 H, vinylic H)]. This compound readily reverted to 10 upon heating with ethanolic hydrochloride for 5 h (67% yield).

When 7 was heated with 3-chloropropylamine hydrochloride (12) in boiling ethanol in the presence of sodium ethoxide for 16 h, the cyclization reaction occurred in situ to give 3-N-azetidyl-cyclohex-2-en-1-one (3) in 59% yield [oil, decomposed on attempted distillation; IR ($CHCl_3$) 1595 (C=O), 1550 cm^{-1} (C=C); NMR ($CDCl_3$) δ 4.79 (s, 1 H, vinylic H)]. In this reaction, compound 3 may have arisen from the initial formation of the haloenaminone 13 as in the formation of 2 from 10.



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Further investigation on ring transformation of these cyclization products is in progress.

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