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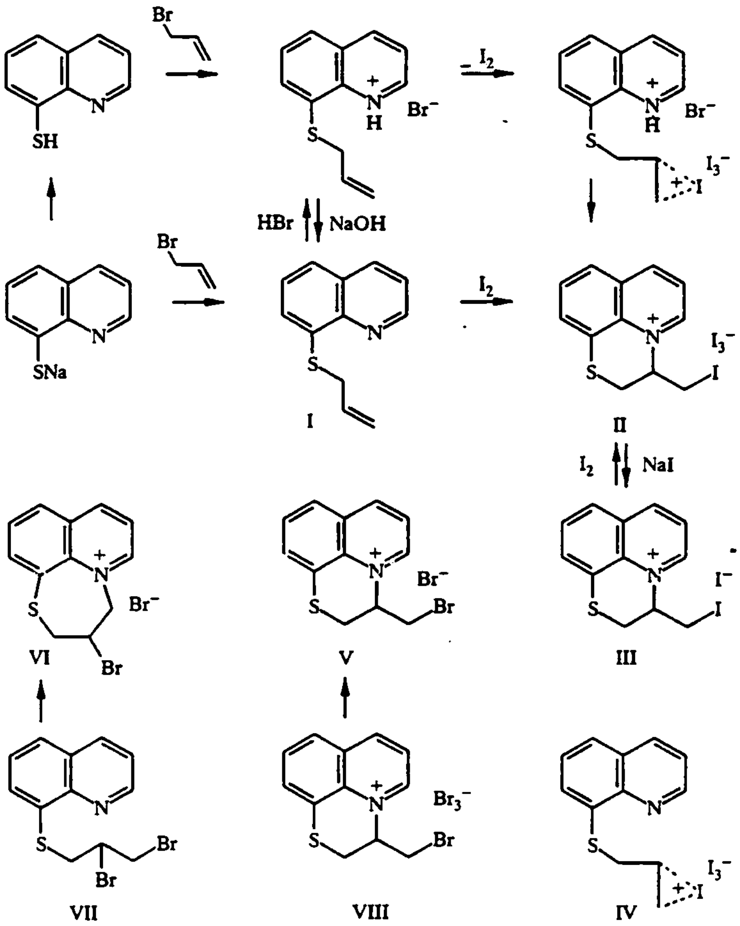
HALOCYCLIZATION OF 8-ALLYLTHIOQUINOLINE

D. G. Kim

In a continuation of work on the halocyclization of allylic quinoline derivatives [1-3], we studied the reaction of 8-allylthioquinoline (I) with halogens.

Sulfide I was obtained by the allylation of sodium 8-mercaptoquinolinate by allyl bromide in alcohols, DMSO, DMF, and water. The allylation in water proceeds more slowly than in alcohols but this reaction is much more rapid in the presence of surfactants such as Sulfonol, sodium stearate, and Syntanol. Sulfide I is also formed in the reaction of 8-mercaptoquinoline with allyl bromide in the absence of base.



The reaction of sulfide I with a two-fold excess of iodine in ethanol, chloroform, diethyl ether, and acetone leads to 3-iodomethyl-2,3-dihydro-1,4-thiazino[2,3,4-*i,j*]quinolinium triiodide (II), which reacts with sodium iodide or sulfide I in acetone to give 3-iodomethyl-2,3-dihydro-1,4-thiazino[2,3,4-*i,j*]quinolinium iodide (III). In turn, iodide III reacts with iodine to give triiodide II. The reaction of sulfide I with iodine generated *in situ* from hydriodic acid and hydrogen peroxide also gives triiodide II.

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The reaction of sulfide I with an equimolar amount of iodine initially gives triiodide II, which then reacts with sulfide I to yield iodide III. Thus, the triiodide is not formed in the reaction of iodide III with iodine but in an earlier step. The iodocyclization apparently proceeds through formation of an iodonium cation with the triiodide anion as the counter-ion (structure IV).

Triiodide II was unexpectedly formed by the reaction of the hydrobromide salt of sulfide I with iodine in 2-propanol and in the reaction of sulfide I with iodine in the presence of hydrobromic acid. This behavior indicates that one of the iodocyclization steps involves intramolecular electrophilic substitution at the nitrogen atom.

The reaction of sulfide I with an equimolar amount of bromine in CCl_4 and CH_2Cl_2 leads to the formation of two yellow crystalline products. One of these products immediately precipitates from solution after mixing the reagents and was found to be 3-bromomethyl-2,3-dihydro-1,4-thiazino[2,3,4-*i,j*]quinolinium bromide (V). The second product, 3-bromo-2,3-dihydro-4H-1,4-thiazepino[2,3,4-*i,j*]quinolinium bromide (VI), slowly precipitates out of the colorless solution, indicating that it is formed by intramolecular quaternization of 8-(2,3-dibromopropylthio)quinoline (VII). Precipitation of reaction products does not occur when the bromination of sulfide I is carried out in chloroform, ethanol, and acetic acid. A mixture of bromides V and VI separates out upon distilling off the solvent.

The reaction of sulfide I with excess bromine in CCl_4 gives a mixture of 3-bromomethyl-2,3- dihydro-1,4-thiazino[2,3,4-*i,j*]quinolinium tribromide (VIII) and bromide VI. The action of acetone on tribromide VIII leads to its conversion to bromide V.

The IR spectra of sulfide I show stretching and deformation vibrations for the double bond at 1630 and 915 cm^{-1}, which are not seen in the IR spectra of halocyclization products II, III, V, and VI.

The PMR spectra of triiodide II and bromide V are similar but differ from the spectrum of bromide VI. The PMR signals for the $N-CH_2$ protons in bromide VI are at lower field (5.35 ppm) than the signals for the CHBr proton (4.40 ppm). The signals for the $N-CH-$ proton in bromide V is at lower field (5.87 ppm) than the signals for the CH_2Br protons (4.05 ppm).

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer for KBr pellets. The PMR spectra were taken on a Tesla BS-497 spectrometer at 100 MHz with TMS as the internal standard.

8-Allylthioquinoline (I). **A.** A sample of 2.19 g (0.01 mole) sodium 8-mercaptoquinolinate and 0.9 ml (0.01 mole) allyl bromide were added to 10-15 ml DMSO, DMF, ethanol, 1-propanol, or 2-propanol and stirred at 20-50°C until the solution became colorless. A sample of 150 ml water was added to the solution. The precipitate formed was filtered off, dried, and recrystallized from hexane to give I in 80-94% yield, mp 41°C (67°C [4]).

B. A sample of 2.19 g (0.01 mole) sodium 8-mercaptoquinolinate, 0.9 ml allyl bromide, and 50 ml surfactant (Sulfanol, Syntanol, or sodium stearate) were added to 25 ml water and stirred for 1 h. The yield of I was 60-73%.

C. A sample of 2 g (0.01 mole) 8-mercaptoquinoline dihydrate and 0.9 ml (0.01 mole) allyl bromide were dissolved in 20 ml acetone and stirred for 6 h. Then, 200 ml 5% aq. NaOH was added and the precipitate formed was filtered off and dried to give I in 88% yield. PMR spectrum in $(CD_3)_2CO$: 3.76 (2H, d, $J = 6.5$ Hz, SCH_2), 5.14, 5.34 (2H, m, $J_{trans} = 17.1$, $J_{cis} = 9.9$ Hz, $=CH_2$), 6.20 (1H, m, CH=), 7.38-7.70 (4H, m, 3-, 5-, 6-, and 7-H), 8.23 (1H, d.d, $J_{34} = 8.2$, $J_{24} = 1.7$ Hz, 4-H), 8.88 ppm (1H, d.d, $J_{23} = 4.2$, $J_{24} = 1.7$ Hz, 2-H).

3-Iodomethyl-2,3-dihydro-1,4-thiazino[2,3,4-*i,j*]quinolinium Triiodide (II). **A.** A sample of 0.63 g (2.5 mmol) iodine in 5 ml acetone was added to a solution of 0.2 g (1 mmole) 8-allylthioquinoline (I). After 2 h, diethyl ether was added to precipitate out the product, which was filtered off and dried. The yield of II was 0.68 g (96%), mp 95°C (dec.).

B. A sample of 0.63 g (2.5 mmole) iodine and 0.2 g (1 mmole) 8-allylthioquinoline were added to 10 ml solvent (diethyl ether, ethanol, or chloroform) and stirred. After 2 h, the precipitate formed was filtered off, dissolved in acetone, and reprecipitated by adding diethyl ether to give II in 85-93% yield.

C. A sample of 0.7 ml 54% hydriodic acid and 0.3 ml 30% H_2O_2 were added to a solution of 0.2 g sulfide I in 5 ml 2-propanol and left for 12 h. The precipitate was filtered off to give 0.54 g (76%) triiodide III.

D. A sample of 0.2 ml 40% hydrobromic acid was added to 0.2 g sulfide I in 3 ml acetone. The oily precipitate was dissolved in 5 ml 2-propanol, 0.63 g (2.5 mmoles) iodine was added, and the mixture was stirred for 1 h to give 0.56 g II. PMR spectrum in $(CD_3)_2CO$: 3.70-4.20 (4H, m, SCH_2, CH_2I), 5.97 (1H, m, 3-H), 7.90-8.45 (4H, m, 6-, 8-, 9-, and 10-H), 9.46 (1H, d.d, J_{76} = 8.2, J_{75} = 1.2 Hz, 7-H), 9.71 ppm (1H, d.d, J_{56} = 5.8, J_{57} = 1.2 Hz, 5-H). Found: S, 4.15; I, 71.93%. Calculated for $C_{12}H_{11}I_4NS$: S, 4.52; I, 71.61%.

3-Iodomethyl-2,3-dihydro-1,4-thiazino[2,3,4-*i,j*]quinolinium Iodide (III). **A.** A solution of 0.63 g (2.5 mmoles) iodine in 5 ml acetone was added to a solution of 0.2 g (1 mmole) sulfide I in 5 ml acetone. After 1 h, a solution of 0.56 g (3 mmoles) $NaI \cdot 2H_2O$ was added. The precipitate formed was filtered off and dried to give 0.39 g (87%) III, mp 199°C (dec.).

B. A solution of 0.37 g (2 mmoles) $NaI \cdot 2H_2O$ was added to a solution of 0.71 g (1 mmole) triiodide II in 10 ml acetone. The precipitate formed was filtered off and dried to give III in 93% yield.

C. A solution of 0.2 g (1 mmole) sulfide I in 3 ml acetone was added to a solution of 0.71 g (1 mmole) triiodide II in 10 ml acetone. After 24 h, the precipitate was filtered off to give 0.28 g (78%) iodide III. Found: S, 6.96; I, 55.89%. Calculated for $C_{12}H_{11}I_2NS$: S, 7.05; I, 55.77%.

3-Bromomethyl-2,3-dihydro-1,4-thiazino[2,3,4-*i,j*]quinolinium bromide (V) and 3-bromo-2,3-dihydro-4H-1,4-thiazepino[2,3,4-*i,j*]quinolinium bromide (VI). A solution of 0.05 ml (1 mmole) bromine in 3 ml CCl_4 was added to a solution of 0.2 g (1 mmole) 8-allylthioquinoline I in 3 ml CCl_4. A yellow precipitate formed immediately, which was separated and treated with acetone to give 0.1 g (27%) bromide V, mp 197°C (dec.). PMR spectrum in $(CD_3)_2SO$: 3.85-4.30 (4H, m, SCH_2, CH_2I), 5.87 (1H, m, 3-H), 7.85-8.35 (4H, m, 6-, 8-, 9- and 10-H), 9.40 (1H, d.d, J_{76} = 8.4, J_{75} = 1.4 Hz, 7-H), 9.61 ppm (1H, d.d, J_{56} = 5.5, J_{57} = 1.4 Hz, 5-H). Found: S, 8.53; Br, 44.38%. Calculated for $C_{12}H_{11}Br_2NS$: S, 8.85; Br, 44.25%.

A yellow, flocculent precipitate formed in the solution upon standing to give 0.22 g (61%) bromide VI, mp 173°C (dec.). PMR spectrum in $(CD_3)_2SO$: 3.94 (2H, m, SCH_2), 4.40 (1H, m, CHBr), 5.35 (2H, m, NCH_2), 7.80-8.35 (4H, m, 7-, 9-, 10- and 11-H), 9.31 (1H, d.d, J_{87} = 8.4, J_{86} = 1.2 Hz, 8-H), 9.51 ppm (1H, d.d, J_{67} = 5.8, J_{68} = 1.2 Hz, 6-H). Found: S, 8.65; Br, 44.15%. Calculated for $C_{12}H_{11}Br_2NS$: S, 8.88; Br, 44.26%.

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