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# FREE RADICAL HALOGENATION OF CAGE AMINES
# AN EFFICIENT PHOTOCHEMICAL SYNTHESIS OF 2-CHLOROQUINUCLIDINE

by

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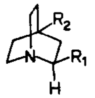
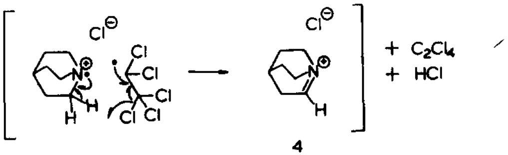
α-Haloamines have been studied extensively during recent years[1)]. In this connection α-halo bridgehead nitrogen heterocyclics are of special interest in view of their anomalous behaviour upon solvolysis (Anti-Bredt behaviour)[2)]. While methods have been developed for the preparation of linear[3)] and cyclic[4)] α-chloroamines, the synthesis of 2-chloroquinuclidine (1) is unreported. Therefore we wish to disclose a new and highly versatile synthesis of 1 which is based on the radical behaviour of amines towards polyhalogenoalkanes[5)].

A soln of quinuclidine (2) in $CCl_4$ shows strong charge-transfer behaviour as is demonstrated from the development of a CT-band having end absorption at 320-330 nm. Irradiation[6)] of a 0·15 molar soln of 2 in $CCl_4$ produced a precipitate consisting of 2.HCl while in the filtrate the presence of 1 could be detected.

The low yield of 1 was ascribed in part to the loss of intensity due to light scattering by the insoluble 2.HCl, which, moreover, is stable to photochemical reactions. Therefore a two phase system was introduced consisting of $CCl_4$ and aqueous $K_2CO_3$ (50%). Under these conditions a significant improvement was reached in the conversion of 2 → 1. However, GLC analysis revealed that after 20 hr no further increase in the amount of 1 occurred, presumably as a result of concurrent decomposition of 1 in the alkaline medium. Work-up, using 10% $NH_4Cl$ soln to selectively remove unreacted 2 and isolation of 1 as its HCl-salt, afforded a yield of 21% (42% based on converted 2). M.p. 215-218°C (dec), PMR $\delta(CDCl_3)$ 6·0 m, 1H($-\overset{\oplus}{\underset{H}{N}}C\underline{H}Cl-$); 3·3 - 3·9 m, 4H; 2·4 - 2·9 m, 1H; 1·8 - 2·3, 6H. After basification the free base 1 was extracted as an oil. Mass : $^m/e$ 147 (9%); 145 (30%); 118 (12%); 116 (40%); 110 (82%); 82 (48%) and 42 (100%), PMR $\delta(CDCl_3)$ 5·20 (t, 1H, $NC\underline{H}Cl$); 2·7 - 3·5 (m, 4H, $N\underline{CH_2}$); 2·1 - 2·5 m, 1H; 1·4 - 2·0 m, 6H. The compound was further characterized by $AgClO_4$-$CH_3OH$ conversion into the known 2-methoxyquinuclidine[7)] and also via $AgClO_4$-$C_6H_5OH$ reaction to 2-phenoxyquinuclidine[2b)]. In addition to 1 a small amount (<3%) of 4-Cl-quinuclidine (3) was formed while also the formation of hexachloroethane (35%, by comparative GLC analysis) was demonstrated. With a procedure at hand to synthesize pure 1.HCl, albeit on moderate scale, attention was focussed on its improvement. Amongst others different polyhalogeno carbon compounds ($\phi CCl_3$; $\phi C_2Cl_5$ and $BrCCl_3$) were tried and experimental conditions varied.



1 $R_1$=Cl ,$R_2$=H
2 $R_1$=H ,$R_2$=H
3 $R_1$=H ,$R_2$=Cl



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It was, therefore, gratifying to observe that upon using $C_2Cl_6$ as chlorinating agent with benzene as a solvent[8)] the synthesis of 1.HCl proved possible in an isolated yield of 66%, while in addition 6% of 4-Cl quinuclidine (3) was obtained. With regard to the mechanism of this versatile photochemical process the following comments are essential.

The rate of the reaction of quinuclidine with $C_2Cl_6$ is significantly higher than that of $CCl_4$, $\frac{k_{C_2Cl_6}}{k_{CCl_4}}$ being estimated as about 40. Quinuclidine with 2 eq of $CCl_4$ in benzene afforded less than 10% of 1 after 90 hr of irradiation while under the same conditions with 2 eq of $C_2Cl_6$ in benzene 70% of 1 was produced after 18 hr. Secondly, when the reaction was carried out in $CCl_4$ soln to which 2 eq of $C_2Cl_6$ were added, a low reaction rate was noted.

Thirdly, in neat $CCl_4$ the principal chlorine containing byproduct is $C_2Cl_6$ while virtually no $CHCl_3$ can be detected. Finally in the $C_2Cl_6$ reaction tetrachloroethene is produced in nearly stoichiometric amount.

For the $CCl_4$ reaction these facts can be accounted for by assuming a rapid complex formation between halogen compound and 2, the strength of which will be determined by halocarbon electron affinity[9]. Collapse of the complex then may occur in the following way : (NQH = quinuclidine)

$$\begin{array}{lll}
1) & NQH.CCl_4 \xrightarrow{h\nu} & [\cdot NQH]^{\oplus} Cl^{\ominus} + \cdot CCl_3 \\
2) & [\cdot NQH]^{\oplus} Cl^{\ominus} + NQH \longrightarrow & [HNQH]^{\oplus} Cl^{\ominus} + NQ\cdot \\
3) & NQ\cdot + CCl_4 \longrightarrow & NQCl + \cdot CCl_3 \\
4) & 2\ .\ CCl_3 \longrightarrow & C_2Cl_6
\end{array}$$

Although other combinations are possible, the sequence of reactions accounts for the principal products observed. On the other hand with $C_2Cl_6$ additional pathways have to be considered. Because of the simultaneous formation of 3 an intramolecular pathway in which a transient anti-Bredt intermediate 4 would play a role seems unlikely. Moreover the constancy of the ratio 1:3 - as compared to the $CCl_4$ experiment - indicates a rate-determining step alike for both processes. An attractive explanation to account for the observed differences is based upon bond dissociation energies. The facile disproportionation of the $C_2Cl_5$ radical[10] which can lose a Cl atom rather easily, might be involved in a complementary chain mechanism as follows :

$$\begin{array}{lll}
C_2Cl_6 + NQH & \xrightarrow{h\nu} & {}^{\oplus}\cdot NQH + Cl^{\ominus} + \cdot C_2Cl_5 \\
\left.\begin{array}{l} \cdot C_2Cl_5 \\ \cdot Cl + NQH \\ NQ\cdot + C_2Cl_6 \end{array}\right. & \begin{array}{c} \longrightarrow \\ \longrightarrow \\ \longrightarrow \end{array} & \left.\begin{array}{l} \cdot Cl + C_2Cl_4 \\ NQ\cdot + HCl \\ NQCl + \cdot C_2Cl_5 \end{array}\right\} \text{propagation} \\
2\ \cdot C_2Cl_5. & \longrightarrow & C_2Cl_4 + C_2Cl_6 \qquad \text{termination}
\end{array}$$

Apparently the chlorine atom is acting as a selective hydrogen abstracting agent, which can only operate effectively after initial photochemical decomposition of the amine-polyhalogeno carbon complex.

The unique properties of $C_2Cl_6$ as a selective chlorinating agent have to the best of our knowledge not been exploited earlier in this type of reaction and further studies seem appropriate. Yet two additional comments have to be made. Similar experiments with 1-azaadamantane[11)] did not lead to chlorination products but instead to the formation of salt like dimers. Secondly, the remarkable preference for the 2- and 4- positions in 2 has not been explained in a satisfactory manner. However, a directing effect of the nitrogen atom seems unmistakable.

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