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Synthesis and Reactivities of 1-Methyl-2-trichloromethyl-1,2-dihydroquinolines

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Quaternary quinolinium salts, 1-methyl-, 1,3-dimethyl-, and 1,4-dimethylquinolinium iodide, react with trichloromethyl carbanion, which is generated from chloroform and sodium hydroxide in methanol, to give the 1,2-dihydro adducts, 1-methyl-2-trichloromethyl-1,2-dihydroquinolines. 1,2-Dimethylquinolinium salt gives a different type of addition product and further reaction also occurs with dichlorocarbene to give a dichlorocyclopropane-fused compound under similar reaction conditions. Reduction of the 1,2-dihydro adduct gives 1-methyl-2-trichloromethyl-1,2,3,4-tetrahydroquinoline or 1-methyl-2-dichloromethyldecahydroquinoline depending on the catalyst used. These adducts are useful intermediates for synthesis of chlorine-containing heterocycles.

Keywords 1-methyl-2-trichloromethyl-1,2-dihydroquinoline; 1,2-dihydro adduct; trichloromethyl carbanion; dichlorocarbene; 1-methyl-2-trichloromethyl-1,2,3,4-tetrahydroquinoline; 1-methyl-2-dichloromethyldecahydroquinoline

N-Alkylquinolinium salts react with various nucleophiles such as hydroxide,[1] cyanide,[2] and nitromethane[3] or malononitrile[4] in alkaline media to afford 1,2- or 1,4-dihydroquinoline derivatives. The former products are kinetically more favorable. There have been very few papers dealing with the addition of trichloromethyl carbanion to heteroaromatic quaternary salts.[5-8]

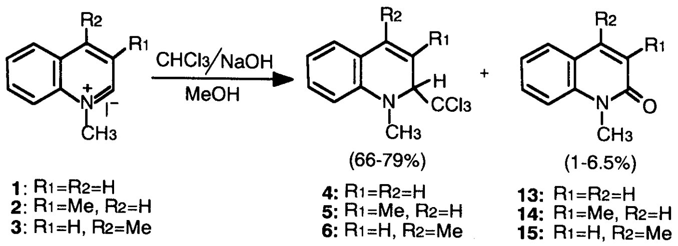
This paper describes the reaction of 1-methylquinolinium salts with trichloromethyl carbanion, which was generated *in situ* from chloroform and methanolic potassium hydroxide, to afford 2-trichloromethyl-1,2-dihydroquinolines or 4-trichloromethyl-1,4-dihydro isomers. 2-Substituted 1,2-dihydro derivatives were preferentially formed from 1-methylquinolinium and 1,3- and 1,4-dimethylquinolinium salts, but a 4-substituted 1,4-dihydro derivative was formed from 1,2-dimethylquinolinium salt. The reactivity of the dihydroquinolines thus prepared is also described.

Results

Reactions with Trichloromethyl Carbanion 1-Methylquinolinium iodide dissolved in chloroform was mixed with methanolic potassium hydroxide and left at room temperature for 1 to 3 d. A major product (mp 33—34 °C) was thereby isolated in more than 60% yield, with small amounts of by-products, from the chloroform-soluble fraction. The mobility value (*Rf*) of the major product was around 0.5 on alumina thin layer chromatography (TLC) developed with benzene–cyclohexane (1.7 : 30), indicating that the product was considerably lipophilic. The mass spectrum (MS) of the major product includes, as the parent peaks, ions at m/z 261, 263, 265, and 267 in the intensity ratio (27 : 27 : 9 : 1), corresponding to the molecular peaks of the adduct between 1-methylquinolinium ion and CCl_3 anion. A high-resolution MS showed 261.0181 which corresponds to the molecular composition of $C_{11}H_{10}Cl_3N$. Ultraviolet (UV) absorption spectra at various pH values (2 to 13) were all the same, indicating that the product is neutral or very weakly basic. In its proton nuclear magnetic resonance (^{1}H-NMR) spectrum, a doublet of one proton newly appeared at around 4—5 ppm and a doublet at the lowest field signal assignable to proton-2 of the starting material was missing. 2-Deuterated (60% isotope content) 1-methylquinolinium iodide treated under the same conditions gave a signal at 4—5 ppm of the major product reduced in intensity to 40% of that derived from the non-labeled material. These data strongly suggest that the major product derived from 1-methylquinolinium salt is 1-methyl-2-trichloromethyl-1,2-dihydroquinoline (**4**), where the electron-withdrawing trichloromethyl group is located at carbon-2 (sp^3), reducing the basicity of the adjacent nitrogen atom. The coupling constants between H-2 and H-3 and between H-3 and H-4 were 6.0 and 8.8 Hz, respectively, which are consistent with the structure **4**. This assignment is supported by the coupling constants of 1,2-dihydroquinoline reported by Bramley and Johnson.[9] One of the minor products from the reaction of 1-methylquinolinium salt was identified as 1-methylquinolin-2(1*H*)-one (**13**) (mp 64 °C) on the basis of spectral data and co-chromatography with an authentic specimen.

Treatment of 1,3- and 1,4-dimethylquinolinium salts under the same reaction conditions afforded 1,3-dimethyl-2-trichloromethyl-1,2-dihydroquinoline (**5**, mp 39—41 °C) and 1,4-dimethyl-2-trichloromethyl-1,2-dihydroquinoline (**6**, oil), respectively. The isolated yields were 72% and 69%, respectively. The structures were identified by examination of the spectra, as for **4**. The ^{1}H-NMR signal of C-CH_3 protons was only slightly shifted upfield in each product. 1,3-Dimethylquinolin-2(1*H*)-one and 1,4-dimethylquinolin-2(1*H*)-one were obtained as minor products, respectively, as in the case of the 1-methylquinolinium salt.

When 1,2-dimethylquinolinium iodide was treated under the same reaction conditions as used for other positional isomers, two main products were identified on an alumina TLC plate developed with chloroform–benzene (1.7 : 30) *Rf* 0.69 (product **8**) and 0.59 (product **9**). These products were isolated by alumina column chromatography from the dark blue reaction mixture. 1,2-Dimethylquinolinium ion turns blue with alkali.[10] The molecular weights of compounds **8** and **9** were measured by mass spectrometry as 275 and 357,



1: R1=R2=H
2: R1=Me, R2=H
3: R1=H, R2=Me

4: R1=R2=H
5: R1=Me, R2=H
6: R1=H, R2=Me

13: R1=R2=H
14: R1=Me, R2=H
15: R1=H, R2=Me

Chart 1

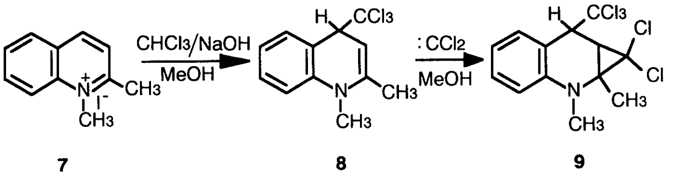


Chart 2

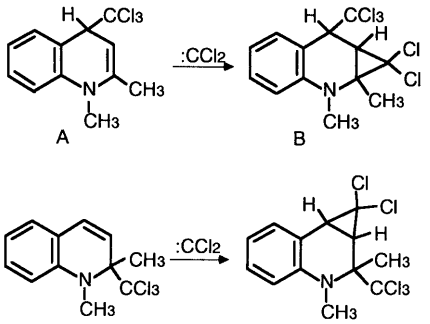


Chart 3

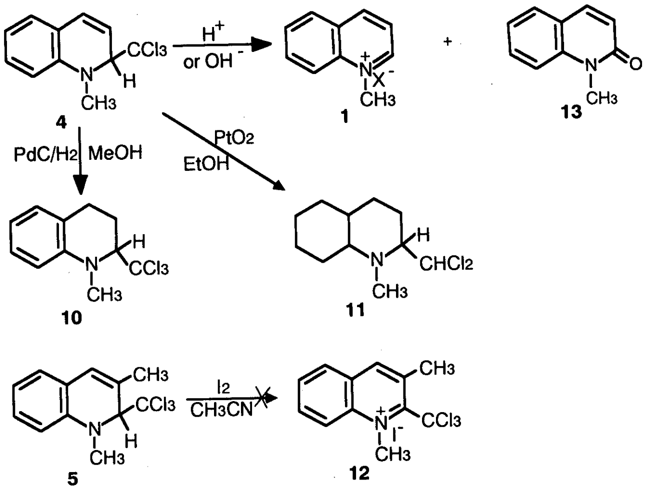


Chart 4

corresponding to $C_{12}H_{12}{}^{35}Cl_3N$ and $C_{13}H_{12}{}^{35}Cl_5N$, respectively. The elemental composition of the former corresponds to an adduct of 1,2-dimethylquinolinium ion and CCl_3 anion, and that of the latter to the adduct produced by addition of dichlorocarbene (CCl_2) to **8** initially produced. The ^1H-NMR spectrum of **8** showed a singlet at 2.14 ppm due to *C*-methyl protons, a singlet at 3.35 ppm due to *N*-methyl protons, a broad singlet at 5.15 ppm due to one proton, and a multiplet at 7—8 ppm due to 5 protons. Two alternatives for the structure of product **8** are shown in Chart 3. Since the signal at 5.15 ppm appeared as an unsplit broad singlet, assignable to either 3-H or 4-H, structure A seems preferable, becasue either 3-H or 4-H of structure A′ would have given rise to a spin-coupled doublet. These data strongly suggest that the 1,2-dimethylquinolinium salt was attacked by a CCl_3 anion preferentially at position 4, probably because of steric crowding at position 2, leading to formation of 4-trichloromethyl-1,2-dimethyl-1,4-dihydroquinoline, formulated as structure A in Chart 3. Concerning further reaction of the 1,4-dihydro product with an electrophilic dichlorocarbene, an enamine structure in formula A makes its 2,3-double bond more susceptible to an electrophilic addition of dichlorocarbene, which might be generated *in situ* by 1,1-elimination of CCl_3 anion.[11]

Therefore, the structures of products **8** and **9** are tentatively formulated as structures A and B, respectively. The MS of compound **9** showed that a CCl_2 fragment was readily eliminated to give a similar pattern of fragment peaks to that of compound **8**.

Addition products with dichlorocarbene could not be detected on the TLC plate in the reactions of other positional isomers.

Reactivity of 2-Trichloromethyl-1,2-dihydroquinoline Derivatives Compound **4** was acid-hydrolyzed under reflux in methanolic 0.1 N HCl for 2.5 h. 1-Methylquinolinium chloride was a major product (39% yield), and there were three other products, now under investigation. Neither the starting material nor **13** was detected by TLC and ^1H-NMR.

Compound **4** was also hydrolyzed with alkali under reflux in methanolic 0.1 N KOH for 2 h.[12] 1-Methylquinolinium chloride (**1**: X = Cl) and **13** were obtained in 54% and 5.7% yields, respectively, together with the recovered starting material (27% yield). When compound **4** was treated in acetonitrile at elevated temperatures, isomerization to the corresponding 1,4-dihydro derivative apparently did not take place.

Compound **4** was hydrogenated in the presence of Adams' platinum. After the consumption of 5 molar eq of hydrogen, the product was isolated in 64% yield as its hydrochloride, which was identified as 1-methyl-2-dichloromethyldecahydroquinoline (**11**) with the aid of ^1H-NMR,[13,14] UV, and mass spectral analyses. Thus, the MS of the product showed peaks at *m*/*z* 235 (M^+), 237 ($M^+ + 2$), and 239 ($M^+ + 4$) in a relative intensity ratio of 9 : 6 : 1, indicating that the product contains two chlorine atoms in the molecule. The ^1H-NMR spectrum of the free base showed multiplets at 0.7—2.4 ppm characteristic of aliphatic amine protons, a multiplet at 2.84 ppm due to 2-H, and a doublet at 6.26 ppm assignable to the substituent $CHCl_2$ proton. The ^1H-NMR spectrum of the hydrochloride showed two doublets assignable to a $CHCl_2$ proton, indicating at least two types of diastereomers,[15] although the stereochemistry was not studied. Hydrogenation of compound **4** with palladium afforded 1-methyl-2-trichloromethyl-1,2,3,4-tetrahydroquinoline (**10**)[16] in 16% yield accompanied with recovery of the starting material (82% yield). A trace of 1-methylquinolinium salt was detected on a TLC plate.

Iodine oxidation was undertaken using **5**, taking account of the ready aromatization of Reisert compounds.[17] Thus, compound **5** underwent iodine oxidation in chloroform at room temperature to result in the formation of 1,3-dimethylquinolinium iodide in 90% yield. The expected aromatized products were not detected TLC or ^1H-NMR.

The antitumor activity of these compounds was tested against intraperitoneally transplanted sarcoma 180,[18] but only compound **11** had a weak antitumor activity.

Discussion

Several quinolinium salts react with trichloromethyl carbanion generated from chloroform and alkali in a methanolic solvent to give 2-trichloromethyl-1,2-dihydroquinolines in high yield at room temperature. It has been reported that 2-trichloromethyl-1,2-dihydroquinolines are not the major products when a phase-transfer catalyst is used as a base.[19] These products can be rationalized as being kinetically controlled products, that is, the products are less stable than the thermodynamic ones. These products did not isomerize under our conditions due to the instability of the trichloromethyl carbanion, which decomposes to chloride and dichlorocarbene spontaneously.[11]

It is worth noting that 1-methyl-2-dichloromethyldecahydroquinoline was obtained as a major product in the hydrogenation reaction with a platinum catalyst.

We have developed a convenient method to introduce a trichloromethyl group at an adjacent position of quaternized quinolinium salts. The trichloromethyl adducts are useful intermediates in synthesis of heterocycles and the method can also be used for analogous compounds. Furthermore, these adducts can be converted to dichloromethyl groups containing aliphatic amines by catalytic hydrogenation. The dichloromethyl function is sometimes important for biological activities.[20]

In the case of the 1,2-dimethylquinolinium salt, however, the reaction occurs at the 4 position to give the 1,4-dihydro derivative and the adduct has a typical enamine structure in the molecule that reacts with the electrophile, dichlorocarbene, to give the second product.

The oxidation reaction of **5** with iodine is expected to form the quaternized salt, 1-methyl-2-trichloromethylquinolinium iodide (**12**). However, such oxidation did not occur under our experimental conditions.

Experimental

All of the reagents used were of extra pure grade, purchased from Tokyo Kasei Co. (Tokyo). The melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on JEOL 3H-60 and 4H-100 spectrometers at 28 °C, with tetramethylsilane serving as the internal standard. Infrared (IR) spectra were recorded on a model 402G IR spectrometer (Japan Optics Co., Tokyo) in KBr disks. Mass spectra were taken on a Hitachi RMU-7L mass spectrometer. UV absorption spectra were recorded on a Cary 14 spectrophotometer in water or in methanol. 1-Methylquinolinium halides were synthesized from corresponding quinolines in our laboratory by a known method and 1-methyl-2-deuteroquinolinium iodide was synthesized from 1-methylquinolinium iodide by base catalyzed hydrogen exchange in D_2O.[21] TLC was done on activated alumina-coated glass plates (Merck Co., Germany) developed with benzene–cyclohexane (1.7 : 30).

1-Methyl-2-trichloromethyl-1,2-dihydroquinoline (4) 1-Methylquinolinium iodide (**1**) (1 g, 3.83 mmol) and potassium hydroxide (1.3 g, 23.2 mmol) were dissolved in 20 ml of a mixture of MeOH and $CHCl_3$ (1 : 1, v/v), and the solution was stirred overnight at room temperature. The reaction mixture was diluted with 40 ml of water and extracted with a 40-ml portion of $CHCl_3$ more than 3 times. The $CHCl_3$ extracts were combined and dried over anhydrous Na_2SO_4 and then the dry $CHCl_3$ layer was treated with concentrated HCl (*ca.* 1 ml), and the $CHCl_3$ was evaporated off under reduced pressure. The residue was dissolved in a small volume of H_2O and re-extracted with 10—20 ml of $CHCl_3$ three times; the extracts were combined and dried over anhydrous Na_2SO_4. The solvent was evaporated off to yield the title compound containing a small amount of 1-methylquinolin-2(1*H*)-one. From the aqueous layer, the starting material was recovered in 11.8% yield as the chloride. The product was purified by column chromatography using activated alumina as the support, and it was eluted with a mixed solvent system of benzene–$CHCl_3$ (1.7 : 30, v/v) to give 630 mg (66%) of pure **4**. Further elution with $CHCl_3$ afforded 43 mg (7.3%) of 1-methylquinolin-2(1*H*)-one (**13**). mp 64 °C. UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 270, 323. **4** was recrystallized from EtOH to give fine needles. mp 33—34 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.4 (3H, s, $\underline{\mathrm{N}}$-Me), 4.9 (1H, d, $J_{2-3}=6.0$ Hz, 2-H), 6.2 (1H, q, $J_{3-4}=8.8$ Hz, 3-H), 6.6—7.3 (5H, m, 4-, 5-, 6-, 7-, 8-H), MS *m/z*: 261.02 (M^+) for $C_{11}H_{10}Cl_3N$, 261 (M^+), 263 ($M^+ +2$), 265 ($M^+ +4$), 267 ($M^+ +6$), 226 ($M^+ - Cl$), 191 ($M^+ - Cl_2$), 144 ($M^+ - CCl_3$). UV $\lambda_{\max}$ nm: 235, 315.

1,3-Dimethyl-2-trichloromethyl-1,2-dihydroquinoline (5) Compound **5** was also synthesized by the above method from 1 g of 1,3-dimethylquinolinium iodide (**2**); the yield was 72% as crystals, mp 39—41 °C, with recovery of the starting material (10%) and 1,3-dimethylquinolin-2(1*H*)-one (**14**) (6%). UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 235, 316. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (3H, d, $J_{4-3\mathrm{Me}}=1.5$ Hz, C-Me), 3.35 (3H, s, $\underline{\mathrm{N}}$-Me), 4.54 (1H, s, H-2), 6.60—7.30 (5H, m, 4-, 5-, 6-, 7-, 8-H). MS *m/z*: 275 (M^+), 277 ($M^+ +2$), 279 ($M^+ +4$), 281 ($M^+ +6$), 240 ($M^+ - Cl$), 205 ($M^+ - Cl_2$), 158 ($M^+ - CCl_3$).

1,4-Dimethyl-2-trichloromethyl-1,2-dihydroquinoline (6) 1,4-Dimethylquinolinium iodide (**3**) (1 g, 2.3 mmol) was treated in the same way as above to give 69% of the product as an oil. UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 234, 316. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, br s, 4-Me), 3.32 (3H, s, $\underline{\mathrm{N}}$-Me), 4.63 (3H, d, 2-H), 5.85 (1H, m, $J_{2-3}=6.0$ Hz, 3-H). MS *m/z*: 275 (M^+), 277 ($M^+ +2$), 279 ($M^+ +4$), 281 ($M^+ +6$), 240 ($M^+ - Cl$), 205 ($M^+ - Cl_2$), 158 ($M^+ - CCl_3$).

Reduction of 4 a) Catalytic hydrogenation of **4** (100 mg) was attempted over 5% palladium on charcoal (13 mg) in EtOH. The solution was shaken under a hydrogen atmosphere at room temperature for 20 h but most of the starting material was recovered. 1-Methyl-2-trichloromethyl-1,2,3,4-tetrahydroquinoline (**10**) was obtained in only 6% yield, with a trace of 1-methylquinolinium salt. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (2H, m, 3-H), 3.00 (2H, t, 4-H),[13] 3.10 (3H, s, $\underline{\mathrm{N}}$-Me), 3.90 (1H, m, 2-H), 7.25—8.00 (4H, m, 4-, 5-, 6-, 7-, 8-H).

b) Compound **4** (253 mg, 0.97 mmol) in 26 ml of EtOH was shaken over platinum oxide (100 mg) under a hydrogen atmosphere at room temperature. The catalytic hydrogenation reaction proceeded until 5 molecular eq of hydrogen had been consumed during 7 h. The catalyst was filtered off and the filtrate was concentrated to dryness under reduced pressure to give 168 mg (64%) of the product, **11**, which was crystallized from acetone to afford white prisms of the hydrochloride. No UV absorption maximum was observed at around 230—300 nm in EtOH. mp 145—150 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s, $\underline{\mathrm{N}}$-Me), 2.84 (1H, m, 2-H), 6.24 (1H, d, 2′-H), 0.7—2.4 (m, others) for free base, and 3.09 (3H, br s, $\underline{\mathrm{N}}$-Me), 3.60 (1H, m, 2-H), 6.60, 6.84 (1H, each d, 2″-H), 0.65—2.60 (m, others) for hydrochloride. MS *m/z*: 235 (M^+), 237 ($M^+ +2$), 239 ($M^+ +4$), 200 ($M^+ - Cl$), 152 ($M^+ - CHCl_2$).

Acid Hydrolysis of 4 A solution of **4** (80 mg) in 0.1 N methanolic hydrochloric acid was refluxed for 2.5 h. The solvent was removed after the reaction and the residue was dissolved in a small amount of H_2O. This solution was made alkaline by addition of aqueous sodium hydroxide. The alkaline solution was extracted with $CHCl_3$; the $CHCl_3$ layer contained only 1-methylquinolinium salt. The yield was 39% as the chloride. None of the starting material or other products could be isolated.

Alkaline Hydrolysis of 4 A solution of **4** (80 mg) in methanolic 0.1 N KOH solution was carried out under reflux for 2 h, then the solvent was evaporated off under reduced pressure, and the residue was dissolved in a small amount of H_2O. This solution was extracted with $CHCl_3$ to afford yields of 54.2% of 1-methylquinolinium chloride, 26.8% of the starting dihydroquinoline, and 5.7% of **13**.

Oxidation of 5 with Iodine The **5** (100 mg, 0.362 mmol) was dissolved in 10 ml of $CHCl_3$, containing 110 mg (0.433 mmol) of iodine. The solution was stirred at room temperature for 14 h and the solvent was evaporated off under reduced pressure. The brown residue was crystallized from EtOH to give crystalline **2** in 90% yield. No other product was observed on TLC or NMR.

Reaction of 1,2-Dimethylquinolinium Iodide (7) with $CHCl_3$ Compound **7** (1 g, 2.39 mmol) was treated with $CHCl_3$ in MeOH in the presence of KOH for 3 d as described for **1**. After work-up, **8** and **9** were obtained as an oil and crystals in yields of 24 and 81 mg, respectively. **8**: ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s, C-Me), 3.35 (3H, s, $\underline{\mathrm{N}}$-Me), 5.15 (br s, 1H, 4-H), 7.10—7.90 (m, 5H, others). MS *m/z*: 275 (M^+), 277 ($M^+ +2$), 279 ($M^+ +4$), 281 ($M^+ +6$), 240 ($M^+ - Cl$), 205 ($M^+ - Cl_2$), 170 ($M^+ - CCl_3$). IR (NaCl cells); 1380, 1460, 1490, 1595, 1655, 2820, 2905 cm^{-1}. **9**: mp 87 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, C-Me), 3.30 (3H, s, $\underline{\mathrm{N}}$-Me), 5.13 (1H, s, 4-H), 5.65 (1H, s, 3-H), 7.05—7.70 (4H, m, 4-, 5-, 6-, 7-, 8-H). MS *m/z*: 357 (M^+), 359 ($M^+ +2$), 361 ($M^+ +4$), 363 ($M^+ +6$), 365 ($M^+ +8$), 367 ($M^+ +10$), 275 ($M^+ - CCl_2$), 240 ($M^+ - CCl_2 - Cl$), 205 ($M^+ - CCl_2 - Cl_2$), 170 ($M^+ - CCl_2 – CCl_3$). IR (KBr): 1495, 1600, 2840, 2915 cm^{-1}.

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