Quaternary Pyridinium Salts from Olefins, Pyridine and Chlorine or Bromine[1]

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Abstract

The reaction of olefins with a halogen and pyridine (or pyridine derivative) to form α-halo-alkypyridinium quaternary halides has been previously reported only for the halogens bromine and iodine monochloride. In the present study, this reaction has been extended to the use of chlorine as halogen, and to the internal double bonds of unsaturated acids and derivatives. Oleic acid, methyl oleate, methyl linoleate, oleic amide and octadecene were used as olefins. Pyridine, quinoline and γ-picoline were used as the amines. Formation of the quaternaries was shown by chemical and infrared analyses.

The reaction occurred rapidly at −20C in excess pyridine as solvent and reagent. The probable mechanism is addition of X^+ to the double bond to give an α-halo-cation plus halogen anion, followed by attack of the cation by the pyridine to form the quaternary pyridinium cation.

The competing reaction of the α-halo-cation with the halo-anion to give the dihalide of the olefin is repressed by the large excess of pyridine used. The quaternary is not formed by reaction of the dihalide with pyridine, since methyl dichlorostearate did not react readily with pyridine. The fatty pyridinium quaternaries show biocidal activity against *E. coli* and *M. pyogenes*.

Introduction

THE REACTION of unsaturated aliphatic compounds with pyridine and bromine or iodine monochloride to give α-halo-alkylpyridinium quaternary halides was established definitely for the cyclic alkenes, cyclohexene and cyclopentene by Hayes et al. in 1950 (1). Earlier (1924), Barrnett et al. (2) had obtained a crystalline quaternary pyridinium bromide from cyclohexene, pyridine and bromine. They reported crystalline pyridinium quaternaries with pyridine and bromine from anethole, isosafrole, stilbene, cinnamic acid and its methyl and ethyl esters. The compound from cyclohexene was considered to be:
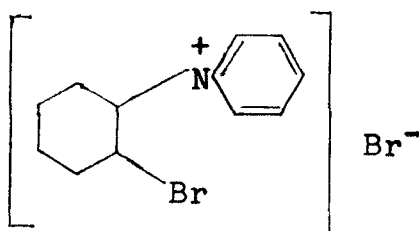

They also reported that "quaternary formation probably occurred" with ethylene, undecenoic acid, styrene, maleic, aconitic, itaconic and citraconic acids, as well as anethole and isosafrole. They stated that the following compounds "underwent bromination" (presumably without quaternary formation): oleic

acid, terpineol, camphene, α-ionone, benzylidene acetone and piperonylidene acetone.

The later work of Hayes et al. (1) was more definitive. They studied the reactions of cyclohexene and cyclopentene as olefin, with pyridine, isoquinoline and quinoline as amines, using bromine and iodine monochloride as halogens. With bromine, the yield of quaternary increased with excess of amine used, and followed the series pyridine > isoquinoline > quinoline. Iodine monochloride gave higher yields than bromine. With iodine monochloride, the anion was Cl^- rather than I^-. The reaction did not go via the direct addition of halogen to the double bond, followed by reaction with pyridine, since neither 1,2-dibromo-cyclohexane nor 1-iodo-2-bromocyclohexane reacted with pyridine under the conditions used. The proposed mechanism was:
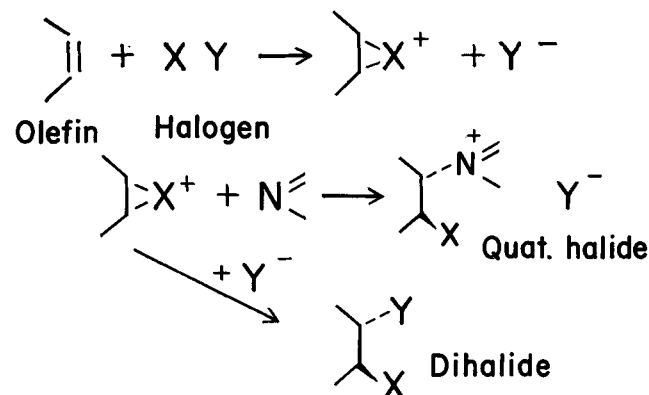
The structure of the cyclohexene, pyridine, bromine reaction product was proven to be 1-(trans-2-bromocyclohexyl) pyridinium bromide by hydrogenation to the piperidinium salt, and hydrolysis to the known 1-(trans-2-hydroxycyclohexyl) piperidine, with retention of configuration due to neighboring group effect.

1-(trans - 2 - hydroxycyclohexyl piperidene
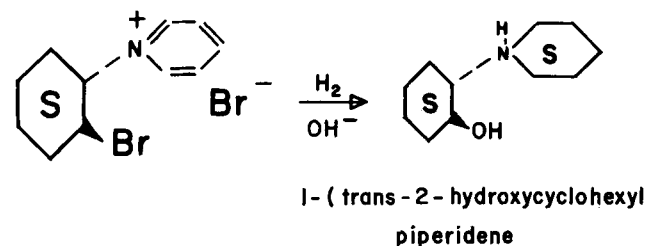
This proposed mechanism seems quite satisfactory for the cycloalkenes described by them and is undoubtedly the same with the noncyclic olefins to be described.

In neither of these previous studies was chlorine alone used as the halogen. The first step is apparently the addition of a positive halogen to the double bond, as shown by Hayes' work, where the more positive iodine added, and the more negative chlorine was the anion of the quaternary. Since chlorine is more negative than either bromine or the iodine of ICl, it was of some interest to determine whether this quaterniza-

TABLE I

Pyridinium Quaternary Syntheses

Unsat. Cpd. Used[a]	Analyses					Biocidal act. ppm	
	Ionic chloride %	Total chloride %	nitrogen %	Total amine No.	Iodine value	E. coli	M. pyog.
Me. oleate (crude product)	6.5 (7.95)[b]	15.9(15.9)	2.0 (3.1)	102(126)	0.0	500	500
Me. oleate (prod. purified)	7.85(7.95)	15.7(15.9)	3.01(3.1)	123(126)	....		
Oleic acid	8.7 (8.2)	17.2(16.5)	3.3 (3.2)	142(130)	0.0		
Me. Oleate[c]	14.8 (14.9)Br	....	2.4 (2.6)	103(105)	0.2	500	500
Me. Oleate[d]	5.5 (7.7)	15.1(15.4)	1.1 (3.0)	89(122)	2.5		
Me. Oleate[e]	.....	13.4(14.3)	2.6 (2.4)	87(113)	0.0		
Oleic amide (crude product)	10.5 (8.2)	19.8(16.4)	6.8 (6.3)	173(125)	....		
Oleic amide (prod. purified)	8.4 (8.2)	18.5(16.4)	....	117(125)	0.0	200	100
Me. linoleate	10.8 (11.9)	23.4(23.9)	4.3 (4.7)	177(189)	0.0	500	500
1-Octadecene	8.75(8.84)	17.0(17.6)	3.4 (3.5)	140(130)	0.0	50	25
Me. oleate + MeOH (Quat. layer)	6.9 (7.9)	17.8(15.9)	2.6 (3.1)	110(126)			

a Pyridine used as base and chlorine as halogen except as noted.
b Theoretical values in parentheses.
c Bromine as halogen.
d γ-Picoline as base.
e Quinoline as base.

tion could be done with chlorine alone, and also whether ·it went well with an internal double bond as in oleate and linoleate.

In the present study this reaction has been applied to methyl oleate, oleic acid, methyl linoleate, oleic amide, and 1-octadecene, as olefins, using chlorine and bromine as halogens; pyridine, quinoline, and γ-picoline as bases. The formation of quaternary compounds was confirmed by chemical analyses and infrared spectroscopy. Pyridine (or derivative) was used as a solvent and reactant, giving a large molar ratio of amine to olefin to favor the desired reaction. Chlorine was added as a gas or as a solution in carbon tetrachloride. With methyl oleate it was shown that the quaternization does not go via the dichloride, since, methyl 9,10-dichlorostearate did not react with pyridine.

When methanol was used with pyridine on methyl oleate, a competitive reaction occurred. However an appreciable amount of quaternary was formed:
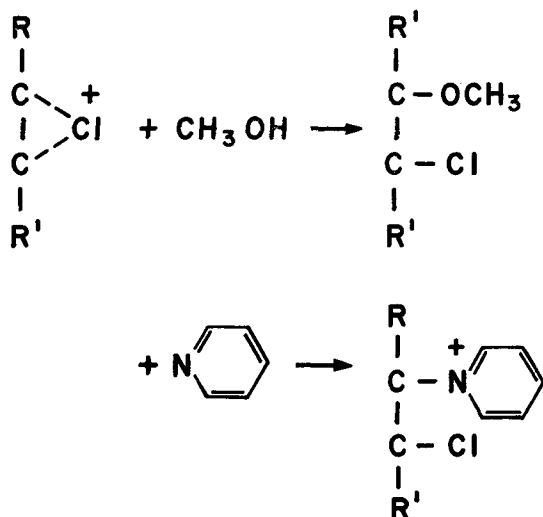
The same structure could result from reaction of methyl hypochlorite (from methanol plus chlorine) with the double bond.

Some of these quarternaries showed significant bactericidal action against *E. coli* and *M. pyogenes*.

Experimental

Analytical Methods

Infrared curves were run with a Beckman IR-4 spectrophotometer, usually on thin films (TF). Ionic chloride was determined by volumetric titration. Total chloride was determined by Parr bomb com-

bustion. Per cent N was determined by the Kjeldall method.

"Total Amine No." was determined by titration with perchloric acid in acetic acid, after adding mercuric acetate to an acetic acid solution of the quaternary, with crystal violet indicator, or a glass electrode (3). This method would also titrate any free amine (pyridine) or amine hydrochloride, as well as the quaternary chloride.

Iodine number was determined by the Wijs 1/2 hr method, with addition of 2.5 g of sodium lauryl sulfate before the final titration, to improve the endpoint color change.

Biocidal activity was determined by the method of Ruehle and Brewer (4). The results are the lowest concentrations found to give a high kill (0-100 count) after a 5 min exposure.

Preparation of Quaternary Compounds

The general method of preparation is illustrated by the following details on the reaction of methyl oleate, pyridine and chlorine: Methyl oleate (91% by GLC), 20 g (0.068 mole) was dissolved in 350 g of pyridine (4.4 mole), kept at −20C while 7.0 g of chlorine (0.099 mole) was bubbled into the mixture with stirring and for 1 hr thereafter. After warming up to room temperature during 1 hr, the reaction mixture was diluted with 300 cc of water, extracted with 3 portions of CH_2Cl_2 (250, 150, 150 cc). The CH_2Cl_2 solution of the quaternary was washed with 6M HCl to acid reaction of the aqueous phase, then with water to neutrality of the aqueous phase. The CH_2Cl_2 solution was dried over $MgSO_4$ and stripped under vacuum to give 31.8 g (104% theory) of crude product, a dark, viscous oil (Table I).

A composite of a number of similar runs was further purified by dissolving in 7 parts of CH_2Cl_2, washing with excess 3M HCl, then with water, drying over $MgSO_4$, stripping off most of the CH_2Cl_2, and precipitating by adding 10 parts of ether and decanting the ether layer. The precipitated oil was freed of solvent under vacuum (Table I).

The following reactions were similarly made: oleic acid, pyridine, chlorine; methyl linoleate, pyridine, chlorine, and oleamide (at 2C), pyridine and chlorine, using ether or ether plus petroleum ether precipitation of the quat from the CH_2Cl_2 solution. In three reactions (a, oleate, pyridine, bromine; b, oleate, γ-picoline, chlorine; c, oleate quinoline, chlorine), the ether precipitation step was omitted, and a small oily upper layer was observed on top of the stripped quaternary compound. The oily layer was removed by decantation. It was probably dichloro (dibromo)
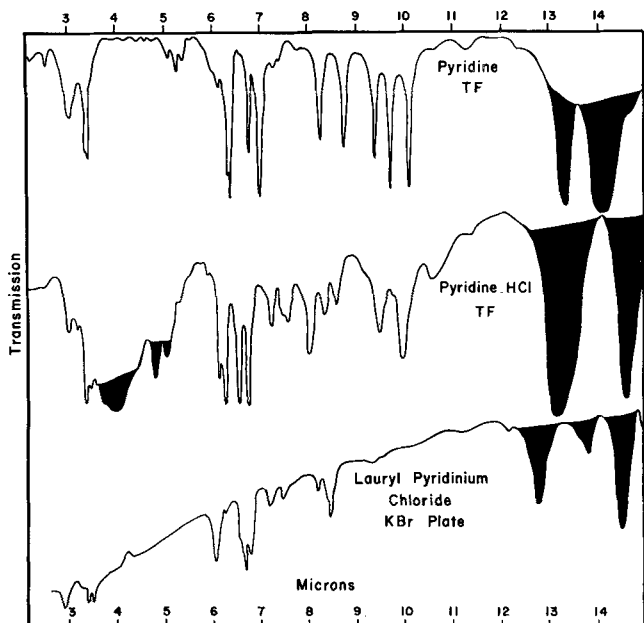
FIG. 1.   Infrared spectra of reference compounds.

FIG. 3.   Infrared spectra of quats from Me · oleate and oleamide.

stearate since IR showed no quaternary. The octadecene, pyridine, chlorine quaternization was run at 2C, since the olefin crystallized out at a lower temperature. The reaction mixture, on being poured into 2 volumes of ether gave a solid preciptate which was filtered and further purified by slurrying with acetone and filtering, repeated several times.

The reaction of pyridine and chlorine on methyl oleate in the presence of methanol was made with methyl oleate 30 g (0.101 mole), pyridine 250 g (3.18 mole) and methanol 100 g (3.12 mole) at −20C with chlorine gas, 8 g (0.113 mole). The reaction mixture, after coming to room temperature was poured into 900 cc of ether, and cooled. The upper ether layer was removed and stripped to give 20 g of an oil which infrared showed to have a strong OCH₃ band at 9.06 μ (Fig. 4). The precipitated quaternary was further purified by dissolving in CH₂Cl₂, precipitation with ether plus petroleum ether, dissolving in CH₂Cl₂, washing with dilute HCl, then with water, drying and stripping. The resulting product 16 g (36% yield) was the expected quaternary,
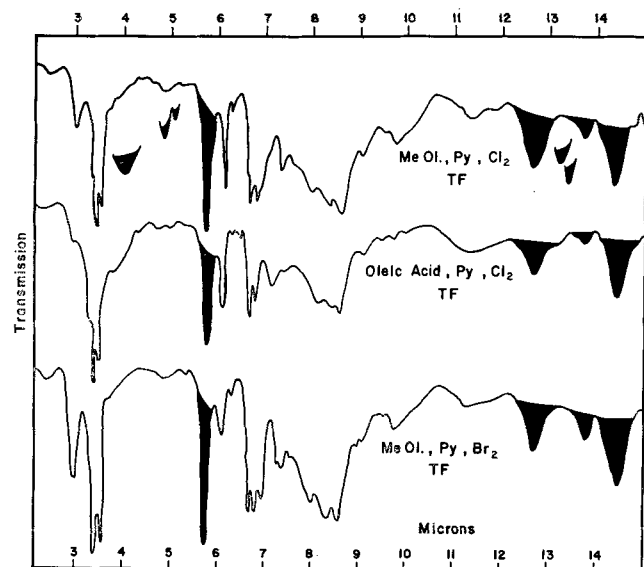
according to chemical analyses and IR.

Methyl dichlorostearate and pyridine: Methyl dichlorostearate 10 g (0.027 mole), pyridine 4 g (0.051 mole) in 100 ml of ether was refluxed for 6 hr and allowed to stand overnight at room temperature. After stripping off the ether, the product dissolved completely in CH₂Cl₂, was washed with dilute HCl, then water, dried and stripped. The resulting product showed no signs of pyridine or pyridinium quaternary by IR, but resembled the original dichlorostearate.

In Figures 2, 3, and 4 the significant bands of pyridine (13.4 μ) and of pyridine hydrochloride (4.0, 4.7, 5.0 μ) are shown as inserts at the top of the figure for convenience in comparison with the spectra of the prepared quaternaries.

Discussion

The results of the chemical analyses of the products are shown in Table I, and are in fairly good agreement with theory with few exceptions.

The infrared curves of the products are shown in Figures 1, 2, 3, and 4. Most of these were run as thin films, and all of the pyridine quats show the band at 12.6–12.8 μ, which is seen in the known lauryl pyridinium quat, but not in pyridine or pyridine

FIG. 2.   Infrared spectra of quats from Me · oleate, oleic acid.
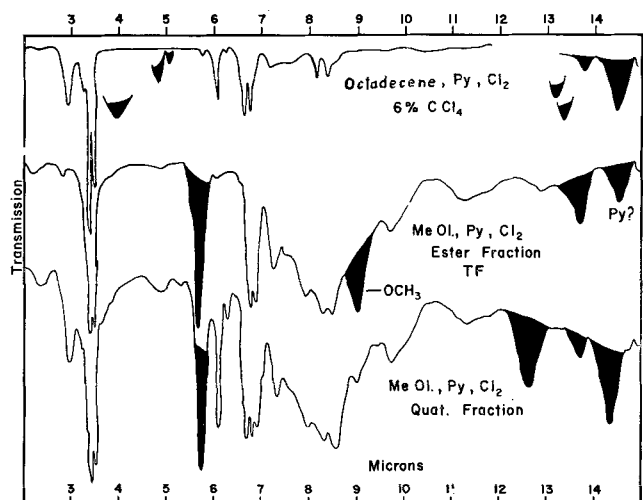

FIG. 4.   Infrared spectra of quats from dodecane, Me · oleate, and non-quat ester fraction from methyl oleate with methanol.

hydrochloride. In the γ-picoline quaternary, this band is apparently shifted to 11.9 μ, and in the quinoline quaternary to 12.0 μ. No standard picoline or quinoline quaternary compounds were available for comparison. The absence of free pyridine is shown by the absence of bands at 13.2–13.3 μ, and the absence of pyridine hydrochloride by the absence of bands at 4.0–4.8, 5.0 μ. The band at 14.4–14.6 μ is common to pyridine, its hydrochloride, as well as the pyridinium quaternary compounds. The C=O of the ester, acid or amide at 5.8–5.9 μ, is evident in all of the quaternary compounds except that from octadecene and the lauryl pyridinium chloride standard.

The γ-picoline product is quite low in all analyses except total chlorine, suggesting contamination with the dichlorostearate. The crude oleic amide product would appear to be contaminated with pyridine hydrochloride. The purified product is in better agreement with theory. The ester fraction from the reaction of methyl oleate plus methanol with pyridine and chlorine is probably contaminated with pyridine (14.6 μ band).

The bactericidal power of the diquaternary from methyl linoleate was no better than that of the monoquaternary from oleate. The quaternary from oleic amide was somewhat better, and the quaternary from octadecene-1 was the best.

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Thin-Layer Chromatography of Aliphatic γ - and δ -Lactones

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Abstract

Homologous aliphatic γ- or δ-lactones are separated by thin-layer chromatography on a mixture of kieselguhr G and silica gel G (1:8). The thin-layer plates are chromatographically impregnated with methanol as the stationary phase and developed 3 times with light petroleum (bp 80–100C) saturated with methanol. γ- And δ-lactones can be separated from each other on the same adsorbent with a 1:1 mixture of light petroleum (bp 30–40C) and isopropyl ether. The systems can be combined 2-dimensionally. The lactones are detected by spraying the chromatoplates either with a 2% solution of iodine in methanol or with alkaline hydroxylamine followed by ferric chloride and acetic acid. These methods were used for the tentative identification of δ-C_{10-16} lactones in commercial Australian butteroil.

Introduction

THE LACTONES CONTRIBUTING to butter flavor have been separated by gas chromatography (2,14) and either as the free compounds or as anilides or hydroxamic acids by paper chromatography (14,2,5,6). The thin-layer chromatography (TLC) of free a,β-unsaturated aliphatic γ-C_{14-26} lactones has been investigated by Kaufmann and Su Ko (4) but their system does not separate lactones below C_{14}. Korte and Vogel (7) separated various C_{4-8} lactones on silica gel G using isopropyl ether as solvent. This and similar systems have been used in the present investigation for the separation of γ- from δ-lactones and for the separation of γ-$C_{4, 5 \& 6}$ lactones from each other. Korte's system does not separate higher homologous lactones.

Tharp and Patton (14) separated the free δ-deca- from the δ-dodecalactone by paper chromatography using the upper phase of a 2:1 mixture of heptane: methanol as mobile phase and the lower phase as the equilibrating phase. This formed the basis of the thin-layer partition system described in the present paper for the separation of homologous lactones above C_7. The mobile solvent used in the present investigation was light petroleum (bp 80–100C) saturated with methanol, on plates consisting of 1 part of kieselguhr G to 8 parts of silica gel G. The plates were impregnated with methanol. Methanol impregnation was found essential; without it the lactones remained near the starting point, presumably due to excessive adsorption. Kieselguhr G was added to the silica gel G to reduce adsorption. Any further reduction in adsorptive capacity reduced carrying capacity below detectable limits or caused trailing due to overloading when detectable amounts of material were used.

In a pure partition system, i.e. where $R_f = 1/1 + a\dfrac{A_s}{A_L}$ (3), reduction in the quantity of stationary phase increases R_f values. However, in TLC on silica gel reduction of stationary phase also bares adsorption sites and so reduces R_f values due to increased adsorption. Therefore, maximum R_f values will be achieved with the minimum amount of stationary phase which still covers all adsorption sites. The optimum amount of stationary phase was determined experimentally.

Since both phases of the partition system are volatile, it was possible to obtain a two-dimensional separation of mixtures of γ- and δ-lactones, with the first direction for homolog separation and the second for class separation.

Experimental

Source of Reference Lactones

γ-*Lactones* were obtained from the following commercial sources and used without further purification: γ-$C_{4 \& 5}$ lactones from L. Light & Co. Ltd., Colnbrook, Bucks., England; γ-C_6 lactone from Tokyo