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Modified Hofmann Degradation for the Analysis of *n*-Alkylbenzyldimethylammonium Chlorides by Gas Chromatography I

C_{14}- to C_{18}-Alkyl Compounds

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The Hofmann degradation of quaternary ammonium compounds has been studied for *n*-alkylbenzyldimethylammonium chlorides. Gas chromatography of the reaction products provides resolution of the benzyldimethylamine and the corresponding alkene. Quantitative analysis of quaternary content and qualitative evaluation of impurities have been obtained for a number of commercial products.

O F THE METHODS for splitting of C—N bonds in amines, such as the von Braun with cyanogen bromide (1), the Hofmann degradation by pyrolysis of quaternary ammonium hydroxides (1), the Emde reduction of quaternary ammonium salts with sodium amalgam (2), and catalytic hydrogenation (2, 3), only the Hofmann and catalytic hydrogenation methods lend themselves readily to the analysis of *n*-alkylbenzyldimethylammonium chlorides. Warrington (3) has determined the alkyl distribution in benzalkonium chloride by the gas chromatographic analysis of the amines produced by catalytic hydrogenation. The determination of impurities was not feasible by this method, and the quantitative assay of the benzalkonium chloride was not afforded. Metcalfe (4) attempted the analysis of long chain quaternary ammonium compounds by a Hofmann degradation with direct injection on an alkaline treated gas chromatographic column. The reaction did not follow the expected course, and the results were not sufficiently precise for quantitative assay. Changing of the column with use also altered the alkyl distributions.

The Hofmann degradation for the analysis of *n*-alkyltrimethylammonium halides (5), and the catalytic hydrogenation of *n*-alkylbenzyldimethylammonium chloride (6, 7) have been reported in connection with gas chromatography for the determination of the long chain alkyl group. It has been suggested that in the Hofmann degradation (5) a disproportion reaction results, giving rise to both alkenes-1 and the corresponding alkanols, although this was not established by quantitative data.

Catalytic hydrogenation requires special equipment and does not afford a ready means of quantitatively determining volatile impurities. The Hofmann reaction suggested a simpler analytical approach. This work was directed toward determination of optimum reaction conditions with subsequent gas chromatography analysis of the reaction products. Assay of volatile impurities prior to Hofmann degradation combined with analysis of the products of the reaction provided a means of complete assay of commercial C_{14} to C_{18} alkylbenzyldimethylammonium chlorides.

APPARATUS AND REAGENTS

An F&M 810R-12 gas chromatograph equipped with a linear temperature programmer and dual hydrogen flame ionization detectors was employed with dual columns, 5 ft. × $^1/_8$ in. (0.101 in. i.d.),

TABLE I—RELATIVE RETENTION DATA FOR CALIBRATION COMPOUNDS

Carbon No.	*n*-Alkanes Rel. Tr[a]	RRT[b]	1-Alkenes Rel. Tr	RRT	*n*-Alkanols Rel. Tr	RRT
12	0.85	0.58	0.89	0.69	1.50	2.5
14	1.02	1.10	1.08	1.22	1.67	3.0
16	1.20	1.64	1.26	1.77	1.78	3.4
18	1.39	2.16	1.43	2.28		3.8

[a] With respect to BDMA = 1.00, Tr = 135°. [b] With respect to BDMA = 1.00, tr = 7.4 min. Benzylmethylamine gave a rel. Tr = 1.15 and RRT = 1.44. Benzylamine gave a rel. Tr = 1.60 and RRT = 2.8.

316 stainless steel, packed with 20% Carbowax 20M on polyvinylpyrrolidone (1%) coated support (Chromosorb W, 60/80 mesh). A total packing of 3.06 to 3.08 Gm. was obtained using only moderate vibration from a hand vibrator.[1] Hydrogen was supplied with an Elhygen generator[2] and tank nitrogen was used as carrier gas. Air for combustion was taken from the laboratory supply line after regulation to 23 psig and filtration through 13X molecular sieve. Samples were injected with a 10-μl. syringe (Hamilton 701 NW/G). A glass insert was placed within the injector chamber to confine the caustic solutions used to the area of this disposable glass liner and to protect the syringe needle from damage by striking any metal tubing. These glass liners were prepared from 3 mm. × 11 cm. glass tubing and were given a slight flare at the septum end. The liners were slotted 1.5 cm. from the flared end to allow entry of carrier gas. An emery disk of a Dremel Moto-Tool[3] was used for slotting.

The chromatograms were recorded with a Honeywell, model 16, recorder equipped with a Disc integrator, model 227.[4]

Even numbered compounds from C_{12} to C_{18} inclusive were obtained in 99% purity from Matheson, Coleman, and Bell for the homologous series of alkanes, alkenes-1, and alkanols and used without further purification.

Benzyldimethylamine was fractionally redistilled before use. Benzylmethylamine and benzylamine were used without further treatment. Reagent grade silver oxide and potassium hydroxide were used as received.

Glass ampuls (5 ml.), Pasteur disposable pipets, 5-ml. gas tight syringe (Hamilton 1005), and an ampul sealing torch (Matheson Scientific) were the only other items that may not be standard supplies in all laboratories.

PROCEDURE

Parameters for Programmed Temperature Gas Chromatography—The injection port temperature was set at 180°, and the oven was given a lower limit of 100°. A post-injection dwell time of 1 min. was used. The temperature was programmed to an upper limit of 240°, at a rate of 6.0°/min. An upper limit dwell time of 8 min. was held prior to the automatic recycling and resetting of initial conditions. All compounds of interest for the determination of the alkyl group distribution were eluted within 20 min. The program provided

[1] Vibro Graver, model V-73, Burgess Vibrocrafters, Inc., Grayslake, Ill.
[2] Milton Roy Co., St. Petersburg, Fla.
[3] Cole-Parmer Instrument and Equipment Co., Chicago, Ill.
[4] Disc Instruments, Inc.

sufficient time to ensure that higher boiling impurities found in most quaternary ammonium salts had been eluted prior to the next run.

The hydrogen pressure was set at 13–15 psig which gave a flow of 40 to 48 ml./min. The nitrogen pressure was set at 60 psig, and flow through each column was adjusted at the upper temperature limit to balance the columns for column bleed. The measuring column had a flow of 25 ml./min., and the reference column a flow of 20 ml./min. The air pressure to the detector was set at 23 psig which gave a flow of 340 ml./min.

Gas Chromatography of Reference Compounds—With 5.0-μl. injections of solutions containing 10 mg./ml. of each reference compound a range of 100 and an attenuation of 128 were used. The relative retention data of all compounds were taken with respect to benzyldimethylamine (BDMA). The detector responses in micrograms per disk unit of integration (mcg./DU) were calculated for a range of 10 and an attenuation of 1×. (Table I.)

Determination of Optimum Hofmann Reaction Conditions—Initially the Hofmann degradation with silver oxide was studied. A modification of the Hofmann degradation, using 4 *N* KOH, was used for a replicate set of experiments. Equal volumes of 8 *N* KOH and aqueous quaternary ammonium salt solution were pipeted into ampuls to provide a final concentration of 4 *N* KOH and 25 mg./ml. of the quaternary ammonium chloride. Ampuls were heated to 110°, and samples were analyzed at 1, 2, and 4 hr.

Determination of Impurities—Injections of the aqueous solutions of the quaternary ammonium compounds were made prior to running Hofmann reactions. Clean glass injection port liners were used in each run to obviate residual alkali from previous experiments that could give rise to a Hofmann degradation. The injector port temperature was reduced to a practical minimum of 180° to minimize thermal pyrolysis of the quaternary ammonium chlorides. Three alkylbenzyldimethylammonium chlorides, C_{14}-alkyl, C_{16}-alkyl, and C_{18}-alkyl, were studied.

From gas chromatographic runs the major volatile impurities were isolated using an effluent splitter at a ratio of 1:1. The impurities were collected directly on a 13-mm. Millipore filter disk, type TH (8). Infrared spectra of isolates were obtained by scanning the Millipore disks on a Beckman IR-8 spectrophotometer. A clean disk was used in the reference beam.

Isolation of impurities was also made by processing a chloroform solution of the quaternary ammonium chloride on a chromatographic column of silicic acid (19 mm. × 100 mm.). The total loading of the column was 2.0 Gm. of quaternary ammonium
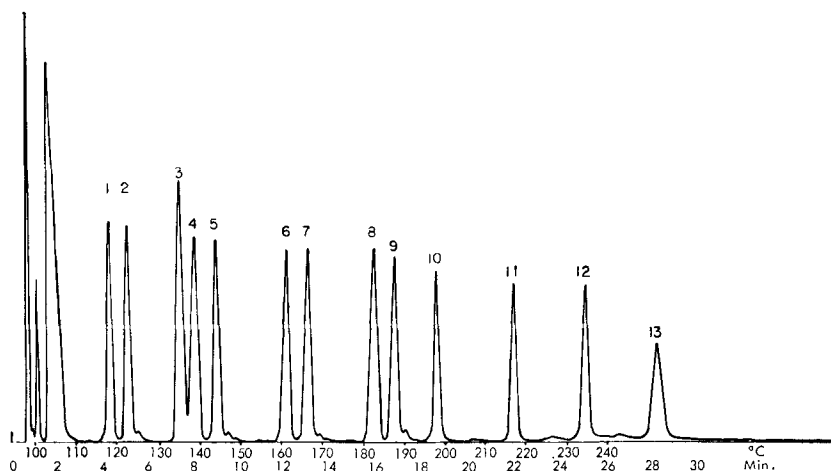
Fig. 1—*Calibration run with temperature programming from 100° to 240°. Key:* 1, n-$C_{12}H_{26}$; 2, 1-$C_{12}HO_{24}$; 3, *BDMA*; 4, n-$C_{14}H_{30}$; 5, 1-$C_{14}H_{28}$; 6, n-$C_{16}H_{34}$; 7, 1-$C_{16}H_{32}$; 8, n-$C_{18}H_{38}$; 9, 1-$C_{18}H_{36}$; 10, n-$C_{12}H_{25}OH$; 11, n-$C_{14}H_{29}OH$; 12, n-$C_{16}H_{33}OH$; 13, n-$C_{18}H_{37}OH$.

TABLE II—HOFMANN DEGRADATION OF C_{16}-ALKYLBENZYLDIMETHYLAMMONIUM CHLORIDE
(PERCENT ALKYL DISTRIBUTION WITH DIFFERENT BASES)

	4 N KOH				Silver Oxide			
				Reaction Time, hr.				
1-Alkene	3/4	1.0	2.0	4.0	3/4	1.0	2.0	4.0
C_{12}	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
C_{14}	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
C_{16}	95.5	96.2	96.3	95.0	96.4	95.5	93.0	78.2
C_{18}	4.5	3.8	3.7	5.0	3.6	4.5	7.0	21.8
Total alkene, μm.	0.142	0.152	0.140	0.142	0.265	0.348	0.315	0.485
BDMA, μm.	0.182	0.197	0.183	0.185	0.359	0.347	0.246	0.188
Ratio: $\dfrac{\text{total alkene}}{\text{BDMA}}$	0.78	0.77	0.78	0.77	0.74	1.0	1.3	2.6

chloride. Development of the column was made with chloroform. During the washing of the column with solvent, the eluate was observed in ultraviolet light (366 mμ), and fraction cuts were made where it appeared that a change in fluorescence could be seen. Finally the column was washed with methanol to remove the quaternary ammonium chloride when the column fluorescence was not further reduced by the chloroform washing. The solvent from each fraction collected was evaporated and the residues were examined (*a*) by microscopy at 100× in polarized light, (*b*) by IR spectroscopy, and (*c*) by gas chromatography of a chloroform solution of the residue. The residues were compared by these methods to known compounds. In the case of the C_{18}-alkyl compound crystals of a major impurity separated from the initial aqueous solution used for the Hofmann reaction. These were subjected also to the foregoing methods of identification.

RESULTS AND DISCUSSION

Preliminary experiments with Hofmann degradation and gas chromatographic studies of the reaction products indicated the possible presence of alkanes and alcohols, as well as the expected alkenes and
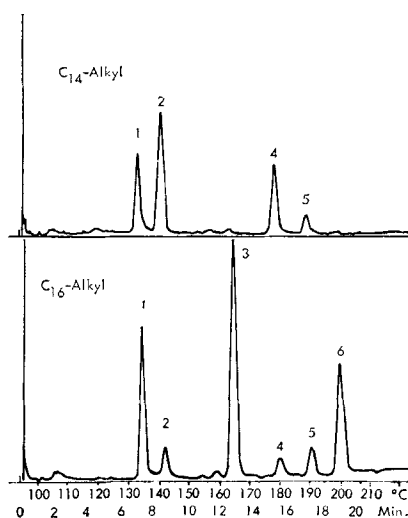

Fig. 2—*Hofmann degradation in* 4 N *KOH, 1 hr. 105°; 5-μl. injection, range 10, attenuation 32×. Key:* 1, *BDMA*; 2, 1-$C_{14}H_{28}$; 3, 1-$C_{16}H_{32}$; 4, n-$C_{18}H_{38}$; 5, 1-$C_{18}H_{36}$; 6, n-$C_{12}H_{25}OH$.

benzyldimethylamine. To identify the products and to ascertain that the materials were being resolved, reference compounds of C_{12} to C_{18} straight chain alkanes, alcohols, and alkenes were obtained and synthetic mixtures chromatographed (Fig. 1). Relative retention data to benzyldimethylamine was used for comparison and identification. (Table I.) Retention data were also obtained for benzylmethylamine and benzylamine considered as possible impurities. Programmed chromatograms resolved all compounds.

For determinations of optimum conditions to conduct the Hofmann degradation, a C_{16}-alkylbenzyldimethylammonium chloride was reacted at several time periods in the presence of silver oxide. With increasing reaction time the composition of products changed. When 4 N KOH was substituted for silver oxide, constant composition results were obtained as shown in Table II. All subsequent

studies used 4 N KOH with 1.0 hr. reaction time in sealed ampuls. Chromatograms for the C_{14}- and C_{16}-alkyl quaternaries after Hofmann degradation are shown in Fig. 2.

The relative retention data for the major impurities in the C_{16}-alkyl compound were consistent with that for the C_{12} and C_{16} straight chain alcohols and the C_{16}-alkane. Some monomethylbenzylamine was present, as was some C_{18}-alkene, the latter attributable to the presence of some C_{18} quaternary in the original product. The C_{12} and C_{16} alcohols from the C_{16}-alkyl compound were also isolated by column chromatography on silicic acid and positively identified. The composition of the volatile components from the gas chromatograms were calculated from the detector sensitivities of the individual components of reference compounds (Table III). The alkyl distribution and quaternary assay for the C_{16}-alkylbenzyldimethylammonium chloride is given in Table IV. The material was approximately 50% quaternary ammonium compounds and 50% impurities, the latter primarily lauryl and cetyl alcohols. A C_{14}-alkyl compound, a second C_{16}-alkyl compound, and a C_{18}-alkyl compound were also subjected to a purity study. The data for these materials are shown in Table V. Based on the total material injected, the total recovery of volatile materials was about 90%, and the total quaternary ammonium content ranged from 59% to 67%. About 10% of the material injected was of a non-

TABLE III—DETECTOR RESPONSE FOR CALIBRATION COMPOUNDS

——— Compd. ———	——Response—— (mcg./DU) at Range 10, 1×
n-Alkanes ($C_{12} - C_{18}$)	$44 \pm 1 \times 10^{-6}$
1-Alkenes ($C_{12} - C_{18}$)	$45 \pm 1 \times 10^{-6}$
n-Alkanols ($C_{12} - C_{18}$)	$55 \pm 3 \times 10^{-6}$
BDMA, BMA, and BA	$66 \pm 1 \times 10^{-6}$

TABLE IV—ASSAY OF C_{16}-ALKYLBENZYLDIMETHYLAMMONIUM CHLORIDE BY THE MODIFIED HOFMANN REACTION WITH 4 N KOH[a]

Compd.	RRT	Av. Peak Area, Range 100, 64×	% Alkyl Distribution		mcg.
BDMA	1.00	604		Total quat.[b]	74.5
MBA	1.48	43		Total impurity	72.3
n-$C_{16}H_{34}$	1.61	63		Total vol. material	146.8
1-$C_{16}H_{32}$	1.72	1070	95.6	% Quat.	50.8
1-$C_{18}H_{36}$	2.31	48	4.4	% Impurity	49.2
n-$C_{12}H_{25}OH$	2.53 ⎫	1960			100.0
n-$C_{16}H_{33}OH$	3.40 ⎭				

[a] Average of data used for Table II. [b] Based on the micromole of BDMA found and the distributed mol. wt. of 397 from the corresponding alkyl distribution.

TABLE V—ASSAY OF THREE COMMERCIALLY AVAILABLE ALKYLBENZYLDIMETHYLAMMONIUM CHLORIDES

	C_{14}-Alkyl	C_{16}-Alkyl	C_{18}-Alkyl
Concn.	2.50 mg./ml.	2.53 mg./ml.	2.79 mg./ml.
Vol. injected	5 μl.	5 μl.	5 μl.
Total material	12.5 mcg.	12.7 mcg.	14.0 mcg.
Alkyl Group	Distrib.	Distrib.	Distrib.
C_{12}	4.7	0	0
C_{14}	90.0	16.8	6.2
C_{16}	5.3	83.2	9.4
C_{18}	0	0	84.4
Total	100.0%	100.0%	100.0%
Distributed mol. wt.	369	392	417
BDMA, μm.	0.0227	0.0201	0.0200
Total quat.[c]	8.38 mcg.	7.87 mcg.	8.33 mcg.
Total vol. impurities[a]	4.60 mcg.	3.46 mcg.	4.31 mcg.
Total recovery	12.98 mcg.	11.33 mcg.	12.64 mcg.
% Recovery	103.8	89.2	89.5
% Quat.[b]	67.0	62.0	59.4
% Impurity[b]	33.0	38.0	40.6

[a] Methylbenzylamine, hexadecane, octadecane, lauryl, myristyl, cetyl, and stearyl alcohols. [b] Based on total material injected. [c] Total quaternary compound is based on distributed mol. wt. and BDMA found.

TABLE VI—ASSAY OF PURIFIED C_{14}-ALKYLBENZYLDIMETHYLAMMONIUM CHLORIDE[a]

Compd.	Peak Area, R10, 1×	Factor	μm.	% Alkyl Distrib.
1-$C_{14}H_{28}$	401920 DU	45.4×10^{-6} mcg./DU	0.09300	90.20
1-$C_{16}H_{32}$	8960		0.00182	1.87
1-$C_{18}H_{36}$	45440		0.00818	7.93
		Total alkenes	0.10300	100.00
BDMA	232960 DU	66×10^{-6} mcg./DU	0.1132	

Impurities	Peak Area	Factor		Amt.
$C_{12}H_{25}OH$	5120 DU			
$C_{16}H_{33}OH$	47360			
Total alcohol	52480 DU	55×10^{-6} mcg./DU		2.87 mcg.
$C_{12}H_{26}$	12800 DU			
$C_{18}H_{38}$	220160			
Total alkane	232960 DU	44×10^{-6} mcg./DU		10.18 mcg.
		Total impurities		13.05 mcg.

[a] Total material injected = (5.0 μl.) (10.31 mcg./μl.) = 51.55 mcg. Total material injected less impurities (total quat.) = 38.5 mcg. Total quat. micromoles (based on distributed mol. wt.) = 0.1145. Total quat. based on BDMA and distributed molecular wt. = 0.1132. Percent yield = 99%.

volatile nature and probably represented inorganic salts that occur in such commercial materials.

It has been reported (5) that a Hofmann reaction can result in a disproportionation reaction with both the alkene and its corresponding alcohol appearing as reaction products. The C_{14}-alkylbenzyldimethylammonium chloride, purified by silicic acid absorption chromatography, was used to study this possibility. Pre-Hofmann chromatograms showed that C_{14} alcohol was absent in the purified material. Following degradation in 4 N KOH no C_{14} alcohol was produced. Results are shown in Table VI.

SUMMARY

It has been shown that the various commercial n-alkylbenzyldimethylammonium chlorides are mixtures of two or more quaternary ammonium compounds and that impurities of higher alkanes, C_{16} to C_{18}, and higher alcohols, C_{12} to C_{18}, are significant.

The compounds investigated contained from 50% to 70% quaternary ammonium chlorides.

The modified Hofmann degradation is a relatively simple procedure and provides for the determination of alkyl distribution, quaternary ammonium salt content, and impurities. Standard deviations obtained show good precision for this type of procedure. Quantitative assay is dependent upon the amount of BDMA formed by the reaction and is directly proportional to the total quaternary ammonium chloride present.

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