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Report

Thermal Decomposition of Thonzonium Bromide

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Thonzonium bromide, a quaternary ammonium compound used as a surface active agent in a phenylephrine nasal solution, gave a gas chromatographic peak which was proportional in height and area to its concentration. Quaternary ammonium salts are nonvolatile and polar, thus the peak was attributed to a thermal decomposition product. It was identified as hexadecyldimethylamine by spectroscopic analysis and comparison with an authentic sample. A second product was identified by mass spectroscopy as 2[(2-hexadecylmethylaminoethyl)(4-methoxybenzylamino)]pyrimidine, the desmethyl bromide product. These decomposition products were detected in stability samples of formulations.

KEY WORDS: thonzonium bromide, thermal decomposition; quaternary ammonium derivatives, gas chromatography; surface active agents, nasal solutions; stability of nasal formulations.

INTRODUCTION

Thonzonium bromide (I) is a quaternary ammonium derivative of the antihistamine drug, thonzylamine. It has been used for its surface active properties, and it was a component of a phenylephrine hydrochloride nasal solution formulation. During the development of a programmed-temperature gas chromatographic (GC) assay for phenylephrine, a peak eluting just after that of silylated phenylephrine was evident in the chromatograms. Its response was proportional to the amount of thonzonium bromide present. GC requires that an analyte be both nonpolar and relatively volatile. Quaternary ammonium compounds satisfy neither of these criteria. Thus, the second peak must be due to a thermal decomposition product. As expected, further investigation showed that the peak from the quaternary ammonium compound was produced if the silylation reaction was omitted. The peak was identified as hexadecyldimethylamine (II). Thermal decomposition of I showed the presence of other decomposition products, the desmethyl bromide derivative (III) being the one characterized. Both of these decomposition products were detected in extracts of stability samples of formulations, so that the reaction has practical significance. The degradation pattern is shown in Fig. 1. An analogous decomposition pattern was described for benzalkonium chloride by Cybulski (1).

MATERIALS AND METHODS

Formulations

A proprietary nasal solution formulation declaring 5 mg/ml of phenylephrine HCl and 0.5 mg/ml of I was studied.

Assay of Thonzonium Bromide and Phenylephrine HCl

Standard Preparation. Weigh accurately 25 mg of I and 165 mg of USP phenylephrine HCl RS, transfer to a 100-ml volumetric flask, dissolve in methanol, and dilute to volume with methanol.

Internal Standard. Dissolve 325 mg of phenacetin in methanol and dilute to 100 ml with methanol.

Procedure. Pipet 1.0 ml of the solution under test and 1.0-, 2.0-, and 3.0-ml volumes of the standard preparation into separate 50-ml round-bottom flasks, add 2.0 ml of internal standard to each, and evaporate the solutions to dryness in a rotary evaporator under water vacuum using a warm water bath (about 45°C). Add 12.0 ml of pyridine to the residues, swirl, and add 0.4 ml of BSTFA reagent. Mix and let stand at least 15 min. Inject 1.2 μl of each solution into a gas chromatograph (a Perkin–Elmer Model 900 with FID detector was used) fitted with a 6 ft × 0.25-in. od glass column packed with 3% OV-1 on 100/200-mesh Gas Chrom Q. Program the temperature from 140°C with an initial hold of 2 min at a rate of 12°C/min to 240°C, using injector and manifold temperatures of 210 and 240°C. Use helium as the carrier gas at a rotameter setting of −4. Use attenuations of ×64 for phenacetin and phenylephrine and ×4 for the peak derived from thonzonium bromide. Employ the average of duplicate injections for determining the peak heights and construct calibration curves by graphing the milligrams of each component against its peak height ratio to the internal standard.

Pyrolysis of Thonzonium Bromide[4]

A mixture of 500 mg thonzonium bromide and 2 ml hexane was placed in a 5-ml Regis reaction vessel, a heavy-

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[4] An attempt to repeat this experiment was conducted several years after the original experiment using the exact procedure described except that an oil bath was used to heat the reaction vessel instead of a heating block. The spots obtained on thin-layer chromato-

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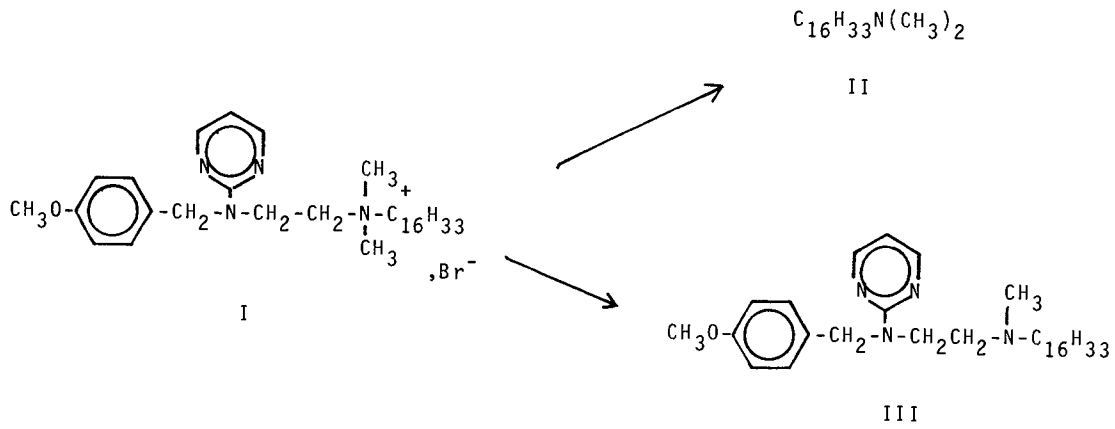

Fig. 1. Decomposition routes for thonzonium bromide.

walled vessel sealed with a Teflon-lined screw cap, and placed in an electrically heated block (Laboratory Supply Co.) at 140°C for 2 hr. The vessel was cooled to room temperature and the hexane was analyzed by the gas chromatographic method described above and by thin-layer chromatography, using silica gel G (E. Merck) and silica gel GF (Analtech) plates and methanol–hexane (85:15) and methanol–glacial acetic acid (95:5) as developing systems in previously saturated chambers.

Analysis of Stability Samples for Degradation Products

A sample of the nasal solution stored at controlled room temperature for 12 months was examined. A 5.0-ml aliquot was extracted successively with two 5-ml portions of hexane and two 5.0 ml portions of ether. The extracts were analyzed by gas chromatography using an authentic specimen of hexadecyldimethylamine for calibration.

Preparation of Authentic Hexadecyldimethylamine

An authentic sample of the amine was synthesized by acylation of dimethylamine with palmitoyl chloride followed by reduction of the amide with lithium aluminum hydride. The purity of the material was estimated at 99.6% by gas chromatography using the area normalization method, and it provided the expected analyses.

NMR Spectra

These were obtained using a Perkin–Elmer R12B spectrometer with internal lock.

Mass Spectra

An AEI Scientific MS902C instrument was used with an accelerating potential of 8 kV, an ionizing energy of 60 eV, and a trap current of 100 μA. Exact masses were obtained by the peak matching technique with perfluorokerosene as the reference. Samples were introduced by means of a direct heated probe.

RESULTS

Assay of Thonzonium Bromide and Phenylephrine HCl

Mixtures of known composition of the two compounds were analyzed by gas chromatography. Plots of the peak height ratio for each compound against concentration were rectilinear and intercepted the origin. The relative standard deviation was 1.59% for I and 0.82% for phenylephrine HCl. A typical chromatogram is shown in Fig. 2.

Characterization of Degradation Products

Thin-layer chromatography of extracts of thermally decomposed thonzonium bromide yielded the R_f values listed in Table I. Compound IV was strongly fluorescent when observed under shortwave UV light, and it was resolved into Compound V, which showed bright yellow fluorescence, and Compound VI, which showed a dark blue fluorescence. Compounds II and III were isolated from thin-layer plates and characterized by chromatography. Compound II was found to have the same mobility as authentic hexadecyldimethylamine in both the thin-layer and the gas chromatography systems, and it gave infrared and NMR spectra consistent with its structure.

Analytical Characterization

The mass spectrum of I showed identical peaks to those of hexadecyldimethylamine at 269 and 58, indicating that it is thermally decomposed in the mass spectrometer probe. Compound III, isolated from thin-layer plates with hexane, was a yellowish oil. Its UV spectrum was closely similar to that of thonzylamine. It was characterized as *N*-hexadecyl-nor-thonzylamine or 2[2-hexadecylmethylaminoethyl)(4-methoxybenzyl)]aminopyrimidine. Its elemental analysis was as follows. Calculated for $C_{31}H_{52}N_{40}$: C = 74.95; H = 10:55, N = 11.28. Found: C = 75.50; H = 10.86; N = 10.74. It was concluded that the data were consistent with the assigned structure for III assuming a trace of hexane in the sample. NMR spectra indicated the presence of the py-

graphy plates were in a pattern quite different from that described, and none of them showed fluorescence. It is speculated that the temperature in the block may have been different, i.e., lower, than the nominal temperature since this was not calibrated. Whatever the explanation, this experiment was not crucial in the study, and it is reported with this caveat.

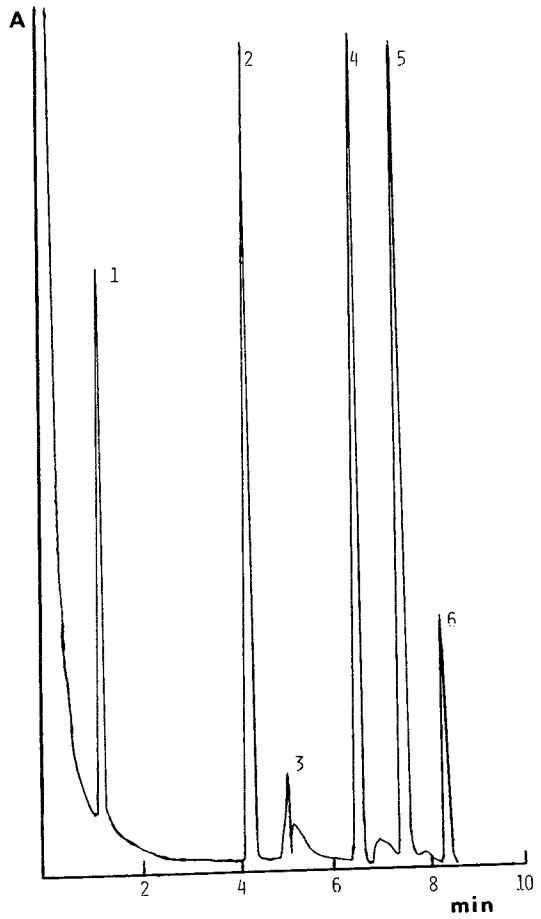

Fig. 2. Gas chromatogram of silylated phenylephrine nasal solution. Peak 1 is a paraben; 2 is phenacetin (internal standard); 4 is silylated phenylephrine; 5 is hexadecyldimethylamine (II); and 3, 6, and unnumbered peaks were not identified. Attenuations were ×64 for peaks 1–4 and ×4 for peaks 5 and 6.

rimidine ring, the 4-methoxybenzyl structure, and the hexadecyl group. Only one N-CH_3 group was present, at 2.2 ppm. These data are consistent with the desmethylbromide product of thonzonium bromide. Its mass spectrum showed a molecular ion at m/z 496, found from exact mass determination to be 496.4105, which corresponds to the 496.4141 calculated for the empirical formula of III. Major fragments were found at m/z 121, corresponding to 4-methoxybenzyl; 216, attributed to a rearrangement from the addition of 2 hydrogens to the 214 fragment (2-aminopyrimidine); 268, corresponding to *N*-hexadecyl-*N*-methylaminomethyl; and 282, *N*-hexadecyl-*N*-methylaminoethyl. The origin of these fragment ions is indicated in Fig. 3. Thonzylamine shows a similar pattern in its mass spectrum, including the m/z 216 mass fragment.

Table I. R_f Values for Extracts of Thermally Decomposed Thonzonium Bromide Yielded by Thin-Layer Chromatography

System 1 (MeOH/Hex)		System 2 (MeOH/AcOH)	
Compound	R_f	Compound	R_f
IV[a]	0.00	V[a]	0.2
II	0.5	VI[a]	0.4
III	0.8	II	0.67
		III	0.93

[a] Unidentified compound.

Detection of Degradation Products in Nasal Solutions

The combined hexane extracts yielded 0.022 mg of II, and the ether extracts 0.019 mg, for a total of 0.041 mg. By area normalization, the amount of III, present in the ether extracts, was estimated to be equivalent to about 0.08 mg of I in 5 ml for a total of 0.162 mg in 5 ml or 0.054 mg/ml as total degradation products. This represents about 10% of the declared content of I.

DISCUSSION

Thermal decomposition of quaternary ammonium salts is a common reaction owing to the distortion of the normal bond angles for nitrogen in amines. Thus it was not surprising that I decomposes on injection into a GC port at 210°C. The evidence in this study is strong that decomposition more likely occurred during processing of the nasal solution than during storage. In the limited studies conducted, there appeared to be no correlation between the storage time of the solutions and their content of intact I. Representative samples examined, whether they were stability samples or freshly prepared, had about the same content of decomposition products. This may well be one of several instances where degradation proceeds rapidly during the heating steps in manufacture and either ceases entirely or goes at a negligibly slow rate at normal temperatures for storage and transport in commerce. The procedure in the assay uses an evaporation step, where II present in the sample would be driven off. Thus, the GC assay of I as II could be considered to be stability-indicating for I. Detection of II and III in solvent extracts of the nasal solutions established that decomposition had occurred, and the material balance of I, II, and III, calculated as I, was within 10% of the formulation amount. Temperature dependence and pH effect were not established for decomposition of I. In single experiments, cetylpyridium chloride, *N*-hexadecylpyridinium chloride was found to give one GC peak (pyridine?) in the procedure described above, and benzalkonium chloride gave eight peaks. Cybulski (1) used a similar GC system to that reported here for the determination of the homologue content of benzalkonium chloride, using OV-17 in place of OV-1, and a higher injection port temperature, 250 vs 210°C. Benzalkonium chloride is *N*-alkyl-*N*-benzyl-*N*-dimethylammonium chloride. The n-

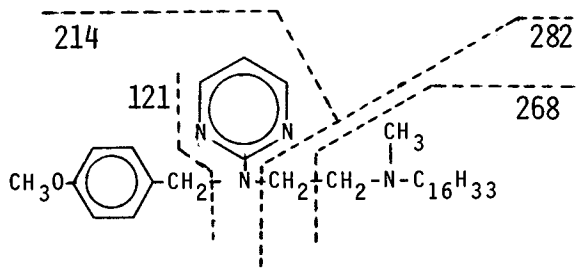

Fig. 3. Diagram of source of mass spectral fragment assignments for III.

alkyl chain can vary from to 10 to 18 carbon atoms, and the commercial quaternary salt may contain as many as 8 homologues. He reported that pyrolysis of benzalkonium chloride proceeded by two routes: scission of the molecule to alkyldimethylamines (and benzyl bromide) and *N*-alkyl-*N*-benzyl-*N*-methylamine (and methyl bromide). The first is analogous to the formation of II from I, and the second is analogous to the production of III.

The work reported here was the result of an investigation of a serendipitous finding during an assay for phenylephrine. These studies indicate that pyrolysis of quaternary ammonium compounds may occur during processing of pharmaceutical preparations containing them and that GC assay may be an effective means for determining them. Finally, GC analysis of quaternary ammonium compounds can be established as stability-indicating if the procedure incorporates a step to eliminate the pyrolysis products before analysis.

ACKNOWLEDGMENT

The synthesis of authentic hexadecyldimethylamine (II) was accomplished by the late Freeman H. McMillan, who, like coauthor John Frank, is mourned as an outstanding chemist, a splendid human being, and a warm friend.

REFERENCE

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