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SPONTANEOUS FORMATION OF 4-METHYL-5-PHENYLOXAZOLIDINE-2-THIONE FROM PHENYLPROPANOLAMINE

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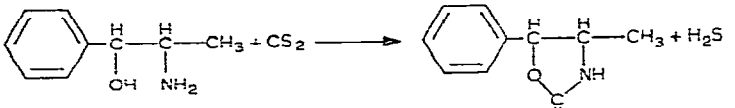
SUMMARY

An additional compound was rapidly formed when phenylpropanolamine dissolved in carbon disulfide was gas chromatographed. The compound was synthesized and isolated, and was shown by chromatographic, elemental, and spectral data to be compatible with the structure 4-methyl-5-phenyloxazolidine-2-thione.

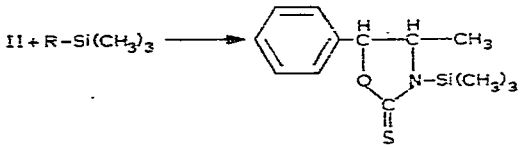
INTRODUCTION

In the course of developing a gas chromatographic (GC) procedure for the determination of belladonna alkaloids in the presence of phenylpropanolamine and chlorpheniramine, a spurious peak developed when carbon disulfide was used as the chromatographic solvent. Mass spectrometry indicated a substance with a molecular weight of 193, while after trimethylsilylation the molecular weight changed to 265. Isotope measurements at 193 showed the best fit for an empirical formula of $C_{10}H_{11}NOS$. The sum of all the available information led to the conclusion that phenylpropanolamine (I) was reacting with carbon disulfide to form 4-methyl-5-phenyloxazolidine-2-thione (II).



(I) (II)

Compound II has a molecular weight of 193 and with silylation forms compound III, which has a molecular weight of 265.



(III)

These postulates were compatible with the data and were further strengthened by the production of a chromatographic peak with the same retention time as that of the unknown from a solution of phenylpropanolamine in carbon disulfide. Neither the belladonna alkaloids nor the chlorpheniramine reacted to produce additional peaks under the same conditions.

This paper describes the formation, isolation, and characterization of 4-methyl-5-phenyloxazolidine-2-thione formed from the reaction of phenylpropanolamine and carbon disulfide.

EXPERIMENTAL

Formation and isolation

Five grams of phenylpropanolamine base were dissolved in methylene chloride (about 20 ml), 150 ml of carbon disulfide were added, and the resulting solution was glass stoppered and allowed to stand overnight at room temperature. The solvent was evaporated under nitrogen with minimum heat and the deep yellow, viscous, oily residue with a strong sulfide odor was solidified into a slightly yellowish amorphous mass by vigorous stirring with a glass stirring rod.

The solid thus obtained was dissolved in 20 ml of methanol, transferred to a 250-ml beaker, and 150 ml of 0.1 *N* hydrochloric acid were added. A yellow oil separated. As much of the supernatant aqueous portion as possible was decanted, and the oily residue transferred to a 250-ml separatory funnel. About 150 ml of 0.1 *N* hydrochloric acid were added to the separator and extraction with four 25-ml portions of methylene chloride was carried out. The methylene chloride extracts were passed through a cotton–anhydrous sodium sulfate filter, combined, and the solvent evaporated under nitrogen and low heat.

An amorphous, white mass was formed by vigorous stirring of the oily residue with a glass stirring rod. This material was gas chromatographed (*q.v.*) and showed peaks corresponding to 1.7% phenylpropanolamine and 98.3% major constituent. Thin-layer chromatography (*q.v.*) showed a major spot at R_F 0.36 with minor spots at R_F 0.0 (phenylpropanolamine) and R_F 1.0 (unidentified).

The residue was dissolved in ethanol, passed through a mixed bed of strong cation–anion-exchange resin (Amberlite MB-3), and the eluate evaporated under nitrogen with minimum heat. The viscous, oily residue was solidified by vigorous stirring with a glass stirring rod into a white, amorphous solid with a faint sulfide odor. Gas chromatography showed one peak with a retention time that was the same as that of the major peak obtained previously and the thin-layer chromatogram had one spot at R_F 0.36. The yield of final material was 1.7 g (41%) and had a melting point of 87.8°.

Analysis. Calculated for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.59. Found: C, 61.84; H, 5.82; N, 7.12; S, 16.89.

Thin-layer chromatography

Fifty micrograms of material were spotted from an acidified methanolic solution (1%, v/v, hydrochloric acid) containing 10 mg/ml on to a silica gel GF plate. Commercial plates were used (Analtech) and were not activated before spotting nor equilibrated before development. The plate was allowed to develop for a distance of 10 cm

in a chromatographic chamber with 1% (v/v) methanol in methylene chloride as the developing solvent. The developed chromatogram was visualized under UV irradiation (254 nm), sodium azide, and ninhydrin reagent. Both phenylpropanolamine at R_F 0.0 and the thiooxazolidine at R_F 0.36 were visible under UV irradiation, the thiooxazolidine with sodium azide reagent and the phenylpropanolamine with ninhydrin reagent. The final isolated material showed a single spot at R_F 0.36.

Gas chromatography

The analysis was performed on a Perkin-Elmer Model 900 gas chromatograph with dual 4 ft. × 3 mm I.D. glass columns packed with 3% methylphenylsilicone gum on 80–100 mesh silanized, acid-washed, flux-calcined diatomite (OV-17 on Gas-Chrom Q). The injection port was maintained at 220°, manifold at 280°, with a helium flow-rate of about 50 ml/min. Sample concentrations of 10 mg/ml in methanol were used with injections of 10 μl. Peak detection was effected by flame ionization detectors. The instrument was operated under the dual-column compensating technique to allow temperature programming. The following program was used: The starting temperature was 130° and held for 5 min, the temperature was then raised to 240° at a rate of 32°/min and was held until the thiooxazolidine peak was recorded. Under these conditions the phenylpropanolamine had a retention time of about 5 min and the 4-methyl-5-phenyloxazolidine-2-thione of about 11 min (Fig. 1). All peak areas

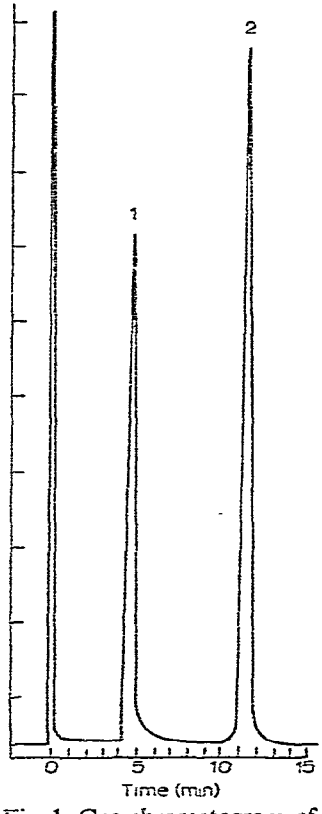


Fig. 1. Gas chromatogram of (1) phenylpropanolamine and (2) the isolated compound.

were automatically integrated and relative percentages calculated by computer. The computer parameters were set so that concentrations of substances as low as 0.01% could be detected. The isolated material showed a single peak with a retention time of about 11 min.

Ultraviolet spectrum

Fig. 2 represents the UV spectra of the isolated compound and phenylpropanolamine in ethanol. The thiooxazolidine wavelength maximum is at 245 nm with a molar absorptivity (ε) of 20,632, while phenylpropanolamine has a maximum at 257 nm with an ε of 191.45. The unsubstituted oxazolidine-2-thione has been reported with a maximum at 240 nm and ε equal to 15,848[1,2]. This accounts for the loss of the typical substituted phenyl spectrum and the corresponding hypsochromic shift of the maximum since the absorptivity of the thioncarbonate chromophore, –NH–CS–O–, completely overshadows that of the substituted phenyl. These observations are proposed as further evidence for the suggested structure of the isolated compound.

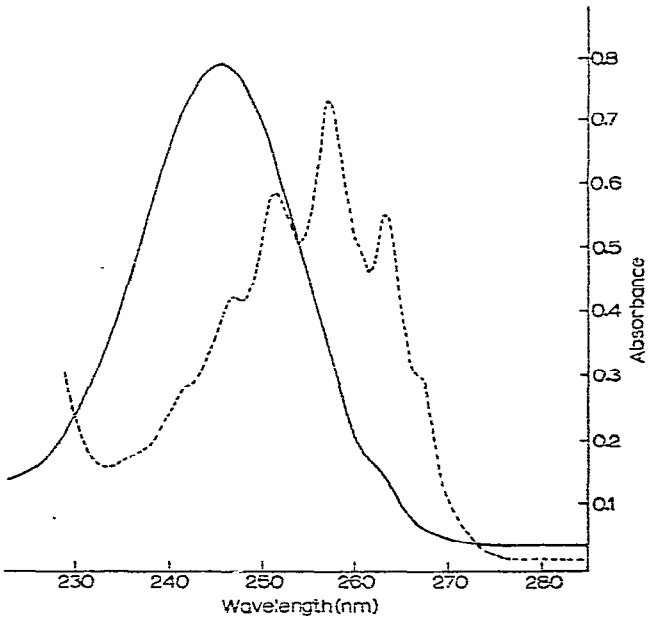


Fig. 2. UV spectra in ethanol and 5-cm cells of the isolated compound (0.00148 mg/ml) (———) and phenylpropanolamine (0.1153 mg/ml) (– – –).

Mass spectrum

The mass spectrum of the isolated compounds gave a molecular weight of 193, which is the same as that of 4-methyl-5-phenyloxazolidine-2-thione. The spectrum also supported this structure. In Table I an interpretation of the significant peaks is presented.

The significant peaks given in Table II were common to both the isolated compound and the phenylpropanolamine.

TABLE I

INTERPRETATION OF THE SIGNIFICANT PEAKS OF THE MASS SPECTRUM OF THE ISOLATED COMPOUND

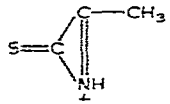
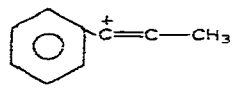
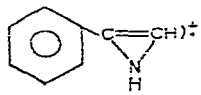
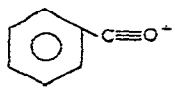
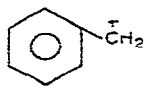
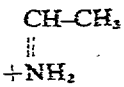
m/e	*Fragment ion structure*
193	molecular ion peak
160	$(M-SH)^+$
133	$(M-O{=}C{=}S)^+$
86	

TABLE II

SIGNIFICANT PEAKS OF THE MASS SPECTRA OF BOTH THE ISOLATED COMPOUND AND PHENYLPROPANOLAMINE

m/e	*Fragment ion structure*
117	
	and/or
	
105	
91	
77	
51	$(m/e\ 77-CH{\equiv}CH)^+$
44	

Nuclear magnetic resonance spectrum

The NMR spectrum was determined in deutero-chloroform with tetramethylsilane as the internal standard (Fig. 3). An interpretation is given in Table III.

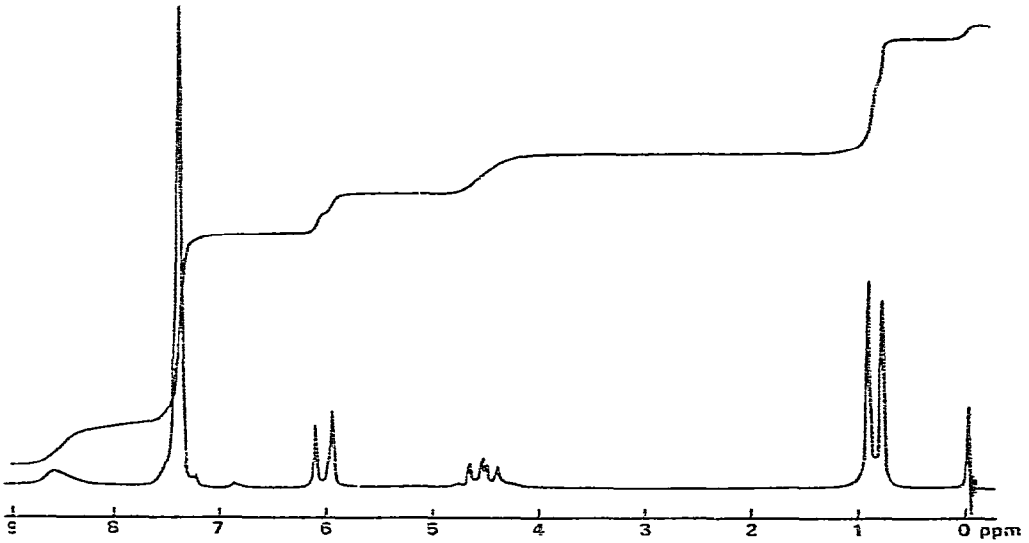
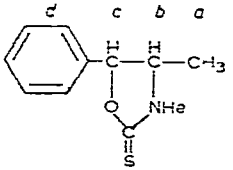


Fig. 3. NMR spectrum of the isolated compound.

Integration of the spectrum showed the protons were present in the ratio of 3:1:1:5:1, which is consistent with the structure. Comparison with the NMR spectrum of phenylpropanolamine (Fig. 4) shows the proton of the OH to be missing (2.42 ppm in the phenylpropanolamine spectrum), which is further evidence for the formation of the oxazolidine.

TABLE III

INTERPRETATION OF THE NMR SPECTRUM OF THE ISOLATED COMPOUND



Position	*ppm*	*Description*
a	1.85	doublet
b	4.51	multiplet
c	6.02	doublet
a	7.42	aromatic protons
e	8.52	NH proton

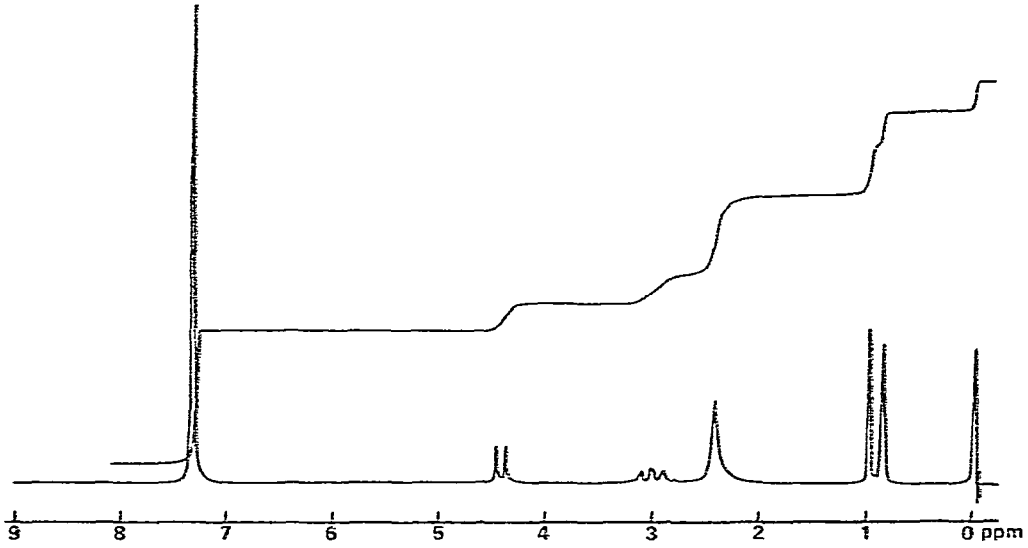


Fig. 4. NMR spectrum of phenylpropanolamine.

Infrared spectrum

The IR spectrum of the isolated compound (Fig. 5) was determined as a mull. Assignments of the principle absorbances establishing the oxazolidine structure are given in Table IV.

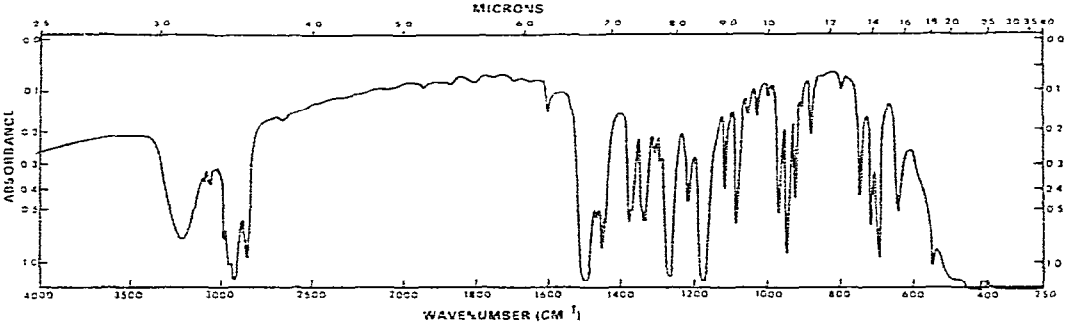


Fig. 5. IR spectrum of the isolated compound.

TABLE IV

ASSIGNMENTS OF THE PRINCIPLE ABSORBANCES IN THE IR SPECTRUM OF THE ISOLATED COMPOUND

Wave number (cm^{-1})	*Assignment*
700, 720	monosubstituted phenyl
1175	thioncarbonate
1270	–C–O– stretching
1500	amide II band from the thioamide
3220	NH

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2 M. J. Kamlet (Editor), *Organic Electronic Spectral Data*, Vol. I, Interscience, New York, 1946–1952, p. 11.